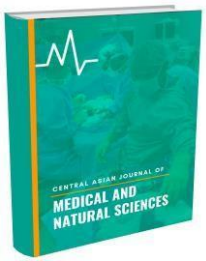

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Article

Selection Of Composition And Development Of Technology "Fordexa" Injection Drug Form

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Abstract: Today, among ready-made drugs produced on an industrial scale, injectable drugs are in the leading positions in terms of their quick effect on the body and the level of low risk in the gastrointestinal tract. The composition and technology of sample solutions of "Fordexa" solutions for injection containing dexketoprofen trometamol, which are recommended for production at the local "BAYAN MEDICAL" LLC were developed.

Keywords: "Fordexa", Dexketoprofen Trometamol, Substance, Excipients, Injection Solution, Composition, Technology.

1. Introduction

According to the WHO statistics, pain syndromes are one of the main reasons for visiting a doctor (from 11.3 to 40%). The prevalence of moderate and severe chronic pain among adults in the United States and Europe is 35.5% and 19%, respectively. The high rate of disability in the working-age population due to musculoskeletal injuries raises the issue of using NSAIDs in the treatment of osteoarthritis (OA) to an urgent level. OA affects 10-12% of the world's population [9]. The disease is age-related, most often developing after 30-35 years of age and occurring in 97% of cases in the age of 60 and older [8,9,20].

It is known that the advantages of injectable drugs are that they can be prepared in large quantities in aseptic conditions, that the drug can be administered even when the patient is unconscious, the shelf life is ensured, the effects of the medicinal substance appear in a very short time, the absence of the effects of the gastrointestinal tract and liver enzymes that break down the medicinal substance, the sense of taste and organs of the gastrointestinal tract are exempt from the effects of the medicinal substance, the ease and accuracy of dividing into doses and that they have the ability to replace blood with various blood substitutes even when a large amount of blood is lost [5,7,12].

According to the use of injectable drugs, as well as the introduction of the drug contained in it into the body, injectable drugs are considered parenteral drugs and due to the fact that these types of drugs are taken by breaking into the integrity of the body (into the skin and under the skin, between the muscles, into the vein, into the artery and blood

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vessel and other body spaces), they have higher requirements compared to oral drugs, they produced in sterile condition and prepared by the weight-volume method [1,6,18]

The aim of the research. Taking into account the above, the composition and technology of the solution for injection "Fordexa" based on the anti-inflammatory dexketoprofen trometamol substance is developed.

2. Materials and Methods

We used the non-steroidal anti-inflammatory substance dexketoprofen trometamol (NN 42 Uz-8979-2018) as an object of research. This substance is a white crystalline powder, freely soluble in methanol and water, slightly soluble in chloroform and slightly soluble in ethanol. Dexketoprofen trametamol is a non-selective nonsteroidal anti-inflammatory drug of the arylpropionic acid group containing the active c-enantiomer of racemic ketoprofen, an analgesic characterized by a rapid onset of action and a relatively short half-life [2,15,17].

Trometamol salt ensures rapid dissolution and absorption, which is especially important in severe pain. The duration of pain relief is 4-6 hours, the mechanism of dual action from the central and peripheral side is of particular interest to him, as a result of which dexketoprofen prevents the exacerbation of pain, and prevents the formation of "pain memory" does [3,7,14].

In order to create the composition of "Fordexa" injection solution, we agreed to create a sample mixture of substances from a number of scientific literature.

We used water for injection, ethyl alcohol, and propylene glycol and diethylene glycol monoethyl solutions to improve the solubility of Fordexa injection solution. All solvents used for injection solution met the requirement of "Bacterial endotoxins" and "Pirogenicity" MH.

Medicines and excipients included in "Fordexa" injection solution were dissolved in the solvents listed in Table 1, taking into account their solubility.

