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Original scientific paper

Analysis of Contents of Calcium, Magnesium and Total Hardness in Water for Pharmaceutical Use

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Abstract: Water is one of the most frequently used raw materials in pharmaceutical industry. Water for pharmaceutical purposes includes the two primary water types: purified water and water for injection. Drinking water used for obtaining purified water is not official in pharmacopoeia. Depending on quality prescribed for a certain product preparation, various water types and procedures have been used to prepare pharmaceutical industry water. Possible ways to obtain water for pharmaceutical purposes are: reverse osmosis, demineralization, electrodeionization, ultrafiltration, distillation. Reasons for the widespread use of water lie in the facts that it is capable of dissolving a great number of therapeutic substances, compatible with a large number of substances, appropriate to be used from a physiological aspect given that it is an integral part of the cell and the major component of body fluids and whenever the drug is administered in the form of an aqueous solution, reabsorption is rapid and complete, it also has suitable physical-chemical properties. In this study, analysis results of 15 samples of water were obtained using pharmacopoeial methods for pharmaceutical purposes. Results showed that 86.6% of water samples were accurate and 13.3% did not have appropriate calcium content, magnesium content and total hardness values.

Keywords: water, pharmaceutical purposes, calcium, magnesium, total hardness

INTRODUCTION

Water is one of the most used raw material in pharmaceutical industry. It is used for:

1. making of preparation for solutions, suspensions, extracts
2. making of parenteral preparations
3. making of preparations for ears and nose.

Water is used as excipient or solvent at synthesis of medical substances, for reconstruction of some preparations such as antibiotic syrups, for washing and cleaning of dishes, bottles, production devices and areas, for process of sterilization (sterilization with saturated water steam), it is also used in analytics of medical substances and pharmaceutical preparations (1,2,3). The reasons for this wide usage of water come from the fact that it is capable to dissolve a huge number of medical substances, it is compatible with numerous substances and it is good for use in physiological aspect, considering the fact it is the constituent part of the cell and the main igredient of body fluids, and in all the cases, when a medicine is applied as a water solvent, resorption is quicker and more complete. Water also has a convenient physical-chemical characteristics: high value of dielectric constant, low steam pressure, high boiling point and good conductivity.

Aqua purificata is prepared by distillation, by ion excange, by reverse osmosis or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by the competent authority.

Aqua purificata is stored and distributed in conditions designed to prevent growth of micro-organisms ant to avoid any other contamination.

Aqua purificata that has been filled and stored in conditions designed to assure the required microbiological quality. It is free from any added substances (4).

The hardness of water is divided on:

1. Carbonate hardness, comes from Ca and Mg ions in form of bicarbonates and,
2. Non-carbonate hardness, comes from Ca and Mg ions in form of sulfates, chlorides and nitrates.

In water boiling, bicarbonates become carbonates, which are insoluble, where carbonate hardness disappears and non-carbonate (permanent) hardness remains.

Compounds of calcium and magnesium may be dangerous for human health. This compounds are found in drinking or destilled water which is used for reconstitution of powders for oral suspensions, they may have negative effects on human health (5).

Hard water is making difficult cleaning laboratory glassware, so in industry during the heating water occurs calculus deposition and that kind of water can't be used in cauldron. If quality of surface water isn't appropriate, regarding to concentrate of Calcium and Mg there is potential risk that high level of these ions be present even in cleaned water for drink and also later in water for pharmaceutical use that can cause many of problems with health with people. High concentrations of calcium in purified waters can make difficult the absorption of minerals from the gut such as iron, zinc, magnesium, and phosphorus, while increased intake of magnesium salts can lead to gastrointestinal tract problems (6,7). Also, calcium and magnesium can interact with the components of the pharmaceutical products they are used for, and may reduce their bio-availability. Decreasing of bio-availability leads to a reduction in the therapeutic effect of these products. Pharmacopoeia regulations therefore limit tests for calcium and magnesium content.

Water hardness also affects kidney function. According to some studies, almost 3/4 of the kidney stones are due to increased intake of calcium salts (6,7).

