

**SPECIFIC FEATURES OF THE PREPARATION OF RAW MATERIALS,
MATERIALS AND INTERMEDIATES IN THE PRODUCTION PROCESS OF A
NEWLY FORMULATED ACYCLOVIR TABLET**

Xaydarov Vosil Rasulovich

Professor, Department of Industrial Technology of Medicinal Products,
Tashkent Pharmaceutical Institute, Candidate of Pharmaceutical Sciences

Raximova Xusnidaxon Abdukarimovna

Lecturer in the subject “Technology of Finished Dosage Forms”
Fergana Institute of Public Health Yangi Turon, 2a, Ferghana City

Tel.: (0373) 245-59-07, (0595) 401-06-63

info-ilmiy@fjsti.uz , fmioz@mail.ru

Abstract

This study describes the specific features of the preparation of raw materials and excipients, their qualitative assessment, and their further processing into intermediates in the industrial production process of a newly formulated acyclovir tablet. The physical and chemical properties of acyclovir are examined, together with the technological characteristics of auxiliary components used in pharmaceutical combination with it, including their sensitivity to moisture, particle size, flowability and compressibility. In developing the new composition, optimal ratios of substances were determined that ensure pharmacological activity, stability and technological adaptability. The efficiency of preparatory stages such as sieving, drying and homogenization of raw materials was investigated, as well as the necessary parameters during granulation and blending. Quality indicators of the intermediate product—uniform distribution, moisture content, bulk density and granule strength—were evaluated as key factors in ensuring the quality of the final tablet.

Keywords: Acyclovir tablets, pharmaceutical technology, raw material preparation, excipients, granulation process, particle size distribution, flowability and compressibility, moisture sensitivity, purified water system, intermediate product quality, tablet formulation stability, industrial tablet manufacturing.

Introduction

The industrial manufacture of medicinal products based on modern technologies first of all requires the correct selection of raw materials and excipients, their qualitative evaluation, and the adequate organization of technological processing stages. Among antiviral drugs widely used in clinical practice, acyclovir has great significance in various pharmaceutical dosage forms, including tablets, and is distinguished by its efficacy against herpes viruses. In recent years, the need to develop new tablet formulations of acyclovir aimed at increasing its bioavailability, enhancing its stability and improving absorption characteristics has been increasing.

The development of a new tablet composition is directly related to the preparation of raw materials and excipients in accordance with pharmacopoeial requirements and demands a detailed analysis of their physical, chemical and technological properties. In particular, such characteristics of acyclovir as crystalline structure, particle size, sensitivity to moisture and degree of flowability exert a direct influence on the quality of the intermediate product. Therefore, at the initial stages of the production process, ensuring the purity, uniformity and technological compatibility of substances is of critical importance.

Research Methodology

In the process of manufacturing a newly formulated acyclovir tablet, the raw materials, materials, intermediates and auxiliary substances received at the enterprise must be supplied in packaging that meets the requirements of the regulatory technical documentation (RTD) and be accompanied by appropriate quality certificates.

After receipt from the supplier, the raw materials must be checked for compliance with RTD requirements, integrity of packaging and absence of any damage that could impair their purity, as well as for the presence of documentation confirming their quality. Each batch of raw material must be registered upon acceptance. The results of tests must be recorded in the relevant test registration journal.

Raw materials authorized for use in production must be stored separately from batches that have not been tested or have been rejected during testing. For each accepted batch of raw material, sufficient samples must be retained for re-analysis when necessary. Rejected raw materials must be clearly labeled and either returned to the supplier or destroyed.

The optimal air temperature for storage of raw materials and auxiliary materials is 18–22 °C, and the relative humidity must not exceed 60 %. Removal of packaging and containers must be carried out in a separate room. Transportation of raw materials and auxiliary materials must be performed in closed containers to prevent microbial contamination. Throughout the technological process, all containers used must be labeled with the name of the raw material or finished product, batch number, quantity and date of production.

Special attention must be paid to the procedure for obtaining purified water. Purified water is obtained by a combination of ion exchange and reverse osmosis. The purified water must comply with ionic, organic, chemical and microbiological purity requirements. In the water purification area, an RO-240-LH (VP-2) unit for producing purified water is installed.