Injection solutions prepared in water for injection: mass-volume method (propylene glycol, metacresol, glycerin); by mass (sodium metabisulfite, mannitol, sodium citrate dihydrate, sodium edetate, sodium dihydrophosphate, sodium dihydrophosphate anhydrous, methylparahydroxybenzoate, sodium sulfite); prepared by volume (ethyl alcohol, sodium hydroxide 1 M solution, hydrochloric acid, benzyl alcohol 10%, sodium hydroxide, aqueous ammonia).

In order to create a high-quality injection drug form, in addition to the following (sterility, absence of visible mechanical additives, pyrogenicity and stability) specified in the publication of DF of the Republic of Uzbekistan, a number of additional requirements are also imposed: indicators such as isotonicity, isohydricity, isoosmolarity and isoplasticity were used using the methods presented in the literature [4,11,19].

In the preliminary research, the theoretical and practical osmotic concentration of the injection solution of the sample contents was studied. The theoretical osmotic concentration in the mentioned model compositions was calculated according to the following equation:

$$Cosm = \frac{m}{M} \cdot n \cdot 1000 \qquad (3.1.)$$

where: Sosm is the osmolarity of the solution, milliosmoles per liter (mOsm/l);

m - amount of substance in solution, g/l;

M is the molar mass of the substance, g;

n is the total number of ions formed from one dissolved molecule as a result of dissociation (n = 1 for substances that do not undergo dissociation, n = 2, 3 for substances that form the corresponding number of ions when dissolved).

The actual osmotic concentration of all prepared sample contents was carried out using a cryoscopic laboratory cryostat and an automatic cryoscopic osmometer OSMOMAT 3000D, which allows monitoring the temperature change.

3. Results and Discussion

In order to develop the technology of an injection drug based on the substance dexketoprofen trometamol, about 15 sample compositions were prepared, 10 compositions that gave satisfactory results were prepared in a small volume in the laboratory at the basis of "BAYAN MEDICAL" LLC and the results are presented in Table No.1.

The pH environment of the model solutions prepared on the basis of the dexketoprofen trometamol substance presented in Table No. 1 was determined by the potentiometric method presented in the DF of the Republic of Uzbekistan. It was determined that the pH of the injection solution prepared on the basis of dexketoprofen trometamol substance is in the range of 6.5-8.5. This meets the requirement [4].

Determination of the density of injection solutions prepared on the basis of the dexketoprofen trometamol substance according to the article "Relative density" provided in accordance with the requirements of the Russian Federation DF (2.2.5), method 1 is determined by a pycnometer, and method 2 uses direct plot nomers. Since our composition contains alcoholic solutions (taking into account the rapid solubility of solutions), we determined directly using a plot number. Compared to the density of water. The density of water equal to 1.0001g/cm3 and dexketoprofen trometamol injection solution is in the range (from 0.9824 g/ml to 1.074g/ml), and the average result is equal to 0.9976 g/ml. This showed that the injection solution is different from water.

The effective osmotic concentration of all sample injection solutions was evaluated by cryoscopic determination of the freezing point depression of the injection solutions compared to the freezing point of the pure solvent. In this case, 1 osmol per kilogram of water lowers the freezing point by 1,860 C.

This relationship can be expressed by the following equation:

$$Cosm = \frac{(T_2 - T_1)}{K} \cdot 1000 \qquad (3.2.)$$

where: Cosm is the osmolarity of the solution, milliosmoles per liter (mOsm/kg);

T2 freezing temperature of pure solvent (°C);

T1 is the freezing temperature of the studied solution (°C);

K is the cryometric constant of the solvent (for water: 1.86).

1.858 - molal cryometric constant number of purified water - corresponds to the decrease in the freezing point resulting from the dissolution of 1 mole of substance in 1 kg of water;

1000 is the coefficient of conversion of osm/kg to mosm/kg;

The calculation of the theoretical osmotic concentration (osmolality, milliosmol (mOsm)) of substances included in the model mixture injection solutions was carried out as follows:

$CmOsm_{\text{dexketoprofen trometamol}}$= (36,9: 375,42) x 1 x 1000 = 98,3

$CmOsm_{\text{sodium chloride}}$ = (8,0: 58,44) x 2 x 1000 = 273,8

98,3+273,8=371,7 CmOsm

Solutions prepared on the basis of dexketoprofen trometamol were divided into mOsm (normally 350 - 450 mOsm) and our result was 371.7 mOsm.

