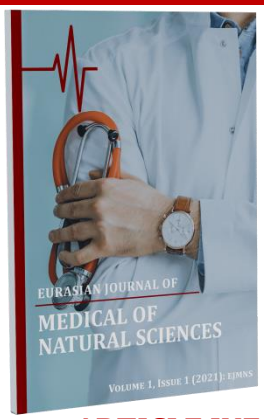
EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 7.921 www.in-academy.uz



RESEARCH ON THE DEVELOPMENT OF COMPOSITIONS AND TECHNOLOGY FOR NEVIRAPIN CAPSULES

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https://doi.org/10.5281/zenodo.14184951

ARTICLE INFO

Received: 14th November 2024
Accepted: 18th November 2024
Online: 19th November 2024

KEYWORDS

Nevirapine, capsules, antiretroviral drugs, excipients, pharmaceutical and technological indicators, technology.

ABSTRACT

This article presents the results of research aimed at selecting the optimal composition and developing the technology of nevirapine capsules with antiretroviral action. For this purpose, model capsules were developed using various fillers and auxiliary substances acting as disintegrators, and they were evaluated based on pharmaco-technological indicators. It has been proven that it is advisable to use a mixture of lactose and microcrystalline cellulose, a mixture of crospovidone and aerosil as a filler, an antifriction agent - magnesium stearate, and a moisturizing agent - purified water. Based on the selected composition, the technology of nevirapine capsules was developed and tested in industrial conditions at the local pharmaceutical manufacturer JV LLC "Samarkand-England Eco-Medical".

Introduction. Human immunodeficiency virus (HIV) is a retrovirus of the lentivirus family that causes a slowly progressing HIV infection. From the time of its discovery (1983) to the present day, it has been the leading cause of death (32 million) and the number of infected people (37.9 million) [1,2,3,4,5].

The discovery of antiretroviral drugs allowed for a significant reduction in the growth of epidemics: over 18 years, starting in 2000, 13.6 million lives were saved. Today, HIV infection has gradually transitioned into the category of chronic diseases that can be cured. This, in turn, serves to some extent to improve the life expectancy and quality of life of HIV-infected individuals [1,6,7,8].

The World Health Organization has published recommendations on the need to start using antiretroviral therapy in the early stages of the disease, which allows for increased treatment effectiveness. According to WHO forecasts, the use of antiretroviral drugs will prevent 3 million deaths and 3.5 million new cases by 2025 [9].

Therefore, antiretroviral therapy helps to solve the following tasks: preserving and restoring the functions of the immune system of an infected person, reducing the

concentration of viral RNA for the longest possible time, improving the patient's quality of life, minimizing complications and mortality from this infection [9,10,11,12,13].

However, numerous studies have shown that antiretroviral drugs suppress the virus, but it is impossible to completely remove it from the body. As a result, it is necessary to use drugs of this pharmacotherapeutic group throughout life [14,15,16,17,18,19,20].

In this situation, the financial aspect becomes a serious concern for patients, as the original medications used to treat HIV infection are highly expensive. The solution to this problem is envisioned in programs of various countries and is aimed at developing generic drugs. This approach allows for a reduction in the cost of treating patients infected with HIV.

A marketing analysis of antiretroviral drugs registered in the territory of the Republic of Uzbekistan has shown that the majority of the medications are imported, while domestic production does not sufficiently meet the needs of patients. [21,22].

Purpose of the research: selection of the optimal composition of nevirapine capsules for the antiretroviral drug, development of a technology for their production and testing in industrial conditions.

Materials and methods: Nevirapine, belonging to the group of non-nucleoside HIV reverse transcriptase inhibitors, was chosen as the active substance. Representatives of this class are localized in the active center of the viral enzyme, stopping further synthesis of HIV RNA.

Studies were conducted to select the composition of the nevirapine capsule, using several groups of auxiliary substances. Lactose monohydrate (Ph. Eur.), microcrystalline cellulose, edition I of the State Pharmacopoeia of the Republic of Uzbekistan, Ph. Eur.), maltodextrin (Ph. Eur.), a mixture of lactose and microcrystalline cellulose, and a mixture of maltodextrin and microcrystalline cellulose. Disintegrating substances, that is, disintegrating substances, were also used. These are potato starch (I edition of the State Pharmacopoeia of the Republic of Uzbekistan, Ph. Eur.), crospovidone (USP), aerosil (CAS:9005-84-9) and a mixture of crospovidone and aerosil.

Depending on the bulk density of the substance, capsules No.00 were used for encapsulation.

