

Pharmaceutical Development of Nitrosourea Compound for the Treatment of Neuroendocrine Tumours

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ABSTRACT

Background: Nitrosoureas are chemotherapeutic alkylating agents, widely used in the treatment of malignant diseases. One of them (streptozotocin) is the standard for the therapy of neuroendocrine tumours. We synthesised a nitrosourea compound, aranoza, which has been effective in preclinical studies on experimental tumour models. **Objectives:** The current research deals with the development of the pharmaceutical dosage form of aranoza and the evaluation of the quality of the finished product. **Methods:** Sterilizing filtration followed by freeze drying was used to prepare the finished product. The acidity of the solutions was determined potentiometrically. Aranoza content in solution and lyophilisate was determined by spectrophotometry method. **Results:** We suggested the composition of the drug for parenteral use. The created product includes polyvinylpyrrolidone and sorbic acid for solution stabilization and regulation of acidity, respectively. We also selected the method for aranozasolution preparation and showed that filters of mixed cellulose esters have optimal characteristics for filtration sterilisation. We chose lyophilisation to obtain a stable product: the freezing temperature was determined as -40°C to -45°C and the duration of freezing as 3–4 hr. The finished product has characteristics corresponding

to requirements of the European Pharmacopoeia and State Pharmacopoeia of the Russian Federation and maintained its quality for the time of observation of 36 months. **Conclusion:** We created the algorithm for the development of a lyophilised antitumor drug, which allowed to obtain an appropriate pharmaceutical dosage form of a nitrosourea compound, aranoza, purposed for the treatment of neuroendocrine tumours.

Key words: Aranoza, Freeze drying, Kollidon 17PF, Sorbic acid, Quality control, Sterilising filtration.

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INTRUDUCTION

Neuroendocrine tumours (NET) are rare human tumours arising from the cells of the diffuse neuroendocrine system. NET may develop in various organs and tissues of the human body, including the gastrointestinal tract, lungs and pituitary gland.¹

One of the standard treatments for pancreatic NET is streptozotocin (2-deoxy-2-(3-methyl-3-nitrosourea)-1-D-glucopyranose, Zanosar (Teva Parenteral Medicines Inc., USA).² Extensive medicinal use of streptozotocin is limited by its toxicity, especially by its significant diabetogenic action.³

Aranoza (3-(α -L-arabinopyranosyl-1)-1-methylnitrosourea) is the original antitumour drug, created by the N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation (Figure 1).

Aranoza, a derivative of methylnitrosourea, is similar to streptozotocinin structure but differs by the carbohydrate component; the carrier of the cytotoxic group is the monosaccharide L-arabinose. These structural features explain some of aranoza's distinct properties, including its biological activity and stability.⁴

A preclinical study showed the effectiveness of aranoza in monotherapy regimens, as well as in combination chemotherapy regimens, along with the antitumor drugs included in the NET treatment standards.⁵ This suggests the possibility of aranoza efficacy in patients with NET.⁶ Thus, we established the task of developing the optimal pharmaceutical dosage form of aranoza for the treatment of NET.⁷⁻⁹

Aranoza is an exceptionally biologically active and toxic substance, with special requirements for pharmaceutical development and technological processes in the manufacture of the finished pharmaceutical product.^{10,11}

The objective of the present study was to create the aranoza dosage form and to evaluate the pharmaceutical obtained according to requirements of the current editions of European Pharmacopoeia (Ph.Eur.) and the State Pharmacopoeia of the Russian Federation (Ph.Ru.).^{12,13}

MATERIALS AND METHODS

Pharmaceutical substance and excipients

Aranoza was obtained from the N.N. Blokhin National Cancer Research Centre, Russia. Polyvinylpyrrolidone (Kollidon 17PF, BASF, The Chemical Company, Germany) and 99% sorbic acid (Fluka, Germany) met to Ph.Eur. Requirements. All other used chemicals and solvents were of analytical grade.

Sterilizing filtration of aranoza solution

Sterilizing filtration was carried out under vacuum through membrane filters from different materials with a pore diameter of 0.22 μ m (Pall Corporation, USA, LLC Pall Eurasia, Russia) with the use of a glass Millipore filter holder (Millipore, France).

