DEVELOPMENT OF EMULSION BASES OF OF THE 1ST AND 2ND KIND FOR EXEMPORAL SEMI-SOLID DOSAGE FORMS

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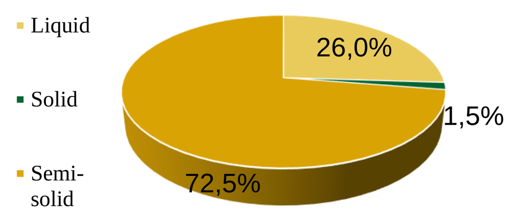
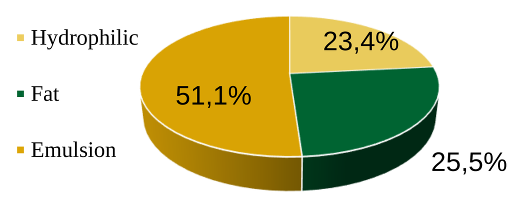
Introduction

World experience indicates that in most countries of the world the priority is the preservation and development of extemporal formulations, as this provides an individual approach to the needs of the patient. In Ukraine today, the concept of the development of "personal medicine" is promising.
It is the extemporaneous preparation of drugs under such conditions that takes on new significance and today is positioned as the preparation of drugs for the needs of each particular patient.
The advantage of extemporaneous drugs is the individualization of medical care for each patient, the choice of the most optimal ratio of ingredients, a wide selection of doses, taking into account the genetic, age, gender characteristics of the human body. However, unfortunately, the most of the extemporal prescriptions are outdated, given the pace of development of modern pharmacy and the production of new substances.
Therefore, the development of modern drugs, which are prepared in reserve, and contain fundamentally new components that compare favorably with those presented in traditional extemporaneous pharmacies, is today a timely and cost-effective task.
An analysis of the range of dosage forms that pharmacies are preparing in reserve showed that solid dosage forms take 1.5%, semi-solid dosage forms take 26%, liquid dosage forms take 72.5%. Semi-sold DFs are available on fat (25,5%), emulsion (51,1%) and hydrophilic (23,4%) bases.
After analyzing the composition of semi-sold DFs, it was found that the emulsion bases are used today in the presriptions, do not change over time and require a qualitative improvement.
Taking into account a number of advantages of emulsion bases, our aim is the development of new carriers of this type for semi-solid dosage forms (SSDF), as they today are the most promising, due to the high specificity of exposure and high levels of bioavailability of active pharmaceutical ingredients (APIs) in the composition of these bases.
Emulsion systems are thermodynamically unstable, therefore, for improving of the stability emulsifiers are used, which must meet the following requirements: ensure the formation of a stable emulsion; be chemically indifferent; show no toxic effect, do not cause skin irritation; have no disagreeable odor; must be approved for use.



Distribution of extemporaneous dosage forms the form of release



Distribution by type of SSDF bases prepared by pharmacies for future use

Aim of the work

Development and research of model samples of emulsions the first and the second kind based on a mixture of emulsifiers OLIVEM® 1000 (cetearyl olivat. sorbitan olivata) sorbitan oleate (Span 80) and sorbitan monostearate (Span 60). Justification of the composition of the emulsion base with a view to the further creation of extemporal semi-solid drugs and cosmetics.

Materials and methods

For the preparation of emulsion bases, the following emulsifiers were used: OLIVEM® 1000 OLIVEM® 1000 Cetearyl Olivate / Sorbitan Olivat (Hallstar Italy) complex emulsifier for producing emulsions of the first kind, sorbitan oleate (PhEur) (Span 80), emulsifier of the second kind (sorbitan mono PhEur) (Span 60) (Croda, United Kingdom), can be used as a monoemulsifier, emulsifier of the 2nd kind, used as a coemulsifier, corn oil (PhEur), purified water SPhUC 2.0).

In terms of quality indicators, the foundations must comply with the requirements of HFC 2., t.1, 2016, p. 1098, articles "Soft drugs for skin application", therefore, the quality criteria when developing the composition of emulsion bases were: organoleptic and sensory properties, thermo- and colloidal stability, pH value and some rheoparameters.

Colloidal stability was determined by centrifugation on a laboratory centrifuge labanalyt dm 0412 for 5 min. at a speed of 6000 s-1. Thermostability was determined in a thermostat (TS-80 M-2) at a temperature of 42.5 ± 2.5 ° C for 7 days. Determination of the pH of the model samples was carried out by potentiometric method in 10% aqueous extraction from the base on a pH meter pH 150 MI (RF). The type of emulsion obtained was determined by dilution. Rheological studies were carried out on a BROOKFIELD HB DV-II PRO viscometer (USA) in the range of shear rates from 18.6 s-1 to 93 s-1 (SC4-21 spindle for a chamber with a volume of 8.3 ml) at a temperature of 20 ° C. The mechanical value was calculated stability (MS) and dynamic rarefaction coefficient.

