Sevelamer Hydrochloride (CAS number-152751-57-0)

TAJMTF-JKTQOI5812

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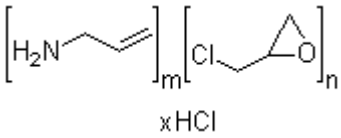

Name:

Sevelamer hydrochloride

CAS Number : 152751-57-0

Synonyms: 2-(chloromethyl)oxirane;
prop-2-en-1-amine;
hydrochloride;
2-Propen-1-amine,hydrochloride,polymer with (chloromethyl)oxirane;
RenaGel (TN);
Sevelamer hydrochloride (JAN/USAN);
Sevelamer HCL;
RenaGel;

Molecular Formula: $(C_3H_7N)_m \cdot (C_3H_5ClO)_n \cdot (HCl)_x$

Assay: 99% min

An Improved process for preparation of **Sevelamer hydrochloride** having phosphate binding capacity of 4.7 to 6.4 mmol/g comprising the steps of: (a) dissolving polyallylamine hydrochloride in water to obtain

an aqueous solution; (b) partially neutralizing the aqueous solution of polyallylamine hydrochloride with 65 to 70 mole % of alkali with respect to polyallylamine hydrochloride; (c) charging dispersing agent to hydrocarbon solvent to obtain solution; (d) mixing partially neutralized aqueous polyallylamine hydrochloride solution with the solution obtained in step (c); (e) stirring the obtained reaction mixture at speed of about 40 to about 250 revolutions per minute to get fine dispersion of aqueous phase in organic phase; (f) heating the suspension obtained in step (e) at elevated temperature; (g) charging 5 to 12 % by weight of epichlorohydrin with respect to polyallylamine hydrochloride to the suspension of step (f) maintaining elevated temperature till cross linking is complete; (h) cooling the reaction mixture at temperature of 25 to 35° C. and isolating the compound by washing the obtained cake with water and (i) drying the wet cake in a Fluidized Bed Dryer at temperature of about 25° C. to about 90° C. to get Sevelamer hydrochloride with phosphate binding capacity of 4.7 to 6.4 mmol/g.

Detailed offer Description

Sevelamer Hydrochloride is a polymeric amine that binds phosphate and is meant for oral administration. Sevelamer hydrochloride is poly(allylamine hydrochloride) crosslinked with epichlorohydrin in which forty percent of the amines are protonated. It is known chemically as poly (allylamine-co-N,N'-diallyl- 1,3-diamino-2-hydroxypropane) hydrochloride. Sevelamer hydrochloride is hydrophilic, but insoluble in water.

Object Of The Invention

The main object of the present invention is to provide industrial process for preparation of Sevelamer hydrochloride having PA in the range of about 4.7 mmol/g to about 6.4 mmol/g and chloride content in the range of about 3.74 to about 5.60 meq/g.

Another object of the invention is to provide pharmaceutical compositions comprising a therapeutically effective amount of Sevelamer hydrochloride along with suitable pharmaceutically acceptable excipients.

Another object of the invention is to provide a novel process for preparation of Sevelamer hydrochloride compositions comprising high shear non-aqueous granulation.

Another object of the invention is to provide improved and simplified process for preparation of Sevelamer hydrochloride which will eliminate the use of acetonitrile and the risk of gelling also avoid use of IPA for removing water.

Another object of the invention is to provide Sevelamer hydrochloride which will meet the stringent ICH (International Committee of Harmonisation) requirements.

Yet another object of the invention is to provide process which yields Sevelamer hydrochloride having consistency in degree of cross linking and avoids the need of specialized equipments for the manufacture of the said product and thereby reducing the manufacturing cost.

Still another object of the invention is to provide compositions for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on hemodialysis.

Another object of the invention is to provide method for reducing the serum phosphorus in patients with Chronic Kidney Disease (CKD) on hemodialysis comprising administering a therapeutically effective amount of Sevelamer hydrochloride along with suitable pharmaceutically acceptable excipients.

Detailed Description Of The Invention

The present invention describes an industrial process for the preparation of Sevelamer hydrochloride. The present invention further involves improved process for crosslinking polyallylamine hydrochloride dispersed in an organic medium with epichlorohydrin to obtain Sevelamer hydrochloride having phosphate binding capacity of 4.7 to 6.4 mmol/g.

The present invention further describes pharmaceutical compositions comprising a therapeutically effective amount of Sevelamer hydrochloride along with suitable pharmaceutically acceptable excipients. A novel process for preparation of said Sevelamer hydrochloride compositions comprising high shear non-aqueous granulation is also described.