As can be seen from Table 1, the results of calculating the theoretical osmotic concentration of the model mixtures of the injection solution prepared on the basis of the dexketoprofen trometamol substance showed that the amount of alcohols as a solvent in composition 1 has increased.

In composition 3, we can see that the amount of alcohols has increased, benzyl alcohol has adverse effects on the body. Also, the amount of mannitol should be 5-10%

based on MH requirements. According to the recommendation of pharmacologists (mannitol can be administered intravenously, intramuscular administration in large concentrations is prohibited).

In composition 5, sodium edetate, sodium dihydrogen phosphate, and sodium dihydrogen phosphate anhydrous were buffer substances, and this composition was removed due to the excess amount of the sample in the injection solution.

In formulations 6 and 7, the pH of the injection solution was not sufficient to ensure stability, the pH indicators and osmotic concentration did not have a positive indicator. According to the requirement of UzR DF (2.2.3), the pH indicator for injection drugs is required to be 6.5-8.5. This indicator is of great importance in the process of injection DV storage and sterilization [4,13].

In compositions 9 and 10 did not give positive results, according to the recommendation of pharmacologists, due to the high level of danger in the use of diethylene glycol monoethyl, propylene glycol and ethylene glycol, these substances are toxic in large quantities, and there is a high probability that propylene glycol will turn into ethylene glycol.

Compositions 2, 4, 8 were colorless, the color intensity did not exceed the GY 5 standard, the pH was from 6.5 to 8.5, the filling volume of all ampoules was not less than the nominal volume, and the maximum permissible deviation was +2%. Sterility also showed a positive result.

In order to prove the scientific basis of the solution for injection prepared on the basis of dexketoprofen trometamol substance, the pH of the solution, appearance, clarity, color, density of mechanical additives (visible and invisible particles), osmotic concentration were checked according to the requirements of the quality regulatory documents of the three components that showed positive results. and quantitative analysis results were determined. The results are presented in Table No.2.

As can be seen from the results presented in Table 2, all studied indicators were positive. The injection solution of all sample contents was prepared in aseptic conditions at the basis of “BAYAN MEDICAL” LLC.

The appearance of the prepared injection solutions was colorless in all compositions, and the color intensity of the drug did not exceed the GY5 standard. Clarity did not change when compared with solution T and standard suspension II.

Mechanical additives in accordance with the requirements of UzR DF (2.9.20) should not contain visible particles (- particles > 10 μm should not exceed 6000 particles/ampoule), in the 2nd composition > 10 μm-145 particles/ampoule, in the 4th composition, > 10 μm - 148 particles/ampoule, in composition 8 > 10 μm-152 particles/ampoule. And invisible particles (- particles > 25 μm: no more than 600 particles/ampoule) in the 2nd composition > 25 μm - 3 particles/ampoule, in the 4th composition > 25 μm - 5 particles/ampoule, in the 8th composition > 25 μm - 4 particles /ampula organized. The density of injection solutions prepared on the basis of DK is in the range (0.9824 g/ml - 1.074 g/ml), 0.9976 g/ml for composition 2, 0.9772 g/ml for composition 4, and 0.9989 g for composition 8 /ml was equal.

Based on the experiments, it was determined that the pH of the injection solution prepared on the basis of DK substance is 6.5-8.5, and the 2nd composition has a pH of 7.4, in composition 4, the pH of the medium was 7.2, and in composition 8, the pH of the medium was 7.0.