In the prepan of emulsion bases, a high-high temperature regime was used. The aqueous and oil phases were heated to a temperature of 70 ± 5, mixed (in the manufacture of samples based on emulsions of the first kind, the phase inversion method was used) was emulsified using a laboratory homogenizer (Homogenizer HG-15A) for 30 minutes at 2000 rpm until a uniform consistency . Physico-chemical studies of the samples were carried out after 24 hours. after complete cooling and structuring of the system.

The composition of the basics are given in Table 1.

The resulting emulsion bases are a mass of creamy consistency of a white-cream color, without visible inclusions, with a slight smell of corn oil.

The first series of experimental samples of emulsion bases was investigated in order to establish the range of concentrations of the oil phase and emulsifier. To create the basics with a minimum amount of oil phase, samples were prepared with 5, 10 and 15% corn oil, in which Olivem 1000 in concentrations of 2, 4%, 6% and 8% (taking into account the manufacturer's recommendations - 1.5-6%). The composition of model samples is given in Table 1. ratio

Table 1 Composition of the experimental samples of emulsion bases

Ingredient % / № sample	1	2	3	4	5	6	7	8
Corn oil	10	10	10	10	15	15	15	15
Olivem 1000	2	4	6	8	2	4	6	8
Purified water	to 100							

Table 2 Properties of the experimental samples of emulsion bases of the 1st kind

Quality indicators	room sample/The properties of the experimental samples of emulsion bases					
	2	3	four	6	7	8
Organoleptic and sensory properties	Liquid creamy texture, easy to spread and absorbed	Light creamy consistency, easy to apply, well distributed and absorbed	Thick creamy consistency. well distributed and absorbed	Liquid light creamy consistency, easy to apply, well distributed and absorbed	Light creamy consistency, easily distributed and absorbed	Thick creamy consistency. well distributed but slow sucked
Type of emulsion	Oil / water					
Thermal stability	stable	stable	stable	stable	stable	stable
Colloidal stability	stable	stable	stable	stable	stable	stable
Structural viscosity, Pa · s at 20 rev / min	0,96 ± 0,048	1.4 ± 0.07	1,73 ± 0,087	0,98 ± 0, 049	1.6 ± 0.08	2,05 ± 0,103
Structural viscosity, Pa · s at 100 r / min	0,2 ± 0.01	0,45 ± 0.0225	0.64 ± 0,032	0.35 ± 0,018	0.59 ± 0.03	0.77 ± 0,039
pH	6.93 ± 0.4	6.68 ± 0.3	6.9 ± 0.3	6.78 ± 0.4	6.9 ± 0.4	6.88 ± 0.5
Dynamic rarefaction coefficient (Kd)	78,13	67,86	63,0	64,29	63,13	62,44
Mechanical stability (MS)	1.17	1.19	1.21	1.19	1.32	1.31

The results of studies of the physicochemical and sensory properties of the samples are given in Table 2.

Test samples that contained 2% Olivem 1000 exfoliated during storage; when using an emulsifier in the concentration range of 4-8%, the samples were stable, had satisfactory organoleptic characteristics, but differed in terms of viscosity. It is naturally noted that an increase in the content of the oil phase and the complex emulsifier contributes to an increase in reoparameters.

The rheograms of the dependence of the shear rate (Dr) on the shear stress (τ) at a temperature of 20 ° C (Fig. 2) demonstrate the yield strength and thixotropic properties of the samples.