According to one embodiment of the invention process for preparation of Sevelamer hydrochloride according to the invention comprises the steps of;

(a) dissolving polyallylamine hydrochloride in water to obtain an aqueous solution;

(b) partially neutralizing the aqueous solution of polyallylamine hydrochloride with 65 to 70 mole % of alkali with respect to polyallylamine hydrochloride;
(c) charging dispersing agent to hydrocarbon solvent to obtain solution;
(d) mixing partially neutralized aqueous polyallylamine hydrochloride solution with the solution obtained in step (c);
(e) stirring the obtained reaction mixture at speed of about 40 to about 250 revolutions per minute to get fine dispersion of aqueous phase in organic phase;
(f) heating the suspension obtained in step (e) at an elevated temperature;
(g) charging 5 to 12% by weight of epichlorohydrin with respect to polyallylamine hydrochloride to the suspension of step (f) maintaining an elevated temperature till cross linking is complete;
(h) cooling the reaction mixture at temperature of 25 to 35° C. and isolating the compound by washing the obtained cake with water and filtration;
(i) drying the wet cake in a Fluidized Bed Dryer at temperature of about 25 to 90° C. to get Sevelamer hydrochloride with phosphate binding capacity of 4.7 to 6.4 mmol/gm.

Sevelamer hydrochloride prepared by the process described by the present invention is used in formulating Sevelamer hydrochloride compositions.

Phosphate binding polymer Sevelamer is water insoluble but it swells in contact with water. Due to this tendency of swelling, formulating Sevelamer by aqueous granulation becomes difficult. Although attempts have been made to formulate Sevelamer by wet granulation method, none of the prior art discloses a successful process for high shear non-aqueous granulation being carried out in an equipment such as a high shear rapid mixer granulator or a planetary mixer.

Inventors of the present invention attempted granulation of Sevelamer hydrochloride using spray granulation technique. However, the results were not satisfactory since the binding solution containing ethylcellulose dissolved in isopropyl alcohol was very viscous and posed problem for uniform spraying of the granulating fluid on to the active ingredient and also the dry mass becomes tacky and forms sticky lumps.

Attempts were also made for preparation of Sevelamer hydrochloride compositions by hot melt granulation and hot melt extrusion techniques but the results were not satisfactory as very high quantity of binder was required and granules produced were lacking adequate flow properties.

Although the prior art states that tableting of a phosphate binding polymer such as Sevelamer hydrochloride is impossible by wet granulation, the inventors of the present invention have successfully developed a novel process for granulation of Sevelamer hydrochloride by high shear non-aqueous granulation.

According to the present invention, the process for preparation of Sevelamer hydrochloride compositions comprising high shear non-aqueous granulation comprises the steps of:

(a) preparing a mixture of Sevelamer hydrochloride and one or more diluents;
(b) optionally wetting the prepared mixture;
(c) preparing a non-aqueous binder solution by dissolving binder in an organic solvent;
(d) granulating the mixture of step (a) or step (b) with non-aqueous binder solution by high shear non-aqueous granulation to form granulated mass;
(e) drying the granulated mass;
(f) milling the dried mass using ball mill or fluid energy mill to form granules of suitable size;
(g) lubricating the milled granules;
(h) compressing the lubricated granules into tablets or filling the lubricated granules into capsules;
(i) coating the compressed tablets.

According to the invention, the particles of **Sevelamer hydrochloride** are round in shape, particularly spherical or oval in shape. Spherical or oval shaped particles of Sevelamer hydrochloride have low bulk density and poor flowability and further resist size reduction. Particles resist deformation and do not rupture or fracture. Due to these characteristics of Sevelamer hydrochloride, formulating Sevelamer hydrochloride by direct compression method becomes extremely difficult. In the practice of the present invention, although the spherical morphology and hydrophilic nature of active ingredient Sevelamer hydrochloride presents a special challenge to the formulator, the inventors of the present invention have successfully prepared Sevelamer hydrochloride compositions by high shear non-aqueous granulation and by using rapid mixer granulator or planetary mixer.

Sevelamer hydrochloride is not a free flowing powder and is bulky. Wetting with purified water helps in decreasing the interparticulate distance and increasing the contact area between the particles; thus making Sevelamer Hydrochloride more amenable for the non-aqueous granulation. Wetting is carried out either in a rapid mixer granulator or a planetary mixer. In the practice of the present invention, wetting of mixture of active and diluent is carried out using about 2% to 9% by weight of purified water. Alternatively, the mixture of active and diluent may be made wet using a solution of polyethylene glycol dissolved in purified water. In an alternate method, polyethylene glycol 6000 may be added into the dry mix as a fine powder during the mixing step. Polyethylene glycols of various grades may be used such as polyethylene glycol 6000 or the like.

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