The pharmaco-technological parameters of mixtures of active substances and samples of encapsulated masses were determined according to the methods outlined in the first edition of the State Pharmacopoeia of the Republic of Uzbekistan and in the fourth edition of the State Pharmacopoeia of the Russian Federation [23,24].

Results and their discussion: 25 compositions of encapsulated masses were developed using various combinations of the aforementioned auxiliary substances (Table 1). The number of fillers and disintegrators was calculated based on the standards presented in regulatory documents and the bulk density of the substances.

Table 1

Nevirapine substance compositions prepared with compositions of various auxiliary substances

Supplementary substances	Dezintegrants				
	potato starch	crospo-vidone	aerosil	crospovidone + aerosil	potato starch + aerosil

lactose monohydrate	1	2	3	4	5
microcrystalline cellulose	6	7	8	9	10
maltodextrin	11	12	13	14	15
lactose + microcrystalline cellulose	16	17	18	19	20
maltodextrin + microcrystalline cellulose	21	22	23	24	25

All prepared compositions were soaked in purified water.

The following parameters of the masses prepared for encapsulation according to the compositions presented in Table 1 were considered: ease of technological process, bulk density (over 6.0*10-3 kg/s) and angle of natural deviation (in the range of 25-45 degrees). In this case, when lactose monohydrate or maltodextrin is used as a filler, the granules formed are fragile, and the proportion of fine fractions increases. When using microcrystalline cellulose, the mass was viscous, which made granulating more difficult. However, when microcrystalline cellulose was used in combination with lactose or maltodextrin, the technological process, i.e., mixing, wetting, granulation, was easy, and high-quality granules were obtained. The angle of natural deviation of these masses corresponded to the “good scattering” indicator according to the standards of the State Pharmacopoeia of the Republic of Uzbekistan. However, when the bulk density of the masses was expressed by numerical values, the bulk density of the compositions containing a mixture of maltodextrin and MCC did not exceed 7.0*10-3 kg/s, regardless of the desintegrators used. The highest bulk density values were observed in the compositions using lactose and microcrystalline cellulose as fillers. Therefore, these compositions (No. 16, 17, 18, 19, 20) were selected for further research.

In the next stage of the research, the following indicators of the masses prepared using these compositions were determined: fractional composition, bulk density, angle of natural deviation, bulk density, granule decomposition, and residual moisture content. The results obtained are presented in Table 2.

If the number of particles with a height less than 0.2 μm exceeds 5%, this negatively affects the bulk density of the mass. Based on the study of the fractional composition of the analyzed encapsulated masses, only two compositions met this requirement: No. 17 and No. 19. Their fractions less than 0.2 μm corresponded to 4.18 and 2.84, respectively. In the remaining compositions, the amount of particles smaller than the specified size exceeded the specified 5%: in composition No. 16 - 9.71%; No. 18 - 18.96%; No. 20 - 14.87%.

This, of course, had an impact on the bulk density of the masses. The data in Table 2 showed that when using potato starch and aerosil alone and in a mixture with each other as a disintegrant, the bulk density of the prepared masses (samples 16, 18 and 20) was positive, but lower than other compositions, and they were 8.35±0.83*10-3 kg/s, 7.39±0.51*10-3 kg/s, and 8.02±0.64*10-3 kg/s, respectively.

This indicator of encapsulated mass containing crospovidone as a disintegrator was higher and amounted to 8.92±1.14*10-3 kg/s. The highest scattering rate (9.27±1.06*10-3 kg/s) was observed when using a mixture of crospovidone and aerosil.

Since the parameter of the natural angle of deviation depends on flowability, a similar trend was observed in this case as well. Specifically, the highest value was observed in the composition with the lowest flowability (No. 18), which was equal to 44.0±2.0 degrees. When potato starch was used as a disintegrant alone (No. 16) and in combination with aerosil (No. 20), this indicator was found to be 32.0±4.0 and 41.0±1.0, respectively. The best results for the natural angle of repose were observed in compositions No. 17 and No. 19 (when crospovidone was used alone and in mixture with aerosil): 32.0±4.0 and 30.0±3.0, respectively..

Analysis of the bulk density of the samples showed that composition No. 18 belongs to the category of light powders (570.27±21.94 kg/m3), while samples No. 16, 17, 19, and 20 belong to the category of medium-weight powders (628.08±36.89 kg/m3, 706.12±44.61 kg/m3, 749.40±32.18 kg/m3, 684.61±29.53 kg/m3).

