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Tablets for internal use solutions replenishing ion deficiency caused by dehydration

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Summary:

Introduction: The provision of proper water and electrolyte metabolism for soldiers of Polish Armed Forces serving on foreign missions in tropical and subtropical climate countries is
a serious challenge for the widely understood nutritional, dietary and medical care. The problem of water and electrolyte deficiency may pose a serious threat to soldiers' health and lives, particularly in face of high physical activity in unfavorable climates. This fact served as an impulse for research and development work aimed at development of technology and production of soluble tablets which in field conditions, after dissolving in water, would form a drink with precisely defined electrolyte content and osmotic pressure, thus preventing the system from excessive hypovolemia and hypoionia. The obtained soluble tablets were subjected to quality control tests according to the pharmacopoeial standard.
Material and Methods: The formula was developed and uncoated tablets designed to dissolve were prepared. The tablets were subjected to quality control tests in the current pharmacopoeial standard.
Results: Two basic formulation compositions of soluble tablets were developed, two different disintegrating compounds: Vivastar type P and Vivasol were used. While maintaining the uniformity of the tablet mass, the material was characterized by a high coefficient of hygroscopy. The measured disintegration time (dissolution) of the tested tablets ranges from 4'31" to 6'14" minutes. The dissolution rate is much more affected by the tablet mass than the percentage share of the disintegrating substance proportional to the tablet mass.
Conclusions: Direct tableting technology of crystalloids after some modifications may form the basis of the manufacturing process of supplement tablets. The disintegration time (dissolution) of the tested tablets induces to undertake research on the development of effervescent supplement tablets.

Key words: soluble tablets, electrolytes, osmotic pressure, dehydration, hypovolemia, hypoionia.

1. Background

The problem of dehydration is a common problem related to human activity. Pathological dehydration may be caused by disease-related factors and occur as a result of diarrhea, vomiting or blood loss. However, dehydration occurs more commonly as a result of increased human activity, particularly during prolonged physical effort. This process may be intensified by climatic conditions (heat and low humidity). In such cases, loss of water is caused by excessive perspiration, which is the body's defense

against excessive heat. During intense physical effort, the amount of water lost with perspiration may reach up to 1.2 liters per hour [1].

The loss of water upon perspiration is always accompanied by a loss of electrolytes. A drop in the electrolyte levels is associated with their secretion with sweat, and the loss is directly proportional to the content of these electrolytes in sweat. The electrolyte content of sweat may be significantly different depending on factors that accompany perspiration. Thus, electrolyte supplementation is required during intense physical effort. The goal of this supplementation is to prevent complications due to stroke conditions. Of highest importance is probably replenishment of sodium and potassium, as well as chloride ions. Ion supplementation is required particularly upon long physical effort [2]. Sodium ions are excreted with sweat in largest amounts, and therefore should be supplemented first [3,4]. The average concentration of sodium ions in sweat is between 20 and 140 mEq/L [4-6]. In addition, secretion of sodium and chloride ions with sweat is higher during physical exercise compared to perspiration that is due only to heat [5].

One should note that supplementation of fluid deficiency caused by excessive perspiration with plain, electrolyte-free water may cause hypoionia, which seems to be particularly dangerous in relation to potassium ions and their effect on cardiac function. When determining the electrolyte composition of supplementation fluid one should remember that the quantity of potassium levels in sweat may be falsified by potassium ions being flushed off the skin [7]. Physical effort in hot conditions leads to the loss of higher amounts of water compared to electrolytes. This results in the increase in osmolarity and hypernatremia. Thus, electrolyte deficiencies should be supplemented using isotonic or slightly hypotonic fluids [8]. When determining the composition of the electrolyte deficiency supplementation fluid, one should also remember that addition of carbohydrates in the amount of ca. 5.5% is important due to their effect on the absorption of the fluid and reduction of the consequences of physical effort [9].

2. The goal of the study

As part of this study, an attempt was made to formulate a tablet for preparation of isotonic solutions in field conditions, which would provide the required supplementation of electrolytes lost upon excessive perspiration. The composition of the proposed tablets was established in an alternative manner based on average sweat composition determined from the literature and on the composition of a multielectrolyte isotonic fluid used for parenteral treatment of hypovolemia.

3. Reagents and equipment

List of reagents:

- double distilled water
- magnesium chloride · $6H_2O$ (POCh-Gliwice),
- potassium chloride (Lach-Ner-Czech Republic)
- calcium chloride anhydrous (POCh-Gliwice)
- sodium chloride (POCh-Gliwice)
- trisodium citrate · $2H_2O$ (Lach-Ner-Czech Republic)
- D-glucose (Lach-Ner-Czech Republic)
- sodium acetate anhydrous (POCh-Gliwice)
- zinc sulfate (POCh-Gliwice)
- iron chloride · $6H_2O$ (POCh-Gliwice)
- sodium dihydrogen sulfate (POCh-Gliwice)
- potassium iodide (POCh-Gliwice)
- sodium carbonate anhydrous (POCh-Gliwice)
- citric acid (POCh-Gliwice)
- sodium bicarbonate (POCh-Gliwice)
- disodium hydrogen phosphate · $2H_2O$ (POCh-Gliwice)

List of equipment:

- disintegration time meter – Erweka ZT 222;
- technical laboratory balance – Radwag;
- analytical laboratory balance – Radwag;
- pH-meter N-5170E with glass electrode ERH-131 – hydrometer.
- high-speed mixer – Erweka
- universal dryer – SUP-4, Sp. Met. Warsaw
- Oscillating tablet press – EK0 Erweka Korsch
- hardness meter – Erweka TBH 225D
- friabilator – F2, Erweka
- electronic caliper – Mitutoyo-Japan

4. Methodology of the experiments

The methodology of the study included the following elements:

1) establishing a formula and preparation of soluble tablets,
2) performing the following quality control tests according to the current Polish Pharmacopoeia VIIIth edition standard:
   - determination of tablet disintegration

(dissolution) time,
– hardness assessment
– abrasion resistance assessment,
– dosage accuracy assessment;

3) measurement of pH and conductivity of the solution formed after tablet dissolution,
4) statistical analysis of the obtained results.

5. Results and discussion

5.1. Establishing the formula and the technology of soluble tablet preparation

Two basic compositions of soluble tablets were developed, with two different disintegrating agents used so as to obtain variant disintegration/dissolution times: Vivastar type P (starch glycolate sodium salt) and Vivasol (croscarmellose sodium), thus forming four test series designated as Tablesol I and II and Tablestar I and II. The following tables present formulation compositions of the tested tablets and the proposed electrolyte composition of the fluid after dissolution of a tablet of particular series.

The biologically active substance provided for in the formula composition were homogenized on 0.5 mm sieve and mixed in a high-speed mixer. Disintegrants were added and the blend was mixed again. Tablets were pressed out of the tablet mass using an Erweka EK0 impact tablet press, aiming at obtaining the average mass as declared in the technological manual. Morphological parameters of tablets are listed in Table 5, while average tablet mass values are listed in Table 6.
The pressed material was characterized by high hygroscopicity, leading to problems with punch sticking during the tablet pressing process. However, the tablet mass was uniform, which translated into statistical distribution of tablet masses in the tested series. Slight statistical deviations from the average tablet mass are confirmed by the standard deviation and variability coefficient values. For proper industrial production of these tablets, production conditions typical for production of effervescent tablets would be appropriate.

5.2. Determination of tablet disintegration (dissolution) time

Determination of the disintegration time of pharmaceutical formulations is very important for the assessment of the quality of the obtained formulation. In cases of wrong formulations, e.g. misuse of excipients, the drug formulation would not undergo disintegration, thus preventing the active substance from being released. Measurement of disintegration time may serve as basis for conclusions regarding the way other quality control studies should be performed.

The disintegration (dissolution time) is the time, after which a tablet immersed in appropriate liquid undergoes disintegration or dissolution with no tablet particles remaining on a 2.0-mm mesh, except for the fragments of insoluble tablet shell. It is acceptable that soft mass containing no hard, not-moistened core is left on the mesh.

The tablets are placed in tubes, weighed down with rings (depending on tablet formulation) and immersed in a beaker containing appropriate liquid. The experiment time depends on the type of tablet. In line with pharmacopoeial requirements, tablets for solutions should be dissolved within not more than 3 minutes. For comparison, effervescing tablets must be dissolved within not more than 5 minutes (disintegration with gas production). pH and conductivity of the solution obtained after dissolution of a model tablet in water was measured. The results are listed in Tables 7-8 and summarized by statistical analysis.

The measured disintegration (dissolution) time of the studied tablet series was in the range of 4.31 to 6.14 minutes. A clear impact of disintegrant on the time of complete transfer of tablet contents into the solution may be observed. The mass of the tablet has a larger impact on the dissolution rate than the percentage content of disintegrant in proportion to the tablet mass.

Tablets of average masses of 2.7-2.8 g dissolve faster than tablets of masses of 4.0-4.2 g. The disintegration time of the obtained tablets as compared to the FP VIII standard encourages taking up studies on switching the production technology from soluble tablets to effervescent tablets or modifying the mass ratio of the disintegrant that facilitates dissolution.

Assessment of the mechanical strength of the tablets

One of the conditions required so that the tablets do not become damaged, crushed or powdered

during transport, storage and application is to maintain appropriate mechanical strength. In practice, quality control is achieved by the measurement of tablet hardness and resistance to abrasion. Pharmacopoeial abrasion measurement involves the assessment of percentage loss of tablet mass after the test compared to mass prior to the test. This loss should not exceed 1%. The tested tablets, despite good average hardness, were characterized by mass loss of 2.37 to 6.67%. This is due to the nearly 100% content of crystalloids in the tablet mass.

Conclusions

1) Tablets for preparation of isotonic solutions to supplement electrolytes lost in field conditions due to excessive perspiration are an example of innovative approach to the problem of hypovolemia.

2) The composition of the proposed tablets was established in an alternative manner based on average sweat composition determined from the literature and on the composition of a multielectrolyte isotonic fluid used for parenteral treatment of hypovolemia.

3) The technology of direct tableting of crystalloids may become, after some modifications, a basis for the supplementation tablet production process.

4) Disintegration (dissolution) time of the studied tablets encourages us to initiate studies to develop effervescent supplementation tablets.

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