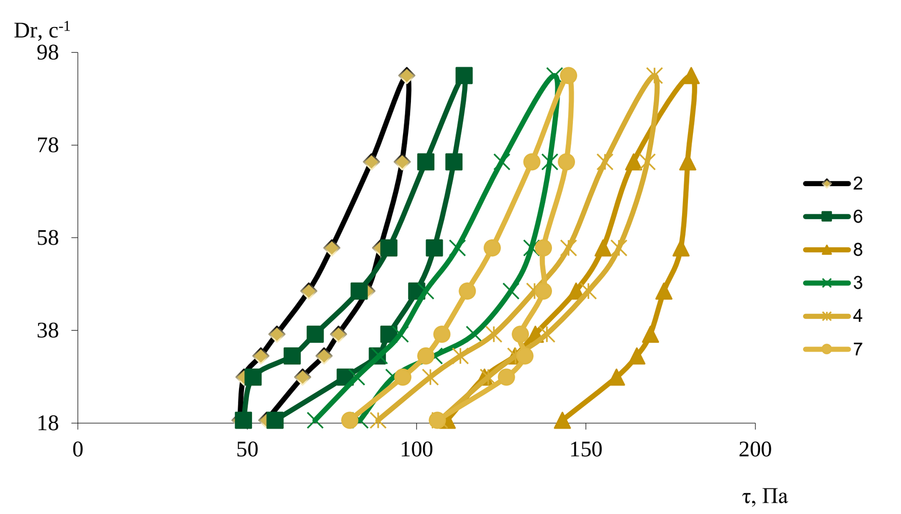


Figure 1 Rheogram of shear rate (Dr) versus shear stress

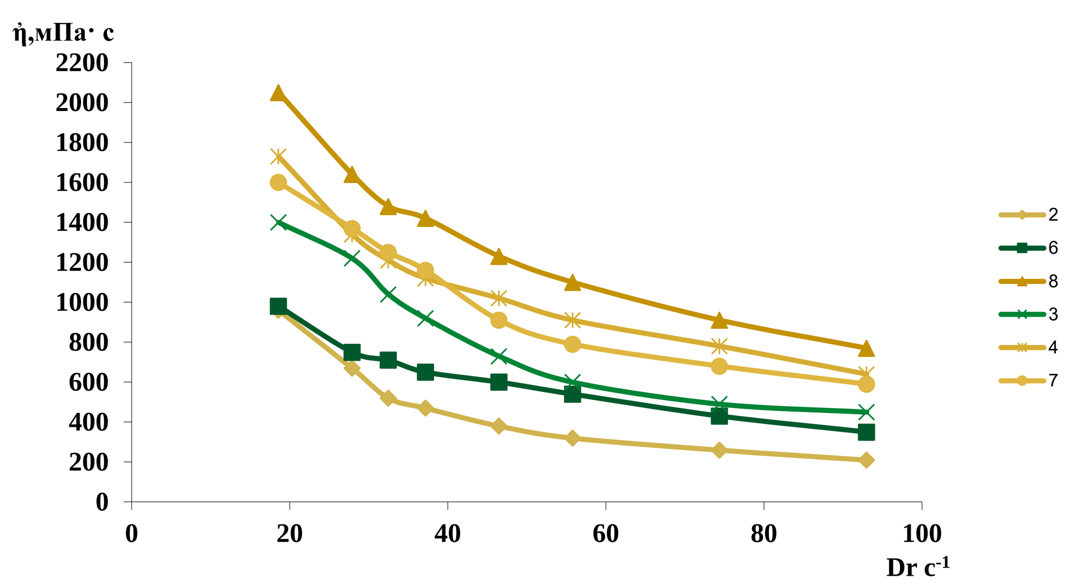


Figure 2 The dependence of the structural viscosity of model samples on shear rate (Dr) at a temperature of 20 ° C

Based on the findings of physico-chemical and organoleptic characteristics bases containing Olivem 1000 (4-6%) and 15% corn oil were selected for the further study.

The second series of experimental designs was aimed at creating and studying emulsion bases of the 2nd kind.

In order to establish the optimal ratio of emulsifiers, the concentration and ratio of the selected emulsifiers were varied within the concentrations recommended by the manufacturer Span 80 from 0.5 to 10% and Span 60 from 0.5 to 6%. The content of corn oil remained constant, since increasing its concentration is impractical.

It was noted that samples containing up to 6% sorbitan oleate exfoliated during emulsification. The composition of the basics are given in Table 3.

To prepare the basis of the second kind, the following technology was proposed: the ingredients were preliminarily weighed, and melted in a water bath taking into account the melting temperature; a mixture of emulsifiers sorbitan oleate (melting point: 65-75 ° C) and sorbitan monostearate (melting point: 50-60 ° C) were heated in a water bath to a temperature of 80-90 ° C, corn oil was added to it. In parallel, the water was heated to a temperature of 80-90 0 C.

Then water was gradually added to the oil phase and emulsified using a homogenizer (Homogenizer HG-15A) (3000 rpm) until a homogeneous mass was obtained. Physico-chemical studies of the samples were carried out after 24 hours. after complete cooling and structuring of the system.

In order to establish the optimal ratio of emulsifiers, their concentration and ratio were varied within the concentration range recommended by the manufacturer Span 80 from 0.5 to 10% and Span 60 from 0.5 to 6%. The content of corn oil remained constant, since increasing its concentration is economically feasible. The composition of the basics are given in table. 3.

It was noted that samples containing up to 6% sorbitan oleate exfoliated during emulsification.

Table 3 Composition of the experimental samples of emulsion bases of the 2nd kind

Ingredient % / № sample	1	2	3	4	5	6	7	8	9	10	11	12
Corn oil	fifty											
Span 80. Sorbitan aboutleate	6	8	10	6	8	10	6	8	10	6	8	10
Span 60. Sorbitan monostearate	-	-	-	4	4	4	5	5	5	6	6	6
Purified water	to 100											

As the research results showed, samples No. 1, 2 were stratified during the colloidal stability test, which indicates an insufficient emulsifier content to stabilize a significant amount of the aqueous dispersed phase. The results of studies of the physicochemical and sensory properties of stable samples are given in Table 4.