Table 2

Pharmacological and technological parameters of encapsulated mass samples prepared using a mixture of lactose and microcrystalline cellulose as fillers

Indicator	Unit of measure	Examples				
		No.16	No.17	No.18	No.19	No.20
Fractional composition -1000 µm + 500 µm -500 µm + 355 µm -355 µm + 250 µm -250 µm + 180 µm -180 µm + 90 µm -90 µm	%	 16,42 18,93 32,14 22,80 8,62 1,09	 29,08 25,41 19,52 21,81 3,31 0,87	 13,44 20,63 26,37 20,60 14,87 4,09	 31,69 24,38 23,40 17,69 2,38 0,46	 18,22 21,64 25,18 20,09 8,73 6,14
Scattering	10-3 kg/s	8,35 ±0,83	8,92 ±1,14	7,39 ±0,51	9,27 ±1,06	8,02 ±0,64
Bulk density	kg/m3	628,08±36,89	706,12±44,61	570,27±21,94	749,40±32,18	684,61±29,53
Natural angle of deviation	degree	39,0±3,0	32,0±4,0	44,0±2,0	30,0±3,0	41,0±1,0
Granule decomposition	min	9,10±0,45	8,25±0,35	8,05±0,45	7,30±0,20	8,55±1,05
Residual moisture	%	1,94±0,49	2,09±0,24	2,33±0,52	2,16±0,21	2,39±0,31

Since the encapsulated mass is granular in shape, their decomposition has been determined. According to this indicator, all compositions met the established requirements and disintegrated within 15 minutes (within the range of 7.30±0.20 - 9.10±0.45 minutes).

In terms of residual moisture content, all analyzed masses met the requirements of regulatory documents (less than 5%) and the highest value was 2.39±0.31%.

Based on the results of a comparative analysis, the most optimal composition for nevirapine capsules was composition No. 19. A mixture of lactose and microcrystalline cellulose, a disintegrator - a mixture of crospovidone and aerosil, and a moisturizing agent - purified water were used as fillers.

The final stage of these studies was aimed at selecting an anti-friction agent. The mass prepared according to composition No. 19 was divided into 4 parts, each of which was powdered with separate anti-friction agents.

No. 1 - stearic acid was added in an amount of 1% of the total mass;

No. 2 - calcium stearate is added in an amount of 1% of the total mass;

No. 3 - magnesium stearate is added in an amount of 1% of the total mass;

No. 4 - talc was added in an amount of 2% of the total mass.

The bulk density and natural deflection angle of these masses were determined, and the results are presented in Table 3.

Table 3

Results of research on the selection of antifriction agent for the encapsulated mass of nevirapine

Indicator	Unit of measure	Model mixtures			
		No.1	No.2	No.3	No.4
Scattering	10-3 kg/s	9,59 ±0,72	10,23 ±0,96	10,84 ±1,06	9,38 ±0,84
Natural slope	degree	30,0±1,0	27,0±1,0	29,0±2,0	32,0±3,0

Based on the results presented in Table 3, the use of antifriction agents led to a more positive change in the identified pharmacological and technological indicators, with changes directly depending on the type of antifriction agent used. Specifically, the use of talc increased bulk density by only 1.2%, while in masses with the addition of calcium stearate and magnesium stearate, this indicator increased by 3.5% and 10.4%, respectively. The best indicator was observed when using steric acid: the bulk density of this mass increased by 16.9% and was 10.84 ± 1.06.

The natural angle of repose for all analyzed materials showed positive values and ranged from 27.0±1.0 to 32.0±3.0 degrees.

Considering the above, the following composition was chosen for neivrapin capsules:

Nevirapine substance - 200 mg

Microcrystalline cellulose (GF RUz I ed., Ph. Eur.) - 25 mg

Lactose (Ph. Eur.) - 40 mg

Krospovidon (USP) - 8 mg

Aerosil (CAS:9005-84-9) -24 mg

Magnesium stearate (USP, Ph. Eur.) - 3 mg

Purified water (FS 42 Uz 0511-2022) - q.s.

The average mass per capsule is 300 mg

The technology for producing capsules based on the chosen composition is presented in Figure 1 and consists of the following stages.

