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Development of a Derivative of 1,4-Dihydropyridine Gels Using Solid Dispersion Technique

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***Abstract*—A method has been developed for obtaining samples of a derivative of 1,4-dihydropyridine-nifedipine gels using the solid dispersion technique. A quality assessment of the obtained soft dosage forms has been performed. The effectiveness of the proposed technique for obtaining nifedipine gels has been proved, which makes it possible to increase the pharmaceutical availability of the poorly water soluble investigational substance, providing better release by increasing its solubility and dissolution rate.**

Keywords—nifedipine, solid dispersions, gel, polyethylene glycol

I. INTRODUCTION

In the process of developing and improving the technology for the manufacture of dosage forms (DF), it is important to have a prudent approach for optimizing such biopharmaceutical characteristics as the solubility and rate of release of the pharmaceutical substance (FS). For the purpose of improving the physicochemical properties of the poorly water soluble FS, a technique for introducing PS into solid dispersions (SD) is currently relevant and promising. SD represent nano-dispersed or colloid-dispersed systems of a bicomponent or polycomponent composition of a highly dispersed phase of FS in the matrix of a carrier or solid solutions with partial formation of variable composition structural complexes with the material of a carrier [1-3]. The technique for obtaining SD makes it possible to optimize the release of FS from the DF, which contributes to influence positively on the indicators of pharmacokinetics and pharmacodynamics of the FS, to ensure the possibility to correct organoleptic properties (taste, odour and colour), to increase the stability of the pharmaceutical drug during storage, as well as to enhance the resistance of the drug to the influence of environmental factors (temperature, humidity, light, oxidizing agents). In addition, the application of the SD technique makes it possible to improve the pharmaceutical technology due to the following: modification of physical and chemical characteristics of the FS (change of the aggregative state due to a phase transition), possibility to combine chemically incompatible substances in the same DF, and possibility to create a new DF for the given FS.

Gels are a soft dosage form (SDF) for local or resorptive administration, which represents monophase, biphase or polyphase disperse systems with a liquid dispersion medium, which are formed in the consequence of a loss of fluidity and an increase in viscosity due to the formation of bonds between the macromolecules or colloidal particles of polymeric substances, which forms a gel net, the cells of which are filled with a solvent medium [4]. Water-based gels have a number of advantages over other SDF in the following aspects: possibility to administer the FS in a dissolved state, ensuring the achievement of the desired pH value through the use of a neutralizer, absence of risks of DF stratification during storage, ease of use (they are easily

washed off without leaving greasy stains). Gels are widely used in various fields of medicine due to the possibility of introduction into the composition of mutually reacting substances, relative ease and safety of use in comparison with other (injectable, oral) DF, as well as due to ease of transportation and storage. A calcium channel blocker, nifedipine, is a synthetic derivative of 1,4-dihydropyridine. The investigational FS has mainly hypotensive, vasodilating and antianginal therapeutic effects. In its physical properties, the FS is an odourless yellow crystalline powder, which is readily soluble in acetone, sparingly soluble in 96% alcohol, and practically insoluble in water. Melting temperature is 171-175°C.

It is known that pathogenesis of the anal fissure is conditioned by the spasm of the internal anal sphincter. Nifedipine prevents the transport of calcium ions into the cells and thereby reduces the anal sphincter tone [5]. Extremely low water solubility, which can considerably reduce the therapeutic effect of the FS in the application of the SDF, is a material factor, which limits the application of the investigational FS.

The objective of this study is to develop the technology and composition of the SDF containing the SD of nifedipine with improved biopharmaceutical and physical and chemical properties, is an urgent problem of modern pharmacy.

II. EXPERIMENTAL

Nifedipine (Unique Chemicals, India) was used in the work as a study subject. A polymer, polyethylene glycol (PEG), with a molecular weight of 400 (Merck, Germany), was used as SD carriers.

Low water solubility of the FS was one of the adverse factors, influencing the technology. In this connection, the FS was introduced into the composition of the gels in the form of a SD with polymers. The peculiarity of the developed gel technology is the absence of a separate technological stage for obtaining the SD itself, requiring the standardization and quality assessment of the intermediate product. In the proposed technological scheme, the SD are obtained immediately at the moment the components were introduced into the base.

