SECTION 3. PHARMACY

10.46299/ISG.2022.MONO.MED.3.3.1

3.1 Some aspects of the production technology of medicinal products in the form of suppositors

Unlike conventional inert pharmacological media, the base for suppositories at different stages of production and distribution of the drug must perform various additional functions. Therefore, a successful choice of foundation should be based on the requirements outlined below. At various stages of suppository development, the inertness characteristics of the base determine the relative success or failure of the final pharmacological agent [249, 250].

Production process. Descent (shrinkage). A slight slope of the substrate during curing and solidification is a desirable property because it facilitates separation from the mold.

Inertia. It is clear that the base should not enter into chemical reactions with the active ingredients.

Assertion. It is necessary to choose the optimal time interval between melting and solidification, because too fast solidification of the melt will create difficulties in feeding the mixture into the molds, and too slow - will reduce production productivity.

Viscosity. If the viscosity is insufficient, the dispersed components of the mixture will precipitate, which will worsen the uniformity of the distribution of the active substance in the final pharmaceutical preparation.

Storage process. Microbiological purity. Contamination by bacteria and fungi can be minimized by properly selecting a non-nutritive base with a minimum water content.

Softening. The formulation of the suppository should be selected in such a way as to exclude the possibility of its softening or melting under the expected conditions of storage and transportation.

Stability. The materials selected for the manufacture of the suppository should not oxidize under the influence of air, humidity or light.

The absorption process. Release The correct choice of the base ensures optimal delivery of the dispersed active substance to the desired target in the body.

Portability. A ready-to-use suppository should have minimal (or no) toxicity and should not cause irritation.

According to the composition of the base, suppositories are divided into three categories: natural, synthetic and "semi-synthetic" [251, 252].

Natural bases. Today, almost all natural bases for suppositories are made from cocoa butter, which consists of a mixture of triglycerides of saturated and unsaturated fatty acids, obtained from roasted cocoa fruits Theobroma cacao Linn [253]. About 97% of fatty acids are unsaturated, mainly oleic (mainly oleopalmitostearic - more than 50%) and oleodistearic (about 25%) acids. Since cocoa butter contains only triglycerides, it does not have a hydroxyl number, and the presence of ethylene bonds causes an iodine number of about 35.

Benefits. Cocoa butter is well tolerated by patients. This filler, when melted, provides a quick release of the active substance dispersed in it. This basis is widely used and has accumulated a long experience of its safe use.

Disadvantages. Cocoa butter does not mix with human body fluids. This prevents the release of lipophilic substances from suppositories based on cocoa butter. In addition, cocoa butter has a fairly high tendency to oxidation due to the content of up to 3% of unsaturated fatty acids, which leads to the possibility of the base becoming bitter. Due to the low curing temperature, the active ingredient may precipitate. When using active ingredients in the form of a suspension, it is not possible to achieve homogeneity of the suppository due to the polymorphism inherent in certain components of cocoa butter, which can cause changes in the crystal structure over time. Since different crystalline forms have different melting points, this affects the hardening process and increases the risk of precipitation of the active substance.

Synthetic bases. Due to the shortcomings of cocoa butter, new bases with improved characteristics were developed. Derived generally from petrochemical derivatives of fractionated fatty alcohols, synthetic bases do not have many of the disadvantages of all-natural bases. The main advantage of this group of bases is the

content of mixtures of polyethylene glycols (PEG), the melting point of which exceeds the internal temperature of the human body.

Benefits. In these bases, the release of active substances is a function of dissolution rather than melting of the base. This makes it possible to effectively solve the problems of production, transportation and storage arising in the temperature range of the surrounding environment.

Disadvantages. The higher range of melting temperatures of these bases must be taken into account when choosing the heat-sensitive active substances of the suppository.