Literature review showed that there are no published scientific papers on testing the quality of distilled water used in pharmacies for the reconstitution of powders for oral suspensions. We found published papers describing the significance the significance of different water purification systems in the pharmaceutical industry for quality of purified water. Also, papers that describe the proper production and storage of distilled water in order to ensure the prescribed microbiological quality have been found (8- 12).

AIM

Determine the quality of water for pharmaceutical use by estimating physical-chemical parameters which are the contents of calcium and magnesium and the total hardness.

MATERIALS AND METHODS

15 waters for pharmaceutical use in total were analysed (Aqua purificata). Samples were collected from pharmacies that produce water in their laboratories. Methods and parameters were determined according to regulations of pharmacopoeia (Ph Jug V, European pharmacopoeia 8. edition) and the results were expressed with "matches" and "does not match".

Samples are taken from 15 different labs, open pharmacies and hospital pharmacies. Procedures that are used in production of some samples are shown in table 1.

Table 1: Procedures that are used in production of some samples

Number sample	Procedures that are used in production
1	ion excange
2	distillation
3	distillation
4	ion excange
5	distillation

6	distillation
7	distillation
8	reverse osmosis
9	reverse osmosis
10	reverse osmosis
11	ion excange
12	reverse osmosis
13	reverse osmosis
14	distillation

The water quality test was performed by the procedures and methods prescribed in the European pharmacopoeia 8. Edition. 2 (4).

Limit test for calcium and magnesium is standard procedure in Pharmacopoeia and it's performed as follows: To 100ml add 2ml of ammonium chloride buffer solution pH 10, 50mg of mordant black 11 triturate R and 0,5ml of 0,01M sodium edetate. A pure blue colour is produced. Buffer solution pH 10, mordant black 11 and sodium edetate were pro analisy quality (p.a.) . Appearance of blue color is sign that vales are satisfying.

At the same time, both the hardness was determined by the method BAS ISO 6059:2000 (13) and the calcium by the method BAS ISO 6058:2000 (14). Examining the hardness of water and calcium is done directly without previous sample preparation with EDTA titrimetric method. Describes a titrimetric method using ethylenediaminetetraacetic acid (EDTA) for the determination of the sum of calcium and magnesium concentrations in ground waters, surface waters and drinking waters. All reagents (ammonium chloride, eriochrom black T and EDTA) were p.a. quality.

RESULTS

Results of the analysis that were made in the examined samples are presented in two following tables. Pharmacopoeias method can't give us numerical limits values, limit test for calcium and magnesium is preformed according method monographs. Appearance of blue color is sign that vales are satisfying.

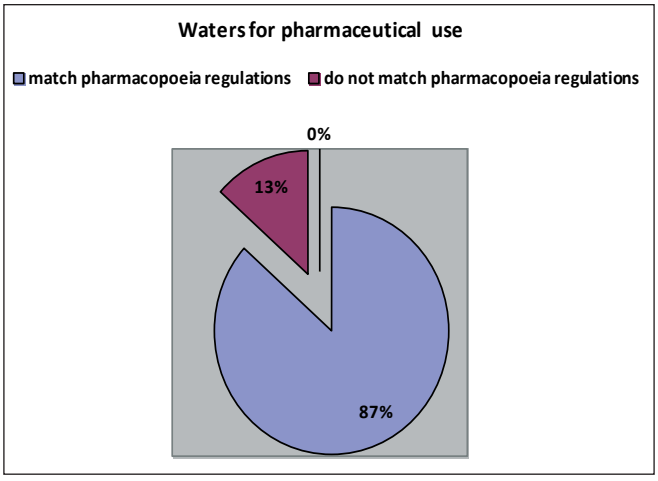
Table 2: Content of calcium and magnesium in samples, determined by pharmacopoeia regulations

Sample No	Calcium	Magnesium
1	x	x
2	✓	✓
3	✓	✓
4	✓	✓
5	✓	✓
6	✓	✓
7	✓	✓
8	✓	✓
9	✓	✓
10	✓	✓
11	x	x
12	✓	✓
13	✓	✓
14	✓	✓
15	✓	✓

legend: x – the examined sample does not match pharmacopoeia regulations
✓ the examined sample does not match pharmacopoeia regulations