The manufacturing technology of gel samples of this FS in various ratios of the components of the base is as follows. A gelling agent was pre-soaked in purified water for 1 h for swelling. A modern and prospective lightly cross-linked acrylic acid polymer, Carbopol 2020 (Carbopol® 2020 NF Polymer, India), used in the pharmaceutical industry, was used. Subsequently, a neutralizing agent – triethanolamine (TEA) aqueous solution (BASF, Germany) – was added to the swollen structure-forming agent for the formation of a gel structure. It is the neutralization of the systems by amines, such as TEA, makes it possible to obtain a gel with substantially constant rheological parameters in a wide range of pH values. The FS was dissolved in PEG-400 at a temperature of 40±2°C, while obtaining the SD. Then the obtained SD (nifedipine solution in PEG-400) was introduced into the previously obtained gel and was mixed until a homogeneous SDF of nifedipine was formed. In this way, gels were manufactured for further study, the compositions of which are given in Table I.

TABLE I. COMPOSITION OF DEVELOPED GELS (PER 100 G)

Ingredient		Composition № 1	Composition № 2	Composition № 3	Composition № 4	Composition № 5
Nifedipine		0.2	0.2	0.2	0.2	0.2
PEG-400		64.7	60.9	52.6	43.9	35.1
TEA solution	**Purified water**	8.0	8.0	8.0	8.0	8.0
	TEA	0.4	0.4	0.4	0.4	0.4
Gel base	**Purified water**	26.2	30.0	38.3	47.0	55.8
	Carbopol	0.5	0.5	0.5	0.5	0.5

The quality of the obtained gels was assessed based on the following indicators: description, authenticity, quantitative determination of the FS content, pH value, release.

The authenticity of nifedipine was identified by means of ultraviolet (UV) spectrophotometry and qualitative reactions. In terms of characteristic peaks, UV spectra of aqueous extracts of gels in a range of 190 to 500 nm should comply with the standard of nifedipine: absorption maximum at 340±2 nm, and absorption minimum at 282±2 nm.

A qualitative reaction to the FS is based on orange-red staining in the interaction with a sodium hydroxide solution. For this purpose, the investigational sample – a test portion (2.0 g) of the developed SDF – is shaken in 50 ml of water and filtered through a paper filter. 10 ml is taken from the obtained solution and mixed with 5 ml of a 0.1 M of a sodium hydroxide solution.

To assess the rate and fullness of release of the FS from the developed SDF, Kruvchinsky's method (equilibrium dialysis through a membrane made of unlacquered cellophane) [references 8, 58, 76] was used. During the experiment, a test portion (2.0 g) of the investigational SDF was applied in an even layer to a 40 μm thick membrane made of unlacquered cellophane at the same time, the membrane was fixed immovably at the end of a hollow dialysis tube. The area of the dialysis surface was 5.90±0.19 cm^2. The tube with a membrane was lowered (4-5 mm) into the dialysis medium – purified water. The incubation temperature was 36±1°C. During 6 hours, dialysate samples in a volume of 5 ml were taken every hour, while the initial volume of the dialysate (30 ml) was restored using purified water. The quantitative content of the FS in the taken sample was identified using the UV spectrophotometry method. Where appropriate, samples were diluted and absorption (A) was measured at the wavelength corresponding to nifedipine (340±2 nm). The experiment was performed in 3 replicates (n=3), using three test portions of the investigational SDF of the same sample. Due to unavailability of SDF of nifedipine in the pharmaceutical market, a hydrophobic nifedipine ointment (manufactured according to the standard technology for low soluble FS – by colour trituration of a calculated amount of this FS with Vaseline) was used as a reference ointment. This ointment is prepared using the following technology: 0.2 g of nifedipine is mixed with Vaseline in an amount of 99.8 g until a homogeneous mixture is obtained. This ointment is a suspension ointment.

Structural and mechanical parameters were studied on a coaxial rotational viscometer (Lamy Rheology RM 200,

France); Rheomatic Software was used. During the experiment, the following measurement system was used: ms din 33 and ms din 11 "cylinder-in-cylinder" (cell volume: 17 and 32 ml, correspondingly), designed to measure samples with different viscosity. Dynamic viscosity was studied according to the "low shear – high shear – low shear" scheme, in two shear rate ranges – from 0 to 10 s^{-1} and from 0 to 300 s^{-1}. The study temperature was 20°C, which corresponds to the storage conditions. To predict the behaviour of the gels in the process of application, structural and mechanical characteristics were studied at a temperature of 37°C at low shear rates. As a result of the experiment, rheograms were obtained, showing a dependence of the shear stress on the shear rate gradient for the samples of nifedipine gel, i.e. the so-called "hysteresis loops", which are represented as destruction and restoration lines. The destruction of the gel structure, described by the ascending curve, takes place due to mechanical impact on the system, in consequence of which the structural viscosity is reduced. The restoration curve characterizes a certain equilibrium condition of the system after the destruction. Based on the area of the loop, one can assess the mechanical stability of structured systems.