Freeze drying of aranoza solution

Freeze drying was carried out on a freeze-drying apparatus Minifast DO.2. (BOC Edwards, UK). Before that aranoza solution was dosed

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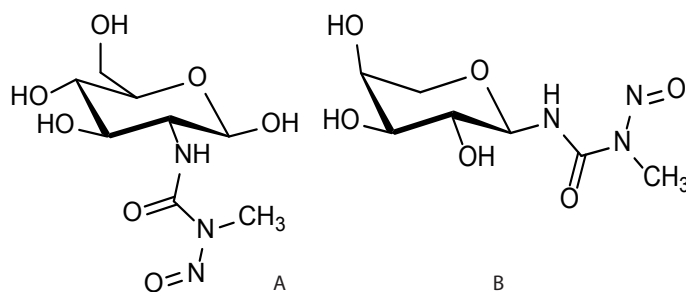


Figure 1: Chemical structure of streptozotocin (A) and aranoza (B).

out 5 ml into the vials of 20 ml, placed on the cold (-40°C - -45°C) shelves of freeze-drying apparatus and lyophilised by different regimens: continuous freezing for 3-5 hr or fractional freezing for 4-6 hr or fractional freezing for 24-46 hr.

Evaluation of eutectic temperature

Eutectic temperature (temperature of complete freezing) was evaluated by the thermal method.¹⁴ With that solution in vials was frozen to temperature -45°C and then warmed to $20\pm 2^{\circ}\text{C}$ and we fixed the temperature at slow thawing of the frozen product.

Determination of the pH of aranoza solutions

The determination of the pH of aranoza solutions and the lyophilisate (upon rehydration) was carried out potentiometrically with a HANNA pH 211 pH-meter (Hanna Instruments, Germany).

Aranoza assay in solution and lyophilisate

The content of aranoza in the solutions and lyophilisate was determined spectrophotometrically at $\lambda=240\pm 2$ nm on a Cary 100 spectrophotometer (Varian, Inc., Australia) by a previously developed and validated technique.¹⁵

RESULTS

The non-clinical studies showed the high efficiency of all methods of aranoza administration—parenteral (intravenous, intraperitoneal, intramuscular, subcutaneous) and oral. But it was established that the parenteral administration of aranoza showed the most significant antitumour activity. The therapeutic effect of aranoza was much lower in the oral administration, probably due to the substance inactivation in the gastrointestinal tract. A pronounced irritant effect limited intramuscular and subcutaneous administration of aranoza; it was manifested by oedema and necrosis at the injection site.¹⁶

Development of the pharmaceutical dosage form composition

Physico-chemical properties of the active pharmaceutical ingredient (API), its photosensitivity, hydrolytic and thermal stability and hygroscopic properties mostly determine the choice of the pharmaceutical dosage form. Aranoza is a white to yellowish powder; it is freely soluble in water, soluble in methyl alcohol, slightly soluble in 95% ethanol and practically insoluble in chloroform. The main physico-chemical properties of aranoza are presented in Table 1.

To create dosage form for parenteral use it is very important to choose the concentration of the API. The solubility of aranoza facilitates a 20% aqueous solution. However, solutions of aranoza in water are volatile in the light and at elevated temperatures and they are also sensitive to changes in solution acidity. The use of excipients is necessary to obtain a stable solution: the polyvinylpyrrolidone (Kollidon 17 PF) was chosen

to stabilize the aranoza solution and as a shaper,¹⁷ and sorbic acid was used as an acidity regulator.¹⁸ Experimental results showed that the use of Kollidon and sorbic acid facilitated a 10% aranoza solution with a pH of 3.0–4.5, which is stable for 6 h - the time required to prepare a sterile aranoza solution (Figure 2).

Selection of filter materials

Since the final thermal sterilization of aranoza is not possible due to the high API thermolability, sterilizing filtration was performed before dosing the solution into vials to obtain a sterile solution. The choice of filter material was justified in a specially constructed study: evaluation of the membranes from various materials was performed using two parameters - filtering rate and aranoza stability during contact with the membranes. To estimate the influence of filtering material on API stability, we determined the dynamics of concentration of aranoza in the solution under filtration.

The data presented in Table 2 demonstrate that neither the membrane material nor the possible traces of chemical reagents had a significant effect on aranoza solution stability.

Testing of the freezing conditions

Based on the chemical instability of aranoza and poor effectiveness of methods of chemical stabilisation of antitumor drugs we have chosen freeze-drying technology to obtain a parenteral pharmaceutical form. This method ensures physico-chemical and pharmacological properties of hydrolytically and thermo-unstable substances during a long time and allows preparing dose form comfortable for administration after dissolution.¹⁹⁻²¹

It was necessary to define the solution freezing temperature and to select a freezing method to determine the conditions for freezing. A special study was conducted to evaluate the effect of the freezing duration on the quality of the finished product. Also, the stability of solutions at low temperatures was investigated.