Another problem with synthetic bases is the potential effect of delaying the release of active pharmaceutical ingredients. This effect is especially pronounced in the case of a high content of PEG with a high molecular weight, which can cause the accumulation of medicinal substances. Since the release properties of the medicinal substance are determined by the dissolution of the base, additional measures are necessary for the proper release of the active ingredient from the base. So, before the introduction of such suppositories, it is sometimes recommended to moisten with water [254, 255]. This also applies to the ability of such bases to cause local irritation. In fact, one of the main reasons for rejecting PEG-based suppositories is their inherent risk of traumatizing sensitive tissue.

Semi-synthetic bases. These auxiliary substances are made from vegetable fats and oils that undergo chemical modification during the production process. These reactions make it possible to obtain at the output products with controlled characteristics, which are required for the manufacture of suppositories. The relative water-oil solubility makes it possible to create substances with melting temperature ranges that precisely meet specific specific requirements. Examples of semi-synthetic suppository bases include Novata, Suppocire, Wecobee and Witepsol.

Benefits. The production of semi-synthetic suppository bases by transesterification ensures the preservation of a greater number of short and medium-chain fatty acids (for example, from C 6 to C 10, which at ambient temperatures are usually in a liquid state) than with esterification, which makes the final product more

elastic. This facilitates production (since the suppository is soft and after production is not prone to cracking), but perhaps a more important advantage is their ease of use and more careful adherence by patients to therapeutic prescriptions. Also, the advantage of such bases is their better stability due to a significant weakening of the phenomenon of hardening after production. Also, the bases made by transesterification of vegetable fats and oils have a lower irritant potential (chemical) and the ability to damage (mechanical) the sensitive mucous membrane.

Disadvantages. As in the case of cocoa butter, the active ingredients are released when the base melts. Therefore, a very low melting point is required, which necessitates precautions against damage to the final product during transportation and storage [256].

Hydrogels are macromolecular structures that do not dissolve in water, but swell. The swelling of hydrogels, that is, the absorption of water, occurs due to the presence of hydrophilic functional groups in the polymer structure. The insolubility of hydrogels in water is the result of crosslinks between neighboring macromolecules. The use of a hydrogel matrix for the production of drug delivery means consists of its dispersion in the matrix and subsequent drying of the system with simultaneous fixation of the medicinal substance. After the drug on such a basis enters the aqueous medium, the hydrogel swells and the diffusion of the medicinal substance from the macromolecular structure begins. The speed and degree of release of the medicinal substance from the hydrogel matrices are determined by the dynamic processes of water migration to the matrix and the diffusion of the medicinal substance from the swollen matrix. Although the industry has not yet produced drug delivery systems based on hydrogels in the form of suppositories or other similar forms, intensive research in this direction is ongoing. It is a very attractive opportunity for manufacturers to obtain a basis for controlled drug delivery based on hydrogel matrices due to the ability of hydrogels to bioadhesion and retention at the site of administration [257].

Selection criteria. In order to choose the most suitable base for the drug, an assessment of the physicochemical characteristics of the fillers is necessary. These parameters affect the chemical stability of the finished drug, as well as the release from

the base and subsequent bioavailability of the active substance. The most important values are the melting point, the iodine number and the hydroxyl number (for hydrophobic bases). These evaluations and measurements are widely used in the pharmaceutical industry for a wide range of applications, so their discussion will be limited to those aspects relevant to the choice of suppository base [258].

Range of melting temperatures. Melting point specifications for suppository bases (especially fatty ones) do not specify a single melting point value, but a range of temperatures. This practice is due not to a control error, but to the presence of a temperature range of transitions between stable and unstable forms or polymorphism. When choosing a base based on the melting point, it is necessary to consider that the temperature range proposed by the manufacturer should provide flexibility in working with this active ingredient and meet specific therapeutic requirements.

Iodine number. For certain LFs, the main problem can be rancidity (oxidation) of the base of the suppository. To avoid these problems, bases with iodine number less than 3 are widely used.