The aggregative stability was studied by centrifugation of the investigational gel samples. For this purpose, investigational samples in a volume of 5 ml were measured and placed into 15 ml Greiner Bio-One centrifugal test-tubes, which were placed into a centrifuge (Biosan LMC-3000, Germany). Samples were centrifuged during 5 minutes at a rate of 3,000 revolutions per minute. In the study of the compositions, the ability to release a liquid phase (water and other components) was investigated. It is characterized by the kinetic stability coefficient, which is calculated according to the following formula:

Кк = H1/H2, where
Кк stands for the kinetic stability coefficient;
H1 stands for the height of the released phase layer;
H2 stands for the height of the gel layer.

Quantitative determination of nifedipine in gels was performed using the UV spectrophotometry method. For this purpose, a test solution and a reference solution (RS) of nifedipine are prepared. To prepare a test solution, a test portion (2.00 g) of SDF is shaken during 5 minutes in 50 ml of purified water at a temperature of 37±1°C. A reference solution (RS) of nifedipine is prepared as follows: approximately 0.05 g (precise test portion) of nifedipine was placed into a measuring bottle with a capacity of 1,000 ml, 500 ml of water was added, then the solution was heated in the boiling-water bath until it was completely dissolved, water was added until the level of the solution reached the given mark, then it was mixed.

Samples with a volume of 5 ml were taken from the obtained solutions and filtered through the filters (such Millipore filters) with a pore diameter of 0.45 μm (nylon was used as a filtering material). Absorption of the test solution and RS was measured using a UV spectrophotometer at an absorption maximum at a wavelength of 340±2 nm in a cuvette with a layer thickness of 10 mm. Purified water was used as a reference solution. The nifedipine content should be 100.0±3.0%.

To study the stability during storage, and the shelf life, the obtained gel samples were left for storage. The study was conducted in accordance with SF (State Pharmacopoeia of Russia) XIII for FS "Shelf Life of pharmaceutical substances". Samples of obtained gels were stored in aluminium tubes with screw caps made from polypropylene. The investigational samples were divided into two groups. One group was stored in a dry location, protected against direct contact with sunlight, at a maximum temperature of 15–25°C, while the other group was stored in a thermostat, at a temperature of 40±1°C. On the day of manufacture and during storage (every 6 months of storage under natural conditions and every 48 days – a period, equivalent to 6 months during storage under "accelerated aging" conditions), the SDF samples were analysed according to the following indicators: description, authenticity, quantitative content of the FS, and pH value.

III. Results and Discussion

The results of the quality assessment of obtained gels are reflected in Table II.

In all cases, hydrophilic gel samples, manufactured using the solid dispersion technique, have the highest release rate in comparison with the reference ointment. In this respect, the best gels are the gels with compositions № 1 and № 2. Release of nifedipine was increased from these gels by 3.54 and 3.72 times, correspondingly. Release of nifedipine from gels with compositions № 3, № 4 and № 5 was increased by 2.80; 1.70 and 2.00 times, correspondingly (Fig. 1).

As a result of the experiment, rheograms were obtained, showing a dependence of the shear stress on the shear rate gradient for the samples of nifedipine gel, i.e. the so-called "hysteresis loops", which are represented as destruction and restoration lines (Fig. 2). The destruction of the gel structure, described by the ascending curve, takes place due to mechanical impact on the system, in consequence of which the structural viscosity is reduced. The restoration curve characterizes the equilibrium condition of the system after the destruction.