Schematic principle of operation of the purified water system

1. Water from the water supply system enters the pre-filters.
2. The water then passes through the reverse osmosis unit.
3. The purified water flows into a storage tank.

Pre-treatment consists of a mechanical (quartz sand) filter and a carbon filter. The mechanical filter removes all insoluble contaminants such as sand and rust. The carbon filter retains various chemical substances, including chlorine-containing compounds and organic and inorganic impurities. Afterward, the water passes through a one-micron mechanical filter, which completes the initial purification and prepares the water for the reverse osmosis procedure.

The reverse osmosis system consists of:

- Cartridge filter for fine purification
- High-pressure pump
- Group of membranes
- Remote control panel
- Supporting frame structure

Before starting operation, the power supply is switched on, the water inlet valve from the water supply system is opened, and the feed pump delivering water to the reverse osmosis filters is activated.

Water from the water supply passes successively through mechanical, carbon and one-micron filters and is then forced through a semi-permeable membrane with a pore size of 0.1–1 nm, which retains organic compounds, bacteria and viruses. A two-stage reverse osmosis system is used for water purification, which represents two successive filtration stages.

Water that has passed through the reverse osmosis system enters a storage tank. The operator evaluates the quality of the purified water based on the conductivity reading on the control panel, which should be in the range of 0.1–0.8 $\mu\text{S}/\text{cm}$. A chemist-analyst from the quality control department takes a sample from the storage tank for analysis. After a positive analytical result, the purified water is supplied to production. Storage of purified water in a special collection tank should not exceed three days.

Weighing of Raw Materials

All components used in tablet production are standardized by weight. Before weighing raw materials, the correct functioning of scales KP-1 and KP-2 must be verified. The check is carried out at zero load, and the accuracy of the balance is recorded by a responsible specialist. The weighing results are recorded by the specialist in the loading and operation journal.

The drug batch size is formed in the range from 45.387 kg to 567.0 kg.

The total amount of raw material per batch is 460.682 kg, including:

- Acyclovir – 406.0 kg
- Potato starch (20 % moisture) – 19.665 kg
- Lactose – 30.450 kg
- Calcium stearate – 4.567 kg

Grinding and Sieving of Calcium Stearate

1. Materials Consumed in the Operation (Total) – Table 4-1

Name of intermediates and raw materials	Assay of active substance, %	Loaded weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Raw material				
Calcium stearate	99.0	4.567	4.52133	–

Total: 4.567 kg

2. Output from the Operation (Total) – Table 4-2

Name of intermediates, wastes and losses	Assay of active substance, %	Received weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Intermediate product				
Calcium stearate, ground and sieved	99.0	4.558	4.51242	–
B. Mechanical losses				
Calcium stearate	99.0	0.009	0.00891	–

Total: 4.567 kg

Operational yield: 99.8 %

Calcium stearate is ground in a GF-14 mill equipped with a 2 mm mesh. Before starting, the cleanliness and serviceability of the mill, the reliability of fastenings and the integrity of the screen are checked. The mill is switched on by pressing the “Start” button. If no extraneous noise is observed, grinding is initiated.

The raw material is fed into the loading opening with a scoop. After completion of grinding, the mill is switched off by pressing the “Stop” button. The grinding quality is visually controlled by the operator. The ground raw material is collected in container E and sent for sieving.

The ground calcium stearate is sieved on a BC-2 vibratory sieve. Before starting, it is necessary to: check the cleanliness of the vibratory sieve, ensure the absence of foreign objects in the sieve housing, test the sieve in idle mode, verify the conformity and correct tension of the mesh, and switch on the supply and exhaust ventilation.

The vibratory sieve is started by pressing the “Start” button. Using a scoop, calcium stearate is fed in small portions into the vibrating screening box. The raw material is passed through a No. 32 mesh. From the hopper, the material enters the sieve, which performs circular oscillations in the horizontal plane and elliptical oscillations in the vertical plane, forcing the particles to move in circular trajectories across the entire screen area. The product passing through the screen falls into radially arranged grooves and then through hoses into the receiving container of the vibratory sieve.

Once a sufficient amount of screened material has accumulated, it is poured from the receiving container into clean containers E. To cool the electric motor, every 40 minutes the vibratory sieve is switched off for 5–10 minutes. After completion of sieving, the sieve is switched off by pressing the “Stop” button. Residues remaining on the screen are collected in a special container and transported to a landfill.