Hydroxyl number. The hydroxyl number depends on the content of mono- and diglycerides in a certain substance, and this number shows the relative rate of crystallization. In general, a lower hydroxyl number allows to increase the speed of suppository production. In addition, materials with a lower hydroxyl number provide better stability of active substances that are sensitive to the presence of a hydroxyl group.

Ratio of components. In addition to the correct choice of fillers, it is necessary to establish their proper ratio. In general, it is advisable to use a higher excipient/active agent ratio because it improves the dispersion of the active ingredient in the suppository and facilitates the release of the active ingredient after administration of the suppository.

Selection of excipients. The addition of individual auxiliary materials makes it possible to significantly improve various aspects of the development and production of suppositories. With the help of the correct selection of these substances, it is possible to increase the homogeneity of the final preparation, increase the dissolution of active

substances in a particular base, facilitate the performance of various technological operations, increase the speed and productivity of production, and so on. In general, auxiliary substances are selected to solve the following tasks [259]:

Facilitating the joining of powder components. A high content of active ingredients in powder form can negatively affect the integrity of the suppository, cause an excessive increase in the viscosity of the melt, which in turn will make it difficult to pour the mass into forms. There are a large number of agents that can help in this situation, some of which are included in the base itself.

Increase in hydrophilicity. The use of excipients affecting hydrophilicity requires caution. The addition of some substances (including those listed below) facilitates the dissolution of the drug in the rectum. However, these substances can negatively affect the absorption of the active substance. In general, when used in low concentrations, these substances enhance absorption, and at high levels - weaken it. And finally, one more warning: some researchers believe that these substances can cause local irritation. Examples of such excipients:

Anionic surfactants (surfactants) - bile salts, calcium oleate, cetyl stearyl alcohol plus 10% sodium alkyl sulfate, sodium dioctyl sulfosuccinate, sodium lauryl sulfate (1%), sodium stearate (1%), and triethanolamine stearate (3% - 5%).

Nonionic and amphoteric surfactants. Esters of sorbitol and fatty acids (Span Arlacel), ethoxylated esters of sorbitol and fatty acids (Tween), ethoxylated ethers and ethers (polyethylene glycol 400 myristate, polyethylene glycol 400 stearate, polyethylene glycol esters of fatty alcohols).

Incomplete glycerides. Mono- and diglycerides (Atmul 84, glycerol monostearate and glycerol monooleate, mono- and diglycerides of stearic and palmitic acids).

To improve viscosity. Viscosity control during solidification of the molten suppository is very important in cases where it is necessary to prevent precipitation. Although cocoa butter is mainly used in these circumstances, viscosity-increasing materials on semi-synthetic bases are also of practical value. In addition to improving

viscosity, these bases also alter the melting range and lower melting point in the desired direction.

Fatty acids and their derivatives. Aluminum monostearate, glycerol monostearate, stearic acid.

Fatty alcohols. Cetyl, myristyl and stearyl alcohols.

Inert powders. Bentonite, colloidal silicon dioxide.

To change the melting point. Sometimes it is required to change the melting point of the suppository mass to facilitate production and to obtain the desired properties of the final drug. In addition, certain active ingredients, such as procaine base, phenols, chloral, and essential oils, lower the melting point to a point where the risk of damage to the drug during storage and transportation increases significantly. Therefore, melting point modulators are used, especially in recipes based on cocoa butter. However, the melting temperature modulators themselves can also cause certain difficulties, which requires caution in their use. In particular, the crystallinity of most of the substances listed below is very different from the crystallinity of glycerides, which are often included in suppositories, and this can contribute to the appearance of defects on the surface of the final suppositories. At the same time, the effectiveness of these materials may depend on their quantity in the composition of the drug. Therefore, in cases where it is necessary to adjust the melting point of the base, often the simplest solution is to use a semi-synthetic base with the desired melting point.