Table No.1

Compositions studied for the selection of the composition of «Fordexa” injection solution

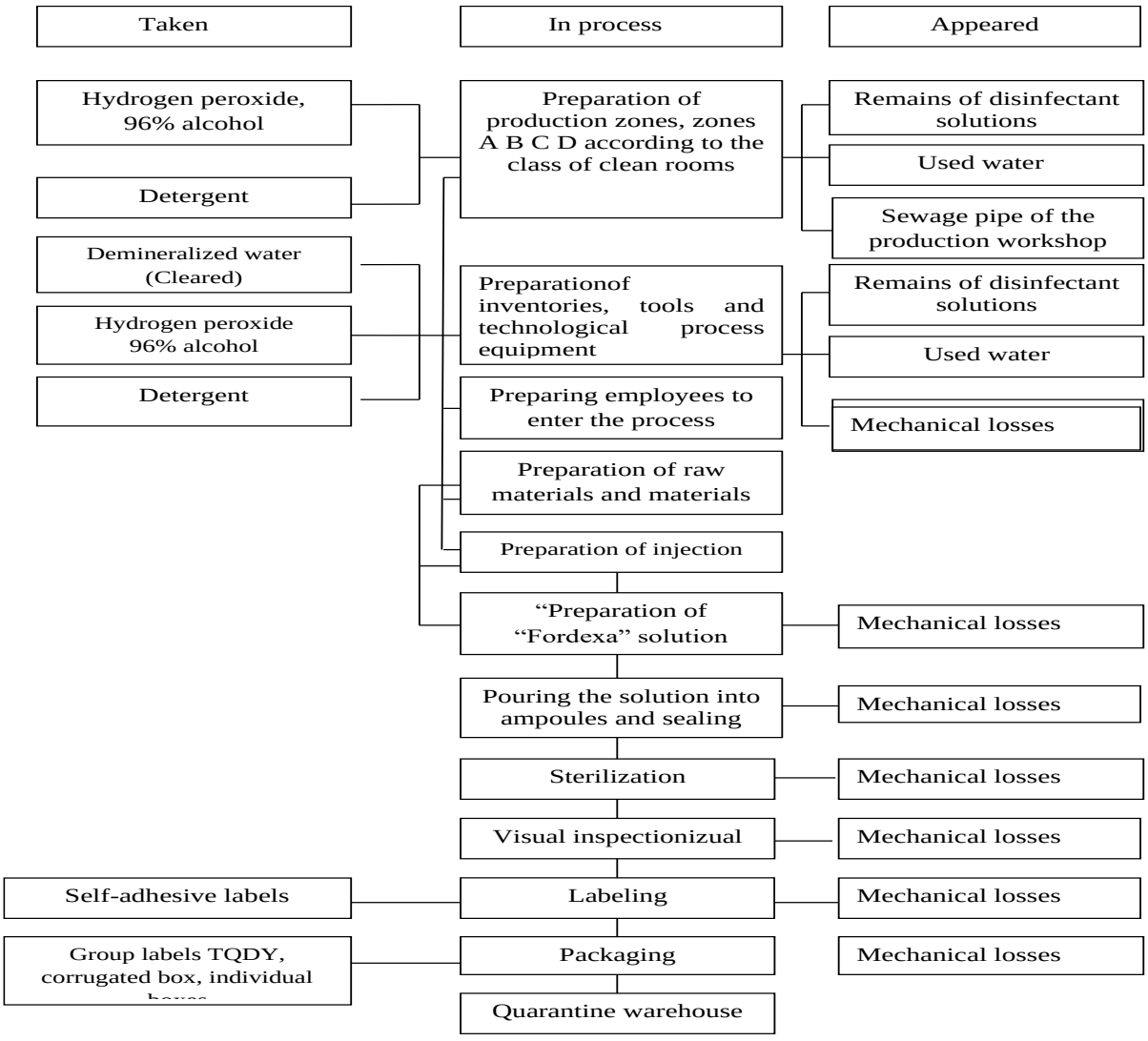
The name of the drug and excipients	Amount of ingredients, mg									
	T-1	**T-2**	T-3	T-4	T-5	T-6	T-7	T-8	T-9	T-10
Dexketoprofen trometamol	36,9	**36,9**	36,9	36,9	36,9	36,9	36,9	36,9	36,9	36,9
Sodium metabisulfite (0.1-1.0%)	2		2	2	2					2
Propylene glycol (20%)	200		100		200					
Ethanol 96%	100	**200**				100				
Mannitol (4.4%)			100							
Sodium chloride (8.3%)		**8**						400		9
Benzyl alcohol (0.5-10%)	9		9		9		+			
Sodium hydroxide (6.5-8.5)	pH 6,5-7,5	**pH 7,4**	pH 8,0-9,0		pH 8,0-9,0		+	pH 7,0-8,0		
Citric acid (1-5%)				pH 6,5-7,5						
Glycerin (1-50 %)							16			
Sodium Citrate (99%)				10,04						
Metacresol							2,5			
Sodium edetate					1,2					
Sodium dihydrogen phosphate					3					
Methyl parahydroxybenzoate									0,60	
Sodium dihydrogen phosphate anhydrous solution					3					
Sodium sulphite						1				
Disodium acid salt								10		
Water for injection	up to 2,0 ml	**up to 2,0 ml**	up to 2,0 ml	up to 2,0 ml	up to 2,0 ml	up to 2,0 ml	up to 2,0 ml	up to 2,0 ml	up to 2,0 ml	up to 2,0 ml