The quality of sieving is checked using a control sieve with mesh No. 32. When the screened product is passed through the control sieve, no residue should remain.

Sieving of Potato Starch

1. Materials Consumed in the Operation (Total) – Table 4-3

Name of raw material	Assay of active substance, %	Loaded weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Raw material				
Potato starch	80.0	19.665	15.732	–

Total: 19.665 kg

2. Output from the Operation (Total) – Table 4-4

Name of intermediates, wastes and losses	Assay of active substance, %	Received weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Intermediate product				
Sieved potato starch	80.0	19.625	15.7	–
B. Mechanical losses				
Potato starch	80.0	0.04	0.032	–

Total: 19.665 kg

Operational yield: 99.8 %

Potato starch is sieved on a BC-2 vibratory sieve. Before starting, the cleanliness of the vibratory sieve, absence of foreign objects in the sieve housing, operation at idle, conformity and tension of the mesh, as well as the functioning of supply and exhaust ventilation, must be checked.

The vibratory sieve is switched on by pressing the “Start” button. Using a scoop, small portions of starch are fed into the vibrating sieve box. Potato starch is passed through a No. 32 mesh. From the hopper, the starch enters the sieve, which performs circular oscillations in the horizontal plane and elliptical oscillations in the vertical plane, forcing the particles to move in circular trajectories over the entire screen area. The product passing through the screen falls into radially arranged grooves and then through hoses enters the receiving container of the vibratory sieve.

When a sufficient quantity of screened material has accumulated, it is poured from the receiving container into clean containers E. To cool the electric motor, every 40 minutes the vibratory sieve is switched off for 5–10 minutes. After completion of sieving, the sieve is switched off by pressing the “Stop” button. Residues remaining on the screen are collected in a special container and transported to a landfill.

The quality of sieving is checked using a control sieve No. 32. When the screened product is passed through the control sieve, no residue should remain.

Grinding and Sieving of Lactose

1. Materials Consumed in the Operation (Total) – Table 4-5

Name of raw material	Assay of active substance, %	Loaded weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Raw material				
Lactose	100.0	30.450	30.450	–

Total: 30.450 kg

2. Output from the Operation (Total) – Table 4-6

Name of intermediates, wastes and losses	Assay of active substance, %	Received weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Intermediate product				
Lactose, ground and sieved	100.0	30.390	30.390	–
B. Mechanical losses				
Lactose	100.0	0.06	0.06	–

Total: 30.450 kg

Operational yield: 99.8 %

Lactose is ground in a GF-14 mill equipped with a 2 mm screen. Prior to operation, the cleanliness of the mill, its serviceability, the reliability of fastenings and the integrity of the screen are checked. The mill is turned on by pressing the “Start” button. If no extraneous noises are detected, grinding is commenced.

The raw material is loaded into the inlet opening with a scoop. After grinding, the mill is switched off by pressing the “Stop” button. The grinding quality is visually assessed by the operator. The ground raw material is collected in container E and sent for sieving.

Sieving of lactose is carried out on a BC-2 vibratory sieve. Before starting, the cleanliness of the vibratory sieve, absence of foreign objects in the sieve housing, operation at idle, conformity and tension of the mesh, and supply and exhaust ventilation are checked.

The vibratory sieve is switched on by pressing the “Start” button. Using a scoop, small portions of lactose are placed into the vibrating sieve box. The raw material is passed through a No. 32 screen. From the hopper, lactose enters the sieve, which performs circular oscillations in the horizontal plane and elliptical oscillations in the vertical plane, forcing the particles to move in circular trajectories across the entire screen area. The product passing through the screen falls into radially arranged grooves and then through hoses enters the receiving container of the vibratory sieve.

Once a sufficient amount of screened material has accumulated, it is poured from the receiving container into clean containers E. To cool the electric motor, every 40 minutes the vibratory sieve is switched off for 5–10 minutes. After completion of sieving, the sieve is switched off by pressing the “Stop” button. Residues left on the screen are collected in a special container and transported to a landfill.

The quality of sieving is checked using a control sieve No. 32. When the screened product is passed through the control sieve, no residue should remain.