Initially, we determined the eutectic temperature (temperature of complete freezing) in aranoza solution by the thermal method, based on the fixation of temperature at slow thawing of the frozen product. Eutectic zone in aranoza solution is in the temperature range -25°C to -28°C .

It is possible to use continuous and fractional freezing, but optimally, continuous freezing on a shelf of a lyophilisation unit at a temperature of -40°C to -45°C , followed by holding at this temperature for 3 to 4 hr.

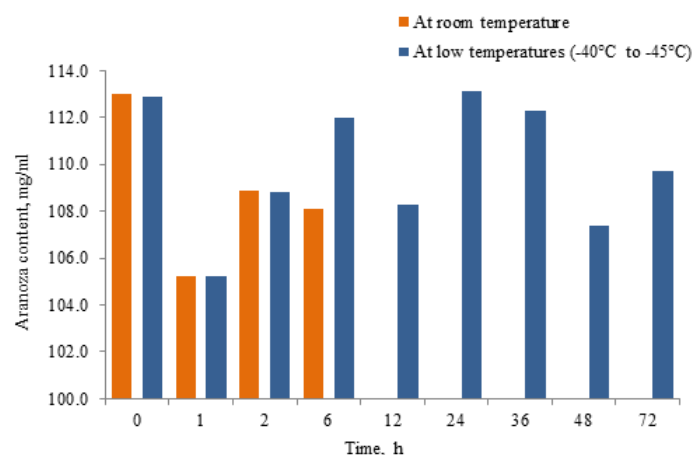


Figure 2: Stability of aranoza solutions at room temperature and at low temperatures. The values were presented as mean \pm SD ($n=6$).

Data in Table 3 show that more prolonged freezing resulted in product caramelisation.

As indicated above, the optimal duration of aranoza solution freezing is 3-4 hr, but in emergencies, duration of freezing may be increased to several days. We have shown that at prolonged storage at low temperatures (-40°C to -45°C), the concentration of aranoza in the solution didn't change in 72 h (three days) (Figure 2).

Quality control of the finished product

The quality of the developed product was confirmed under the requirements of the general monograph of the State Pharmacopoeia of the Russian Federation, XIV edition "Pharmaceutical dosage forms for parenteral use". Notably, the requirements of the Russian State Pharmacopoeia were harmonized entirely with the corresponding monograph of the European Pharmacopoeia.

Studies of aranoza dosage form stability were performed to evaluate the chosen formulation and method of production. From Table 4, it is clear that all characteristics of the preparation are stable for 36 months.

Table 1: The main physical and chemical properties of the pharmaceutical substance aranoza.

| Property | Information | Note |
|----------------------|---------------------------|--|
| Molecular weight | 235.20 | |
| Appearance | White to yellowish powder | |
| Water solubility | 1:4 | At 20°C |
| Thermal sensitivity | Yes | Rapid spontaneous decomposition of substance at temperatures over 30°C forming nitrogen, nitrogen oxide and/or diazomethane. Beginning of 10% solution hydrolysis in 5-10 min at 23-25°C |
| Photo sensitivity | Yes | Decomposition of aranoza in 10% solution at 200 lux in 2 h |
| Hydrolytic stability | No | Hydrolysis of glycosidic bond at pH ≤ 3, complete destruction during 3h at pH 10-11 (0.5% NaOH solution) |
| Hygroscopicity | Yes | |

Table 2: Stability of aranoza solutions by sterilizing filtration.

| Filter* (material) | Rate of filtration (ml/min/cm ²) | Aranoza (mg/ml) | |
|---|--|-------------------|------------------|
| | | before filtration | after filtration |
| Triton [®] -free mixed cellulose esters GSTF | 18 | 102.3±1.8 | 100.2±1.3 |
| Mixed cellulose esters GSWP | 18 | 110.1±0.9 | 107.8±1.4 |
| Hydrophobic polyvinylidene difluoride GVHP | 15 | 106.3±1.3 | 102.9±0.6 |
| Cellulose acetate | 14 | 115.1±0.6 | 111.3±1.7 |
| Polycaprolactam | 16 | 98.2±1.9 | 89.7±1.2 |

*Filter diameter of 47 mm and a pore size of 0.22 µm. The values were presented as mean± SD (n=6).