Table No.2
The results of the study of quality indicators for the selection of the composition of «Fordexa" injection solution

№	Learned indicators		Requirements for MH	Analysis results		
				Content -2	Content-4	Content-8
1	Appearance	Color	The drug should not be colorless or the color intensity of the drug should not exceed the GY5 standard	suitable	suitable	suitable
		Clarity	A clear solution or standard suspension should not pass when compared to II	suitable	suitable	suitable
2	Mechanical attachments	Visible particles	There should be no visible particles. - Particles > 10 μm Do not exceed 6000 particles / ampoule - Particles > 25 μm: not to exceed 600 particles/ampule	suitable > 10 mkm-145 particle/ampoule	suitable > 10 mkm-148 particle/ampoule	suitable > 10 mkm-152 particle/ampoule

		Invisible particles	- Particles > 25 µm: not to exceed 600 particles/ampule	> 25 mkm - 3 particle/ampoule	> 25 mkm - 5 particle/ampoule	> 25 mkm - 4 particle/ampoule
3	Density, g/cm3		0.9824 g/ml - 1.074 g/ml	0,9976 g/ml	0,9772 g/ml	0,9989 g/ml
4	pH		from 6.5 to 8.5	7,4	7,2	7,0
5	Osmolarity, suitablelem/kg		350-450 suitablem/kg	371,7	371,7	371,7
6	Quantitative analysis, mg/ml		(UsSX) 47.5 - 52.5 mg/2ml. (95.0% - 105.0% of the amount as a percentage)	49,16 mg/2ml.	48,12 mg/2ml.	47,22 mg/2ml.

The theoretical and practical osmotic concentration of DK injection solution was studied and was in the range of 350-450 mOsm/kg, and was equal to 371.7 mOsm/kg in all formulations. At the same time, quantitative analysis methods of the injection solution prepared by us are 47.5 - 52.5 mg/2ml. (95.0% - 105.0% of the amount in percentages), 49.16 mg/2 ml (96.0%), 48.12 mg/2 ml (97.0%) and 47.22 mg/2 ml (96%) and showed a positive result.



Picture 1. The technological process of obtaining “Fordexa” solution for injection

According to the requirements of "BAYAN MEDICAL" LLC, we selected the 2nd composition, which is easy to produce on an industrial scale, sterile, non-pyrogenic, stable, with abundant auxiliary substances, prepared in small quantities, and which met the requirements of MH and showed positive results. The type of injection drug offered by the company was named "Fordexa".