Grinding and Sieving of Acyclovir

1. Materials Consumed in the Operation (Total) – Table 4-7

Name of raw material	Assay of active substance, %	Loaded weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Raw material				
Acyclovir	100.0	406.0	406.0	–

Total: 406.0 kg

2. Output from the Operation (Total) – Table 4-8

Name of intermediate losses	Assay of active substance, %	Received weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Intermediate product				
Acyclovir, ground and sieved	100.0	405.188	405.188	–
B. Mechanical losses				
Acyclovir	100.0	0.812	0.812	–

Total: 406.0 kg

Operational yield: 99.2 %

Acyclovir is ground in a GF-14 mill equipped with a screen with 2 mm openings. Before starting, the cleanliness of the mill, its serviceability, the reliability of fastenings and the integrity of the screen are checked. The mill is switched on by pressing the “Start” button. If no extraneous noise is observed, grinding is initiated.

The raw material is fed into the loading opening with a scoop. After completion of grinding, the mill is switched off by pressing the “Stop” button. The grinding quality is visually controlled by the operator. The ground raw material is collected in container E and sent for sieving.

Acyclovir is sieved on a BC-2 vibratory sieve. Before starting, it is necessary to check the cleanliness of the sieve, ensure the absence of foreign objects in the sieve housing, test it in idle mode, verify the conformity and correct tension of the mesh, and switch on the supply and exhaust ventilation.

The vibratory sieve is switched on by pressing the “Start” button. Using a scoop, acyclovir is fed in small portions into the vibrating sieve box. The raw material is passed through a No. 32 mesh. From the hopper, acyclovir enters the sieve, which performs circular oscillations in the horizontal plane and elliptical oscillations in the vertical plane, forcing the particles to move in circular trajectories over the entire screen area. The product passing through the screen falls into radially arranged grooves and then through hoses enters the receiving container of the vibratory sieve.

When a sufficient amount of screened material has accumulated, it is poured from the receiving container into clean containers E. To cool the electric motor, every 40 minutes the vibratory sieve is switched off for 5–10 minutes. After completion of sieving, the sieve is switched off by pressing the “Stop” button. Residues remaining on the screen are collected in a special container and transported to a landfill.

The quality of sieving is checked using a control sieve No. 32. When the screened product is passed through the control sieve, no residue should remain.

Drying of Potato Starch

1. Materials Consumed in the Operation (Total) – Table 4-9

Name of intermediates and raw materials	Assay of active substance, %	Loaded weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Raw material				
Sieved potato starch	80.0	19.625	15.7	–

Total: 19.625 kg

2. Output from the Operation (Total) – Table 4-10

Name of intermediates, wastes and losses	Assay of active substance, %	Received weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Intermediate product				
Potato starch, sieved and dried	97.0	16.28875	15.80009	–
B. Mechanical losses				
Atmospheric moisture	–	3.33625	–	–

Total: 19.625 kg

Operational yield: 83.0 %

Potato starch is dried in an SSH-6 drying oven. Before starting, it is necessary to check the cleanliness of the drying chamber, the operation of the fans, the correct placement of the shelves, and to prepare clean, dry trays.

Using a scoop, the calculated amount of potato starch with 20 % moisture content is spread on a tray in a uniform layer 2–3 cm thick, placed into the drying oven and the chamber is filled from bottom to top, after which the oven doors are closed. The fan is then switched on to supply hot air to the drying chamber. The drying temperature is set on the instrument display mounted on the oven housing and is maintained at 100–110 °C for 2–3 hours.

One and a half hours after the start of drying, the mass is mixed with a spatula; for this time the fan is switched off. Protective gloves are used to prevent burns. The drying parameters are recorded by the operator in the loading and operation journal. The dried starch is poured into

clean containers E, unloading the drying chamber from bottom to top. This is performed with supply and exhaust ventilation switched on and using gloves. Part of the dried starch is subsequently used in operation TP 1.4 “Dusting”.