DISCUSSION

The first technological step in the manufacture of lyophilized dosage forms is the preparation of the solution for freeze drying. To obtain 10% aranoza solution for freeze-drying, we used excipients - Kollidon 17 PF and sorbic acid. In our case, the Kollidon 17 PF functioned not only as a stabiliser but also as a high-molecular structure-forming component, creating a stable lyophilisate with satisfactory physical properties. Sorbic acid was chosen because of its antimicrobial action and as acidity regulator to pH 3.0-4.5. The composition of aranoza, Kollidon 17 PF and sorbic acid is compatible with tissues and physiological fluids of the body and we showed that they decrease product-induced irritation.²² It should be noted that a high concentration of aranoza solution facilitated a reduction in volume of the dosed solution for lyophilisation, as well as increased the load of the sublimation chamber per unit and accelerated the drying process.

To develop the technology, the preparation of the solution for lyophilisation was required to be in strict adherence to the order and method of preparation of the components (Figure 3), as well as adherence

Table 3: Relationship of aranoza finished product quality from the method and duration of freezing.

| Freezing method | Freezing duration (h) | Quality of the finished product |
|-----------------|-----------------------|---|
| Continuous | 3-5 | Complies with the monograph requirements |
| Fractional | 4-6 | Complies with the monograph requirements |
| Fractional | 24-26 | The appearance of caramelized product, prolongation of the dissolution time of the finished product |

Table 4: Results of aranoza lyophilisate 500 mg stability tests.

| Batch No | Time, months | Quality attributes* | | | |
|----------|--------------|-------------------------|------------------------|-------------------|---------------------|
| | | pH | Related substances (%) | Loss of drying(%) | Aranoza** (mg/vial) |
| | | Limits by specification | | | 450.0-550.0 |
| 1 | - | 3.6±0.05 | 0.62±0.015 | 0.18±0.011 | 504.2±8.3 |
| | 12 | 3.5±0.08 | 0.74±0.028 | 0.23±0.012 | 501.6±7.9 |
| | 24 | 3.6±0.12 | 0.58±0.032 | 0.21±0.008 | 503.3±8.1 |
| | 36 | 3.5±0.17 | 0.71±0.017 | 0.19±0.010 | 505.6±8.4 |
| 2 | - | 3.5±0.08 | 1.58±0.081 | 0.21±0.013 | 514.1±9.0 |
| | 12 | 3.4±0.05 | 1.72±0.054 | 0.19±0.009 | 515.8±7.5 |
| | 24 | 3.6±0.15 | 1.53±0.056 | 0.26±0.010 | 516.4±7.3 |
| | 36 | 3.5±0.12 | 1.84±0.027 | 0.30±0.011 | 515.1±8.4 |
| 3 | - | 3.1±0.11 | 1.13±0.066 | 0.32±0.015 | 508.3±7.2 |
| | 12 | 3.3±0.06 | 1.29±0.048 | 0.31±0.009 | 510.6±6.6 |
| | 24 | 3.3±0.03 | 1.30±0.036 | 0.26±0.010 | 507.5±8.2 |
| | 36 | 3.2±0.13 | 1.16±0.013 | 0.31±0.013 | 508.6±7.4 |

*All tested batches complied the monograph requirements during all observation time, ** All values are Mean±SD (n=6)

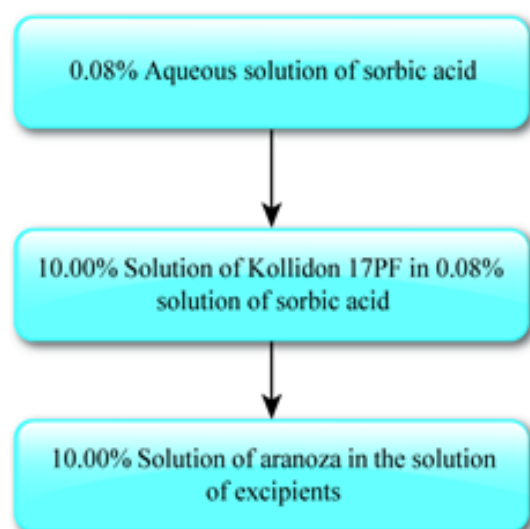


Figure 3: Sequence of operations on aranoza dissolution.

