Abstract:
This invention relates to a process for the preparation and purification of a pure crystalline Hydrochlorothiazide with overall purity 99.9% or greater and single impurity below 0.1%. This is a two step process. In first step crude hydrochlorothiazide is prepared which is in second step purified to get highly pure crystalline hydrochlorothiazide.
A NOVEL PROCESS FOR PREPARATION OF HIGHLY PURE CRYSTALLINE HYDROCHLOROTHIAZIDE

FIELD OF THE INVENTION:

The present invention relates to a novel process for the preparation of highly pure crystalline Hydrochlorothiazide, a common diuretic used for the treatment of hypertension.

BACKGROUND OF THE INVENTION:

Hydrochlorothiazide, 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, having formula I, is a diuretic drug belongs to the thiazide class of compounds and is used in the treatment of hypertension. Among the different diuretic agents used in the treatment of hypertension, thiazide class of diuretic drugs is perhaps the most commonly administered diuretic substance. It acts by inhibiting the kidney's ability to retain water, and also acts on the kidney to reduce sodium (Na) reabsorption in the distal convoluted tubule. This reduces the osmotic pressure in the kidney, causing less water to be reabsorbed by the collecting ducts. Hydrochlorothiazide is used in combination with most of the antihypertensive drugs like losartan potassium, telmisartan, eprosartan mesylate, fosinopril sodium, benazepril hydrochloride, bisoprolol fumarate, captopril, lisinopril etc.
PRIORART:-

A number of methods for the synthesis of Hydrochlorothiazide have been reported but all of these methods generally suffer from the problem of low purity.

Ciba patent, US 3163645 describes a process of preparation of Hydrochlorothiazide by heating a mixture of 5-chloro-2,4-disulfamyl-aniline in anhydrous diethyleneglycol dimethylether, hydrogen chloride dissolved in ethyl acetate and paraformaldehyde. The product is recrystallized from water. It is silent about the yield and purity of Hydrochlorothiazide.

Werner et al. in J. Am. Chem. Soc. 82, 1161 (1960) has reported a process for preparation of Hydrochlorothiazide using 4-amino-6-chloro-m-benzenedisulfonamide, paraformaldehyde, hydrogen chloride dissolved in ethyl acetate and dimethyl carbitol to achieve a theoretical yield of 74%. However they are also silent about the purity.

Jones et al. in US 3025292 has disclosed a process for preparation of Hydrochlorothiazide by reducing 6-chloro-7-sulfamyl-1,2,4-benzothiadizene-1,1-dioxide in presence of 5% ruthenium with 83% yield but they are also silent about the purity.
US 3164588 disclose a method for the preparation of Hydrochlorothiazide by reducing chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide) in presence of ethanol and sodium hydroxide, formaldehyde, hydrochloric acid and ammonia. Although it is mentioned that obtained product is white crystalline solid but there is no mention about the purity. The yield reported is 62.3 - 79%.

US 3,043,840 report a process for purification of crude Hydrochlorothiazide by ammonia or water-soluble primary or secondary amine and crystallizing the product from basic aqueous medium. The purity achieved by this process is 97-98%.

A recent Chinese patent 1421441A, which discloses a process for purification of Hydrochlorothiazide, describes achieving of 99% purity by crystallizing the crude Hydrochlorothiazide in a solvent system, which contains alkali & organic solvent. According to this process the total impurity is less than 1% and single impurity is less than 0.5%. Even this purity is not acceptable according to ICH and USFDA guidelines.

All the above processes result in the formation of two known impurities 4-amino-6-chloro-1,3-benzenesulfonamide and chlorothiazide, as well as a unknown recurring impurity, which is generally 2:1 hydrochlorothiazide-formaldehyde adduct of parent drug substance.

The impurities of Hydrochlorothiazide have been a major concern of the researchers, since the effect of impurities on human body haven't been studied deeply, the toxicity is also unknown, so far. Hence it is very important to control quality, improve purity
and reduce the impurity below the threshold of ICH guidelines. A lot of efforts have been made to bring down the total impurity below 0.15% and single impurity below 0.1% but none can achieve this limit.