Table 3: Content of calcium and total hardness in sapmles, determined by standard methods, BAS ISO 6058:2000 i BAS ISO 6059:2000

Sample No	Calcium (mg/L)	Total hardness°D
1	<2,0	2,5
2	<2,0	<0,4
3	<2,0	0,5
4	<2,0	<0,4
5	<2,0	<0,4
6	<2,0	<0,4
7	<2,0	<0,4
8	<2,0	<0,4
9	<2,0	<0,4
10	<2,0	<0,4
11	<2,0	2,7
12	<2,0	<0,4
13	<2,0	<0,4
14	<2,0	<0,4
15	<2,0	<0,4



Picture 1. Display of ratio of waters for pharmaceutical use for those waters that match and those that do not match pharmacopoeia regulations, in case of calcium and magnesium

DISCUSSION

Water for pharmaceutical use has to meet very high standards of quality that are issued by pharmacopoeia. Drinking water, by its standards does not match those demands because it contains both, organic and non-organic substances and microorganisms that contaminate it and therefore, they can destroy the products and the production tools. From the aspect of water quality that is used in pharmaceutical industry around the world, there are numerous and various demands. In more than 130 countries, American pharmacopoeia is being used, and European pharmacopoeia has some fundamental distinctions from American. There is also a great deal of other standards, such as pharmacopoeia of Japan, India, China etc. Yugoslavian pharmacopoeia from 2000. (Ph Jug V), issued by Federal Institution of health care and advancement is an adjusted translation of European pharmacopoeia from 1997.

Analysis of results established that results are not appropriate for samples that we got by method of ions changes. We can suppose that machines that we used for preparing cleaned water are not ordinarily serviced and that eventually ion excange are saturated

Water is one of the most used raw material in pharmaceutical industry and it is used for making of many preparations; for washing and cleaning of dishes, bottles, production devices and areas, for process of sterilization in analysis of medical substances and pharmaceutical preparations. It is also very important that all physical-chemical parameters are correspondent to pharmacopoeia regulations, which is the way to ensure safety and quality of preparations for which that water is being used. The reasons for this wide usage of water come from the fact that it is capable to dissolve a huge number of medical substances, it is compatible with numerous substances and it is good for use in physiological acspect, considering the fact it is the constituent part of the cell and the main igredient of body fluids, and it all the cases, when a medicine is applied as water solvent, resorption is quicker and more complete.

Aqua purificata used to reconstitute oral suspensions should be of high quality with minimal content of metals. Heavy metals (mostly mercury, aluminum, cadmium, lead, etc.) in human organism take places of trace elements (magnesium, calcium, etc.) found in vital enzymes and amino acids that participate in decisive metabolic processes. Excessive exposure to metals could cause various chronic diseases, systemic exhaustion, damage of nervous and endocrine system, as well as digestive tract (15-16).

CONCLUSION

In this work, results of 15 samples of water for pharmaceutical usage were obtained by pharmacopoeian methods. The results showed that je 86,6% of water samples was good, and 13,3% did not have the appropriate content of calcium and total water hardness value. That has been confirmed by comparation with the results of standard BAS ISO methods. Because of high importance of this kind of water, we highlight the importance of regular control of this water, so possible interactions could be stopped, and to prevent possible instability of preparations that are made by using purified water.

Further study that would include greater number of samples should be conducted to confirm these results.

Pharmacies rarely control the quality of the aqua purificata water internally. The results indicate the need for enhanced internal control, by introducing procedures to define what is the timeframe for repeated control. and laws should provide for external controls, which would be defined by legislation and which do not exist today.

It is also recommended that appliances used to obtain purified water be regularly serviced and that records be kept.

It is recommended to make regular changes to the resins, to keep a record of them, and to carry out an internal quality control of the water obtained once a week, e.g. and, where appropriate, external control in an accredited laboratory.

Purified water is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

In order to ensure the appropriate quality to the water, validate procedures and in-process monitoring of the calcium and magnesium, and other parameters.

The goal is to use only purified water that meets the neccessary demands issued by regulation standards, mainly pharmacopoeian standards. We emphasize that inevitable and continuous control of water for pharmaceutical use is made by relevant institutions.

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