TABLE II. Specification of Developed Gels

Indicator	Method	Results
Description	Visual, organoleptic	Yellow, transparent odourless gels
Authenticity of nifedipine	A) UV spectrophotometry	UV spectrum of aqueous extract of gels of all samples in an area of 190 to 500 nm have an absorption maximum at 340±2 nm, and an absorption minimum at 282±2 nm.
	B) Qualitative reaction	Orange-red staining in the interaction with a 0.1 M sodium hydroxide solution.
Aqueous extract pH	Ionometry	5.0 to 6.0 (1.0% aqueous solution)
Quantitative determination of nifedipine (%)	UV spectrophotometry	A minimum of 97% and a maximum of 103%
Packing		50 g in an aluminium tube with a screw cap made from polypropylene. 1 tube is placed into a carton pack together with an applicator and application manual.
Marking		In accordance with the requirements of regulatory documents
Storage		In a dry location, protected against direct contact with sunlight, at a maximum temperature of 25°C
Shelf life		24 months

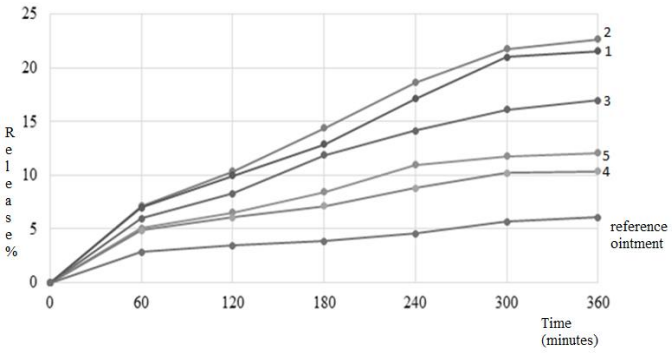

Fig. 1. Figure 1. Release of Nifedipine from Developed Gel Samples.

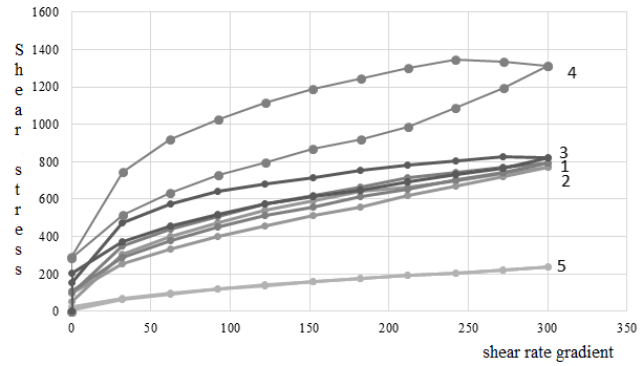

Fig. 2. Figure 2 Rheograms of Dependence of the Shear Stress on the Shear Rate Gradient for the Samples of Nifedipine Gel Samples.

Based on the area of the loop, one can assess the mechanical stability of structured systems. The largest areas of hysteresis loops are observed in samples № 4 and № 3, which contain maximum amounts of purified water and minimum amounts of polymer. The narrow hysteresis loop for compositions №: 1, 2 and 5 indicates their low fluidity, which will allow one to avoid losses in the process of application in the future. In addition, the presence of ascending and descending curves indicates that the investigational gels have thixotropic properties. Thixotropic properties of the investigational gels characterize satisfactory spreadability in the process of application and ability to be displaced from the tubes in the process of use of the substance.

The obtained results of the experiment with respect to aggregative stability of the obtained samples are given in Table III.

TABLE III. KINETIC STABILITY COEFFICIENTS OF NIFEDIPINE GEL SAMPLES

Sample Number	Storage Duration (Days)			
	1	7	30	180
	Кк	Кк	Кк	Кк
1	0	0	0	0.1
2	0	0	0.2	0.2
4	0	0	0.2	0.3
3	0	0.1	0.2	0.4
5	0	0.1	0.3	0.3

[a.] Кк stands for the kinetic stability coefficient

In the study of the compositions, the ability to release a liquid phase (water and other components) was investigated. Based on the results of the experiment, it was proved that the investigational gel samples retain stability during storage, and have resistance to stratification and syneresis.

IV. CONCLUSIONS

The proposed technology using the SD technique makes it possible to introduce a poorly water soluble nifedipine substance into a hydrophilic gel base in the form of a solution. This makes it possible to create a prospective and easy-to-apply soft dosage form of nifedipine – a hydrophilic gel, providing better release of the FS. Thus, theoretical prerequisites for reducing the FS dose have been created.

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According to the results of the study, a patent of the Russian Federation “Method for preparation of nifedipine gel” (patent RU2684326C1).

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