According to our study as well as a study reported in Chinese patent 1421441A, it is not easy to recrystallise crude Hydrochlorothiazide to ensure a purity of 99.9% by available methods and by using normal solvents like alcohol, acetone, ethyl acetate, petroleum ether, etc. The operation of column chromatography is not easy and cost effective, hence, it is not suitable for industrial production.

Thus there is a need to have an economical and industrial viable process for the synthesis of Hydrochlorothiazide having purity of 99.9% and single impurity level less than 0.1%.

Surprisingly, we found a novel process for preparation and purification of hydrochlorothiazide having purity of 99.9% or greater as confirmed by high pressure liquid chromatography (HPLC) and overall yield of 86%.

SUMMARY OF THE INVENTION:-

The present invention provides a novel process for the preparation and purification of highly pure Hydrochlorothiazide, which is economical and easy to carry out at industrial scale.
Another embodiment of this invention is to provide a process for the preparation and purification of diuretic drug Hydrochlorothiazide that is of high purity of the order of 99.9% and single impurity less than 0.1% in good yield.

**DETAIL DESCRIPTION OF THE INVENTION:**

The present invention provides a process for the preparation of diuretic drug Hydrochlorothiazide 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, having formula I.

It is a two steps process, in the first step crude Hydrochlorothiazide is prepared and in the second step the crude hydrochlorothiazide is purified to get a highly pure hydrochlorothiazide having purity of 99.9% or greater as confirmed by high pressure liquid chromatography (HPLC), in 86% overall yield.

![Formula I](attachment://formula.png)

Hydrochlorothiazide is prepared by heating 4-Amino-6-chloro-1,3-benzenedisulfonamide and paraformaldehyde in alcohol to reflux and adding a solution of inorganic acid in alcohol to the refluxing reaction mass.

The inorganic acid may be either sulphuric acid or hydrochloric acid, preferably sulphuric acid.
The alcohol may be selected from the group comprising of methanol, ethanol and isopropyl alcohol, preferably methanol.

After refluxing for about one hour, additional paraformaldehyde is added. After further reflux for about one hour, one more lot of paraformaldehyde is added. The combined reaction mass is refluxed for 4 hours to 10 hours, preferably for 6 hours. The reaction mass is cooled, stirred for one more hour and filtered. The obtained mass is optionally washed successively with alcohol and water to get off white to white crude wet product.

The alcohol used for washing may be selected from the group comprising of methanol, ethanol and isopropanol preferably methanol.

This crude Hydrochlorothiazide is purified by dissolving it in aqueous acetone or acetone and heating it to reflux.

Activated carbon is added and refluxed for 20 minutes and carbon is filtered through hyflow bed and washed with acetone. The pH of the filtrate is adjusted to below 3.0 by adding aqueous inorganic acid and is heated to reflux. The inorganic acid may be either sulphuric acid or hydrochloric acid preferably 20% aqueous sulphuric acid. Water is added to this refluxing reaction mass and the solvent is distilled off till the reaction mass temperature reaches 101-102° C. After that it is refluxed for 2 more hours and the temperature of the reaction mass is maintained in the range of 25 to 85° C, preferably 45 to 60° C. The solid is filtered and the filtered solids are washed...
twice with water. The product is dried to get pure white crystalline compound with HPLC purity more than 99.9% and individual impurity less than 0.1%.

The starting material, 4-Amino-6-chloro-1,3-benzenedisulfonamide, used in this process is known. It is easily commercially available and also it can be prepared by Novello process as given in example 1 of US 2,809,194.

The invention can be better illustrated by the following non-limiting examples.

**Preparation of Hydrochlorothiazide:**

**Example 1**

A suspension of 1000 g (3.5 mol) of 4-Amino-6-chloro-1,3-benzenedisulfonamide and 78.9 g (2.63 mol) paraformaldehyde in 1264 ml of methanol was heated to reflux and a solution of 55.56 ml of concentrated sulphuric acid in 180.54 ml of methanol was added to the refluxing reaction mixture. After refluxing for one hour additional 23.34 g (0.78 mol) paraformaldehyde was added. The reaction mass was further refluxed for one hour and one more lot of 13.88 g (0.46 mol) paraformaldehyde was added. The combined reaction mixture was refluxed for six hours followed by cooling to 20-30°C. It was further stirred at this temperature for one hour and filtered; the solid mass was washed successively with methanol and water to get 980 g off white crude wet product.
Example 2