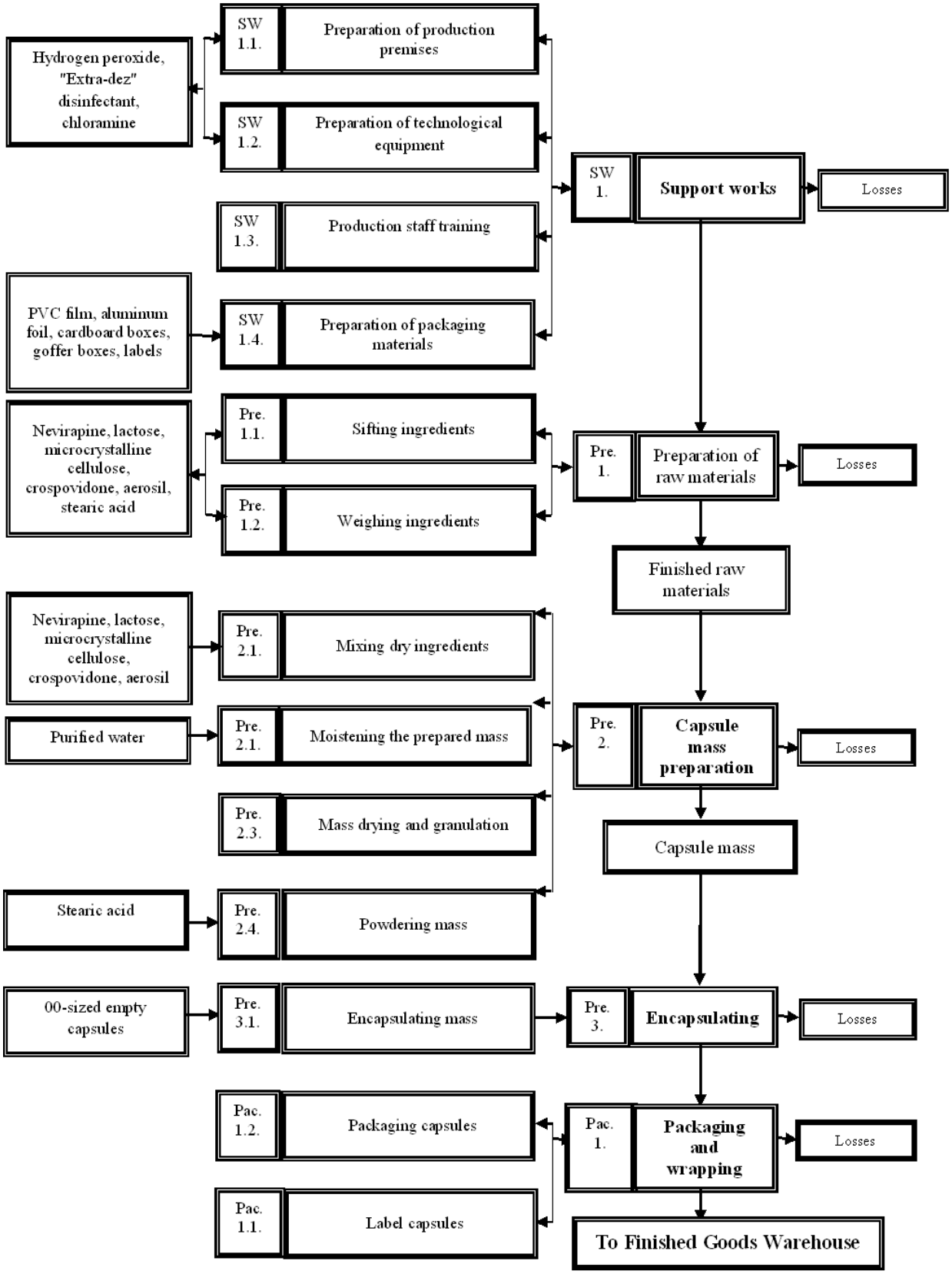

Figure 1. Technological scheme for the production of nevirapine capsules

The required amount of nevirapine, lactose, microcrystalline cellulose, crospovidone, aerosil, and stearic acid is separated and weighed through a sieve with a hole diameter of 150

μm. The ingredients (except stearic acid) are mixed according to the general rules for preparing powders until a uniform mass is formed. Then, with constant stirring, the prepared mass is moistened with the selected moisturizing agent (cleaned water) and dried in a drying cabinet at a temperature of 40-50°C until the residual moisture reaches 10-15%. The dried mass is granulated by friction granulation and continued drying until the optimal moisture content in the drying cabinet reaches (2-3%). The granulated mass is powdered with stearic acid and packaged in 0.3 g of capsules No. 00.

The developed technology for nevirapine capsules was tested in industrial conditions at the local pharmaceutical manufacturer JV LLC “Samarkand-England Eco-Medical”.

Conclusion: The selection of the composition of nevirapine capsules has been scientifically substantiated. It has been proven that the addition of a mixture of lactose and microcrystalline cellulose, a mixture of disintegrating substances - crospovidone and aerosil, a moisturizing agent - purified water, and antifriction agent - magnesium stearate as fillers allows for the production of encapsulated mass with satisfactory pharmaceutical and technological parameters. A technology for producing nevirapine capsules has been developed and tested in industrial conditions at the joint venture of the domestic manufacturer, LLC “Samarkand-England Eco-Medical”.

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