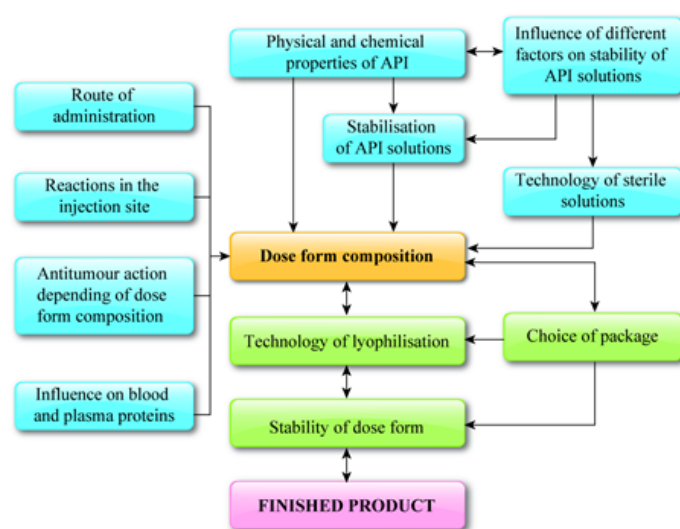


Figure 4: Algorithm for the development of a lyophilised antitumour drug.

to the environment conditions (temperature and illumination): the solution of aranoza was prepared at a room temperature of 20-22°C at an illuminance of not more than 200 lx. First, the sorbic acid 0.08 % solution in water was prepared, then Kollidon in this solution was dissolved and in the result, aranoza was dissolved in a pre-prepared solution of excipients. This sequence of operations was used to reduce the likelihood of toxic API spraying.

We determined experimentally the replacement rates (the coefficient of the aqueous solution volume increase) of Kollidon 17PF and aranoza were and they were found to be 0.67 ml/g for both compounds. Use of the replacement rates facilitated the preparation of large volumes of the solution for lyophilisation using the exact amount of solvent. The quantity of aranoza was adjusted to 100% of the substance to obtain a solution.

Taking in consideration high reactivity of aranoza we justified the choice of filtering material. The highest filtration rate was achieved using the mixed cellulose esters (GSTF and GSWP) filters (18 ml/min/cm²) and was slightly decreased in the sequence polycaprolactam > hydrophobic polyvinylidene difluoride > cellulose acetate. At the same time it was

found that the concentration of aranoza in the solution didn't change under contact with filtering materials.

Except API concentration, conditions of freezing and lyophilisation are the technological factors influence on the results of freeze-drying.

It is known that non-crystallized water may interact with Kollidon 17 PF at a temperature of -22°C with the formation of a vitreous mass.²² At this temperature and lower, the substance is in the solid state. Therefore, for the aranoza solution containing Kollidon 17 PF, the freezing temperature was determined within the range -40°C to -45°C.

Evaluation of the effect of freezing on the quality of the finished product demonstrated that the freezing duration of the pharmaceutical dosage form of aranoza should not exceed 6-8 h. In an emergency, therefore, it is possible to keep the solution of aranoza at a low temperature with resolution and freeze-drying. Also we established that caramelization of the product during long term storage at low temperature (24-26 hr at -40°C to -45°C) is the character of active substance. We evaluated the quality of aranoza dosage form and showed that all characters of the product don't change in a long-term study in a long-term study at 8°C/60% RH.

Many factors have been considered to create aranoza lyophilised drug:

- Biological factors (biological activity, route of administration, local tissue reactions, the effect of solutions on blood and plasma proteins);
- Physico-chemical factors (physical and chemical properties and the stability of the API);
- Technological factors (the possibility of preparing the solutions with pre-set concentrations and freeze-drying of the selected composition, method and duration of freezing, drying mode, type of primary packaging).

The experience of aranoza dosage form for injection permits us to create the algorithm for the development of a lyophilised antitumor drug, which is presented in Figure 4.

The trueness of choice of technological solutions at aranoza dosage form development has been confirmed by analytical data, which characterize the standard nature and stability of the product. The results of aranoza pharmaceutical dosage form development are employed in organisation of the product manufacture.²³

CONCLUSION

The composition of the drug was chosen for parenteral use, consisting of polyvinylpyrrolidone (Kollidon 17PF) as a stabilizer and shaper and sorbic acid as a pH regulator. The method of lyophilisation was suggested to obtain the stable finished product and the main parameters of the process (freezing temperatures of -40° to -45°C and duration of freezing of 3-4 hr) have been evaluated. We have demonstrated that the created product has characteristics corresponding to the requirements of Ph. Eur. and Ph. Ru. For lyophilisates for injection and is stable within a storage time of 3 years. Summarising, we created an algorithm for the development of a lyophilised antitumor drug to obtain an appropriate pharmaceutical dosage form.

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CONFLICT OF INTEREST

The authors report no conflicts of interest. The author alone is responsible for the content and writing of this article.

ABBREVIATIONS

NET: Neuroendocrine tumours; **Ph.Eur.:** European Pharmacopoeia; **Ph.Ru.:** State Pharmacopoeia of the Russian Federation; **API:** active pharmaceutical ingredient; **SD:** standard deviation.

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