Preparation of Starch Paste

1. Materials Consumed in the Operation (Total) – Table 4-11

Name of intermediates and raw materials	Assay of active substance, %	Loaded weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Intermediate product				
Potato starch, dried and sieved	97.0	2.5	2.425	–
B. Raw material				
Purified water	–	47.5	–	–

Total: 50.0 kg

2. Output from the Operation (Total) – Table 4-12

Name of intermediates, wastes and losses	Assay of active substance, %	Received weight, kg	Volume, L	Amount as 100 % active (calculated)
A. Intermediate product				
Starch paste, including:		49.9	24.95	2.42015
– Potato starch (5.0 %)	97.0	–	–	–
B. Mechanical losses				
Starch paste, including:		0.1	0.005	0.00485
– Potato starch (5.0 %)	97.0	–	–	–

Total: 50.0 kg

Operational yield: 99.8 %

Starch paste is prepared in a stainless steel vessel E-2. The preparation is carried out as follows: the calculated amount (2.5 kg) of dried and sieved potato starch is weighed and poured into vessel E-2; approximately one third of the calculated volume of water (16.0 L), preheated to 30–35 °C, is added, and the suspension is stirred until homogeneous. In another stainless steel vessel E-2, the remaining volume of water is heated to 70–80 °C, after which the prepared starch suspension is slowly added with continuous stirring; the mixture is brought to a boil and then cooled.

The operation is monitored by a responsible specialist. The mass of potato starch and the volume of water are recorded by the specialist in the loading and operation journal.

Conclusion

The studies conducted on the production of a newly formulated acyclovir tablet have shown that technological factors in the stages of preparation of raw materials and excipients, as well as their processing into intermediates, are of critical importance. It has been established that changes in the physical and chemical properties of acyclovir, its sensitivity to moisture and particle size directly affect the flowability, compressibility and stability of the blend. By evaluating the technological characteristics of auxiliary components, optimal ratios were selected that ensure both the pharmacological activity and the technological adaptability of the new formulation.

The efficiency of preparatory stages such as sieving, drying and homogenization proved to be a decisive factor in achieving uniform distribution within the blend and in forming stable granules. Optimal parameters for granulation and mixing processes were determined, and their influence on the final quality characteristics of the product was investigated. The moisture content, density and granule strength of the intermediate product were defined as the main criteria ensuring the stability and quality of the final tablet.

Overall, the results of the study made it possible to develop an effective, technologically convenient and stable new formulation for acyclovir tablets and confirmed that every stage of the production process plays an important role in quality control.

REFERENCES:

1. O'z DSt 2766:2018. Yaxshi ishlab chiqarish amaliyoti (GMP).
2. Steril bo'lmagan dori vositalarini ishlab chiqarish, saqlash va tashish jarayonida mikrobial ifloslanishning oldini olish bo'yicha me'yoriy hujjatlar (yo'riqnomalar) to'plami. RDI 64-28-84, RDI 64-29-84, RDI 64-30-84, RDI 64-31-84.
3. O'z RH 19-06:2003. Steril bo'lmagan dorivor mahsulotlarni ishlab chiqarish uchun binolarni havodagi mikroorganizmlar tarkibiga qarab tasniflash.
4. ONTP 24-86 texnologik dizayn uchun sanoat standartlari.
5. Sanoat korxonalarini uchun yong'in xavfsizligi standart qoidalari. Moskva 1976 r.,.
6. Tibbiyot sanoatida qo'llaniladigan dori vositalari, ularning yarim tayyor mahsulotlari, xom ashyo va aralashmalarning yong'in va portlash xavfi. General ostida. N. I. Shustrov tomonidan tahrirlangan. Kupavna, 1984 r.
7. Portlash va yong'in xavfli kimyo, neft-kimyo va neftni qayta ishlash sanoatida portlash xavfsizligining umumiy qoidalari . OPVB-99.
8. Moddalar va materiallarning yong'in xavfi va ularni o'chirish vositalari. 2 ta kitobda ma'lumotnoma nashri. A. N. Baratov, A. Ya Korolchenko, G. N. Kravchuk, va boshqalar 1990r.
9. Elektr o'rnatish qoidalari - PUE. Davlat energetika nazorati xizmati .
10. Iste'molchilarning elektr qurilmalarini ishlatishda xavfsizlik qoidalari, Davlat energetika nazorati xizmati . "Atrof-muhitdagi kimyoviy moddalarning ruxsat etilgan maksimal konsentratsiyasi" nashri. Bespamyatny G.P.