To change the melting point, the following auxiliary substances are used: fatty acids and their derivatives (glycerol stearate and stearic acid), fatty alcohols (cetyl alcohol and cetylstearyl alcohol), hydrocarbons (paraffin) and wax (beeswax or carnauba).

To increase mechanical strength. Fragility of suppositories is a common problem with synthetic bases (cocoa butter and semi-synthetic bases are less fragile and therefore less likely to crumble and irritate the rectal mucosa with solid particles). To solve this problem, various special agents are added to synthetic bases, in particular: polysorbates, castor oil, monoglycerides of fatty acids, glycerin or propylene glycol.

Improving appearance. Although generally discouraged, dyes may be added to suppository bases for a number of purposes. They can be used both for psychological reasons (to mask an unpleasant appearance or to obtain a placebo identical to the active drug), and for practical purposes (for example, to ensure the same color of a batch of products). Color coding of various drugs is often required, especially in hospital pharmacies, also dyes make it possible to hide manufacturing defects, such as crystallization or separation on the surface of the drug. Water-soluble, fat-soluble and insoluble dyes can be used for coloring suppositories.

To prevent schedule. If the suppository contains plant materials or moisture (which is more common), antimicrobial and antifungal agents become especially important. For aqueous solutions with a pH of less than 6, sorbic acid or its salts are used. Parahydroxybenzoates or sodium salts are used to reduce pH. However, the potential ability of these materials to cause rectal irritation should be considered.

Antioxidants such as butylated hydroxytoluene and butylated hydroxyanisole can be successfully used to increase shelf life by solving the rancidity problem inherent in cocoa butter-based formulations.

To adjust suction. If the drug is characterized by poor absorption, sometimes agents are used to correct the absorption of the active substance. To increase the bioavailability of the active ingredients of suppositories, many such activators are offered today (and even more new such substances are still being researched) [260].

Before starting a discussion on the production of suppositories, it is necessary to consider what polymorphism actually is. In general, for all fat-based fillers, polymorphism is a characteristic of materials existing in different crystalline states and a function of the natural aging process. Therefore, this issue must be considered and evaluated at the stage of developing the suppository formulation. Semi-synthetic and natural glycerides show complex thermal behavior. This behavior is determined by the characteristics of each glyceride component of the mixture with, usually, a relatively large amount of glycerides in the composition of the mixture. In general, these changes are manifested by an increase in the melting point during storage of the material. Such

an increase in the melting temperature is more intense at a higher storage temperature and can reach a value when the suppository is completely softened. At this temperature value, the drug can be considered as having undergone "factory processing". After that, the process of changes begins again, as in newly produced drugs. Such growth is more intense at a higher initial melting time of the base.

In addition to an increase in the melting temperature during aging, an increase in the hardness of the suppository mass may also occur. It is believed that this effect is the result of several factors, which in some cases can be prevented by the addition of certain excipients, such as soy lecithin. These phenomena are the result of changes in the fatty materials included in the composition of the suppository during the transition from an unstable to a stable crystalline form. The speed of this process is a direct function of the temperature of the material after production; the higher the storage temperature (and, accordingly, the closer it is to the melting point), the faster the transformation rate will be.

The goal of any production process is to obtain a stable final product. In this case, this goal is achieved by accelerating the rate of polymorphic transformation by storing suppositories at a temperature approximately 3 °C lower than the theoretical melting temperature. This process of accelerated aging, or as it is now called "hardening", is an important step in the production of this dosage form, and it requires a non-destructive measurement of the melting temperature (for example, by the P-tube method). The polymorphism can also cause numerous production defects, the most prominent of which are fatty plaque and whitishness. Fatty plaque appears as clouding of the surface of the suppository, and examination under a microscope shows the release of fatty acid chains.

Measurement of changes in melting point during storage allows for assessment of the effect of active ingredients on the base. This effect, depending on the relative solubility (or insolubility) of the active substances in the base, can strengthen or weaken polymorphic changes [261].