Based on the results of the study, the following composition of "Fordexa" injection solution (composition per 2 ml) was developed:

Dexketoprofen trometamol (equivalent to dexketoprofen) (BP, Eur.Ph, USP, CP)	73,8 mg (50mg)
Ethyl alcohol 96% (FS 42 Uz-0171-2020, GOST 5962-67)	200 mg
Sodium chloride (Eur.Ph BP, USP, CP, GOST 4233-77)	8 mg
Sodium hydroxide 0.1 M solution (Eur.Ph, BP, USP, GOST 4328-77)	pH= up to 7,4
Water for injection (FS 42 Uz-0512-2022)	up to 2,0 ml

Technology: Solution for injection «Fordexa" in glass ampoules of 2 ml was prepared in the pharmaceutical enterprise "BAYAN MEDICAL" LLC, in the laboratory of quality assessment. Production processes are schematically presented in Picture 1.

According to the results presented in Table 3, the proposed «Fordexa" injection solution was prepared taking into account the solubility of the included drugs and auxiliary substances. The prepared solution was filtered and poured into 2 ml ampoules, then sterilized in a terminal sterilizer (based on steam). Terminal sterilization is the application of a sterilizing agent to a finished product in a closed container to achieve a sterility assurance level of 10^{-6} or higher. Today, on an industrial scale (ampoules and vials, glass bottles), specially designed for terminal sterilization, terminal sterilization with hot water is used, which does not affect the quality, safety and effectiveness of the drug. Sterilization results are presented in Table 3.

According to the results in table 3 above, it should be said that «Fordexa" injection solution during the sterilization period of the terminal sterilization method (100 oC for 30 minutes and 100 oC for 40 minutes) and the solution did not change its color, clarity and free of foreign substances, but the pH environment (6.3 and 6.7) and showed an unsatisfactory result. And during the sterilization period of the terminal sterilization method (121 oC for 8 minutes and 121 oC for 15 minutes), the solution did not change its color, clarity, free of foreign substances and pH environment and responded to sterility.

Technological processes consist of the following stages: preparation of equipment, rooms and personnel for the technological process; preparation of water for injection; preparation of pyrogenic ampoules, weighing of drugs and auxiliary substances; Preparation of «Fordexa" injection solution, solution filtration, filling and caulking into ampoules, sterilization, quality assessment, visual inspection, labeling and packaging

Table No. 3
Results of selection of different sterilization methods of "Fordexa" solution for injection

№	Sterilization method	Sterilization temperature and time	pH	Appearance of the solution	Foreign substances
1.	Terminal sterilization	121 oC for 8 minutes	7,4	clear, colorless	not identified
2.	Terminal sterilization	121 oC for 15 minutes	7,2	clear, colorless	not identified
3.	Terminal sterilization	100 oC for 30 minutes	6,3	clear, colorless	not identified
4.	Terminal sterilization	100 oC for 40 minutes	6,7	clear, colorless	not identified

Solution preparation process. Preparation of "Fordexa" injection solutions was carried out in a hermetically sealed R-1 reactor with double walls and provided with a mixer. About 0.5 of the volume of the prepared solution was transferred from the water storage tank to the clean reactor R-1 for injection. Then it was cooled to 40-45°C. Raw materials (sodium chloride, dexketoprofen, ethanol) withdrawn for this 200-liter series were injected into the injection water through the hatch of the reactor. The hatch was closed, the stirrer at the bottom of the reactor was started, and the mixture was stirred for 20-30 minutes until the mixture was completely dissolved. When the substances were completely dissolved, the volume of the solution was brought to 200 liters with water for injection and mixed for another 20 minutes. After mixing, a sample of the solution was taken and its pH value was checked. The pH of the solution was adjusted to 7.4 by adding 0.1 M sodium hydroxide solution.

4. Conclusion

As a result of the experiments, on the basis of "BAYAN MEDICAL" LLC the composition and technology of the recommended "Fordexa" solution for injection based on the substance dexketoprofen trometamol with nonsteroidal anti-inflammatory effect was developed. It is also easy to produce on an industrial scale, sterile, non-pyrogenic, stable, has a wide range of auxiliary substances, and has been proven to meet the requirements of MH.

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