A suspension of 20 g (0.07 mol) of 4-Amino-6-chloro-1,3-benzenedisulfonamide and 1.57 g (0.052 mol) paraformaldehyde in 28.8 ml of ethanolic hydrochloric acid was heated to reflux. After refluxing for one hour additional 0.46 g (0.015 mol) paraformaldehyde was added. The reaction mass was further refluxed for one hour and one more lot of 0.27 g (0.009 mol) paraformaldehyde was added. The combined reaction mixture was refluxed for six hours followed by cooling to 20-30°C. It was further stirred at this temperature for one hour and filtered; the solid mass was washed successively with 10 ml ethanol and water to get 21.33 g off white crude wet product.

Example 3

A suspension of 20 g (0.07 mol) of 4-Amino-6-chloro-1,3-benzenedisulfonamide and 1.57 g (0.052 mol) paraformaldehyde in 28.8 ml of methanolic hydrochloric acid was heated to reflux. After refluxing for one hour additional 0.46 g (0.015 mol) paraformaldehyde was added. The reaction mass was further refluxed for one hour and one more lot of 0.27 g (0.009 mol) paraformaldehyde was added. The combined reaction mixture was refluxed for six hours followed by cooling to 20-30°C. It was further stirred at this temperature for one hour and filtered. The solid mass was washed successively with 10 ml methanol and water to get 22.35 g off white crude wet product.

Purification of crude Hydrochlorothiazide:

980 g of crude and wet hydrochlorothiazide was dissolved in a mixture of 2700 ml of acetone and 1350 ml of purified water by heating to reflux. 19.8 g activated carbon
was added, reflux for 20 minutes and the activated carbon was filtered through hyflow bed and the bed washed with 100 ml of acetone. The pH of filtrate thus obtained was adjusted to 1.0-2.0 by adding 20% aqueous sulphuric acid and the filtrate was heated to reflux. To this reaction mass was added 3600 ml of purified water. Portion of the solvent of this mixture was distilled off till the reaction mass temperature reaches 101-102°C and then reflux for 2 hours followed by cooling to 40-45°C. The solid mass was filtered, washed with purified water (2X 1000 ml) and dried in air drier at 105°C for 10 hours to get 896 g (86 % iii two step) of pure white shining crystalline compound with HPLC purity more than 99.9 %, individual impurity less than 0.1%.
We claim:

1. A process for preparation of hydrochlorothiazide comprising:
   a. treating of 4-amino-6-chloro-1,3-benzenedisulfonamide with paraformaldehyde which was added in portion and alcoholic inorganic acid to give crude hydrochlorothiazide; and
   b. purification of the crude hydrochlorothiazide with acetone and water

2. A process according to claim 1 where the treatment in step (a) comprises:
   a. heating 4-amino-6-chloro-1,3-benzenedisulfonamide and paraformaldehyde in alcohol;
   b. adding alcoholic inorganic acid to above reaction mixture;
   c. periodic addition of paraformaldehyde to above reaction mass;
   d. heating the mixture for 4 to 10 hours preferably for 6 hours; and
   e. isolation of crude product from hot or cooled reaction mass by filtering and washing using alcohol or without washing.

3. A process according to claim 1 where purification in step (b) comprises:
   a. dissolving crude hydrochlorothiazide in acetone or aqueous acetone followed by optional treatment with activated carbon;
   b. acidifying the reaction mass with inorganic acid;
   c. addition of water, partial distillation off solvent; and
   d. filtration of the solid from the hot reaction mass.

4. A process according to claim 1, 2 or 3, wherein the inorganic acid is either sulphuric acid or hydrochloric acid preferably sulphuric acid.

5. A process according to claim 1 or 2, wherein the alcohol used is methanol, ethanol or isopropyl alcohol preferably methanol.
6. A process according to claim 2, where heating in step (a) & (d) is done to reflux.

7. A process according to claim 3, where acidification of the reaction mass in step (b) is done to pH below 3.

8. A process according to claim 3, where in step (d) during filtration the temperature of reaction mass is above 35°C preferably in the range of 45-60°C.