Theoretical bases of suppository production. It is clear that in order to achieve maximum efficiency and productivity of suppository production, maximum efforts are

made to avoid all possible obstacles. With a proper understanding of certain physical principles of production, most potential problems can be at least minimized. Processes that are extremely important for the production of suppositories are melting, mixing or sequential addition of components, feeding the molten mass and solidification [262].

Melting. In general, the production of suppositories requires the melting of most, if not all, components of the formulation. The equation for the rate of melting of a solid material in contact with the same material in a molten state can be obtained by simultaneously considering the heat transfer and mass values in a two-phase system. The change in size or linear size and, accordingly, the change in the cube root of the mass of a solid material of a given geometric shape during a steady state of melting, has a linear dependence on time. So:

$$L = -m\,\Theta + L_0; \quad (1)$$

and

$$W^{1/3} = -m'\Theta + W_0^{1/3}; \quad (1)$$

where: W_0 i L_0 – is the initial mass and size of the solid;

Θ – respectively, is time;

m i m' – this is the value of the slope of the linear equations.

Let's extend this equation to the case of melting a certain number of particles N, and denote the total mass and area of the particles by W and A, respectively:

$$W = N\rho bL^3; \quad (3)$$

and

$$A = NeL^2; \quad (4)$$

where: ρ - is the density [g sm^{-3}];

b – is the ratio of the shape to the volume;

e – shape factor relative to area.

then:

$$[W/N]^{1/3} = –me + [W_0/N]^{l/3}; \quad (5)$$

When the substance is completely melted, W and L are equal to zero, which makes it possible to calculate the melting time using the two equations given above.

The heat flow q in the tank with a stirrer will mainly depend on the heat transfer coefficient U, the heat transfer area A, and the temperature difference ($\Theta_0 - \Theta_i$) between the melt and the heat carrier, i.e. the liquid layer that is in direct contact with the heat transfer surface:

$$q = UA(\Theta_0 - \Theta_i); \quad (6)$$

The heat transfer coefficient depends on the geometric and technological parameters. The heat transfer area (A) of contact with the melt depends on the geometry and the heat transfer surface. The temperature difference is mainly controlled by the corresponding operating modes. The heat transfer coefficient U can be described in terms of three heat transfer processes: the first is the coefficient of the middle layer, h_i, which describes the efficiency of heat transfer through the melt layer from the melting surface of the tank or reactor wall; the second - describes the state of heat transfer through the walls; and the third - reflects the efficiency of heat transfer from the outer wall of the tank. The coefficient of the middle layer, h_i, covers the convective and heat conduction effects in the melt directly contacting the heat transfer surface.

In fact, the temperature distribution in the reservoir is a function of relative thermal conductivity and momentum. Given the need for significant processing times in large-batch production, mass production is associated with additional challenges due to time-dependent temperature transformations of the molecular structure. If we take into account the problems associated with the different chemical and physical composition of bases produced by industry, the presence of polymorphs, different degrees of crystallinity, polytypism, wide and narrow ranges of molecular weights, as well as the mutual influence of time and temperature effects, it is clear that the problems of mass production there could be many more suppositories.

Mixing or sequential addition of components. The task of the process of mixing or sequential addition of components is to obtain a homogeneous mixture and maintain it in a homogeneous state. Non-Newtonian systems are quite problematic, which is connected, in particular, with ensuring uniformity of mixing in the tank, especially in the presence of solid materials. The intensity of shaking and the speed of rotation of the blades to ensure complete homogeneity throughout the volume of the tank, as well as the completeness of the "bottom suspension" of the entire mixture increases exponentially with the viscosity of the suppository melt. However, if at too high a stirring speed during mixing or sequential addition of components, churning or bubbling occurs, incomplete mixing or air entrapment can cause melt inhomogeneity, reducing oxidative stability.

For the same melt viscosity, buckling occurs more often in large tanks than in small ones. The higher the viscosity of the melt, the less prone to spalling or bubbling. Also, upwelling and bubbling occur more often in tanks without baffles than in baffled tanks. Since in factories where experimental batches of products are manufactured, equipment without partitions is mainly used, for the mass production of suppositories, it may be necessary to install partitions in the tanks to ensure the homogeneity of the mixture and minimal air entrainment. The presence of solid particles in the melt can also significantly complicate the matter. For a turbine blade, the homogeneity of the suspension is described by the ratio:

$$(D/T)^{1.5}; \quad (7)$$

where: D - is the blade diameter;

T - is the diameter of the tank.

Therefore, the larger the relative sizes of the blades, the better the production results [263]. After analyzing the features of the mass production of products from viscoplastic plastics, a reliable correlation was established with the blade tip speed, blade diameter, and flow rate.

Other complications may arise due to centrifugal effects near the stirrer blade and the complexity of the types of flow caused by the blade, due to which the blade

"does not notice" the viscosity and density of the melt in the immediate vicinity. In addition, insufficient homogeneity can lead to increased temperature fluctuations, which beyond a certain limit can cause changes in density and composition: mass production simulations and evaluations that do not take into account changes during processing or holding time can give unreliable results [264].

Supply of molten mass. The issue of supplying the molten mass of the suppository from the mixing or storage tanks to the filling line or to the injector, or from the injector to the mold, becomes especially difficult for non-Newtonian melts. In some cases, engineers need to determine the optimal size of pipelines for a given flow in accordance with fluid requirements.

It should be taken into account that the presence of suspended solid particles (LR or suppository base) can significantly complicate the rheological behavior and transport properties of the melt of the suppository mass. This is due to interactions both between the particles themselves and between the particles and the melt.

Also, when considering the mass production of suppositories, it is worth paying attention to practicality - if the rheological behavior of melts is similar to viscoplastic bodies or non-Newtonian fluids, the risk of uneven distribution increases, and this will require maintaining different temperatures in capillaries, nozzles and pipelines [265, 266].

Assertion. Recently, specialists generally studied the negative aspects of cocoa butter polymorphism: when heated to a temperature of about 40°C, all polymorphic forms of this substance melt.

Upon rapid cooling of melts of suppositories in molds to a temperature below 15 °C, crystallization occurs in the γ form. When the form is gradually heated to room temperature, a sequential transformation of the γ polymorph into the α form begins with 22 °C, then in the β’ form with with the melting point 28 °C and into the finally stable β form with with the melting point 34.5 °C. The suppositories obtained in this way consist of an unstable mixture of polymorphs that melt at room temperature. With slower cooling of the melt, the formed polymorph γ turns into a stable β form and a material stable at room temperature is formed. This classic example of the importance

of polymorphism for fat-based suppositories is a clear demonstration of the effect of not only temperature but also cooling rate on crystallization form.

Formal analysis of the solidification process begins with the study of heat transfer from the flow to the surface of the solid. The rate of heat flow along the liquid-solid interface depends on the temperature difference between the two phases and the contact area:

$$q = -hA\Delta; \quad (8)$$

where: q – is the heat transfer rate along the contact area A;

Δ – is the temperature difference between the two phases;

h – is the proportionality coefficient, which corresponds to the heat transfer coefficient.

This equation is also called Newton's law of cooling.It is necessary to determine in advance the requirements for suppository recipes, regarding the time, temperature and speed of hardening. Modeling the temperature distribution in the cavities of the molds for non-Newtonian fluids makes it possible to state that such assessments are expedient to perform during mass production [267].

In recent years, domestic manufacturers in Ukraine have been gradually losing many segments of the domestic goods market, which is associated with significant structural deformations in the national economy and the low competitiveness of enterprises in the conditions of an open economy. The imbalance of demand, the high cost of drug production, its relatively low technological level and outdated infrastructure cause a persistent tendency to exceed the volume of imports of goods compared to their exports.