Table 3 Properties of the experimental samples of emulsion bases of the 2nd kind

Quality indicators	No. sample									
	3	four	5	6	7	8	9	10	eleven	12
Organoleptic and sensory properties	Fluid, creamy texture, easy to to apply, for distributed and well absorbed	Creamy texture, easy to nano-happen, for distributed and well absorbed	Creamy consistency, easily distributed and absorbed	Thick creamy consistency. well distributed but slow sucked	Liquid light creamy consistency, easy to apply, well distributed and absorbed	Thick creamy consistency, easy distributed and absorbed	Thick creamy consistency. well distributedbut slow sucked	Creamy consistency, easy to apply, well distributed and absorbed	Thick creamy consistency, easily distributedbut slow sucked	Thick, creamy texture, well distributed, but it is slowly absorbed
Emulsion	Water / oil									
Thermal stability	stable	stable	stable	stable	stable	stable	stable	stable	stable	stable
Colloidal stability	stable	stable	stable	stable	stable	stable	stable	stable	stable	stable
Structural viscosity, Pa · s at 20 rev / min	1.4 ± 0.07	2.3 ± 0.045	4.2 ± 0.21	5.9 ± 0.13	3.5 ± 0.03	5.8 ± 0.09	5,5 ± 0,07	4.1 ± 0.11	6.0 ± 0.12	6.6 ± 0.13
Structural viscosity, Pa · s at 100 r / min	0,5 ± 0,035	0,65 ± 0.33	1,5 ± 0,075	1.8 ± 0.03	1,0 ± 0.05	1,6 ± 0.08	1.8 ± 0.09	1,4 ± 0.07	1.8 ± 0.09	1,5 ± 0,075
pH	7.2 ± 0.2	7.3 ± 0.1	7.3 ± 0.1	7.2 ± 0.2	7.3 ± 0.2	7.1 ± 0.2	7.2 ± 0.3	7.1 ± 0.2	7.2 ± 0.2	7.2 ± 0.2
Dynamic Dilution factor (Kd)	64.29	71.74	64.29	69.49	71.43	72.4	67.28	65.85	70.0	77,27
Mechanical stability (MS)	1.18	1.05	1.07	1.04	1.08	1.04	1.05	1.04	1.05	1.03

According to the study of structural and mechanical properties of the experimental samples were constructed rheogram depending on shear rate (Dr) Shear stress (τ_r) At a temperature of 20 ° C (Fig. 3) and the graphs of viscosity versus shear rate samples (Fig. 4).

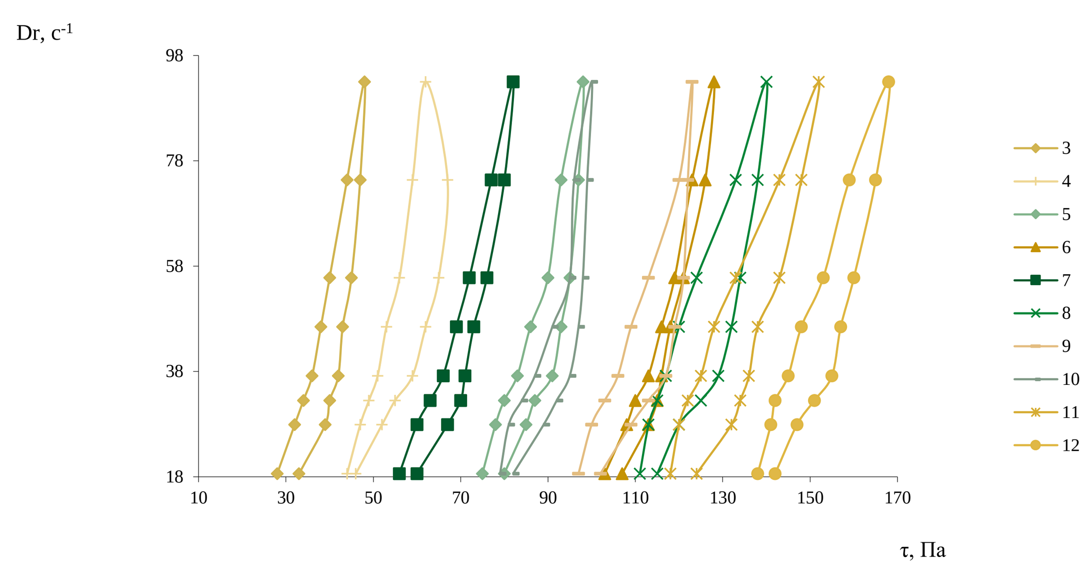


Figure 3 Rheogram of shear rate (Dr) versus shear stress

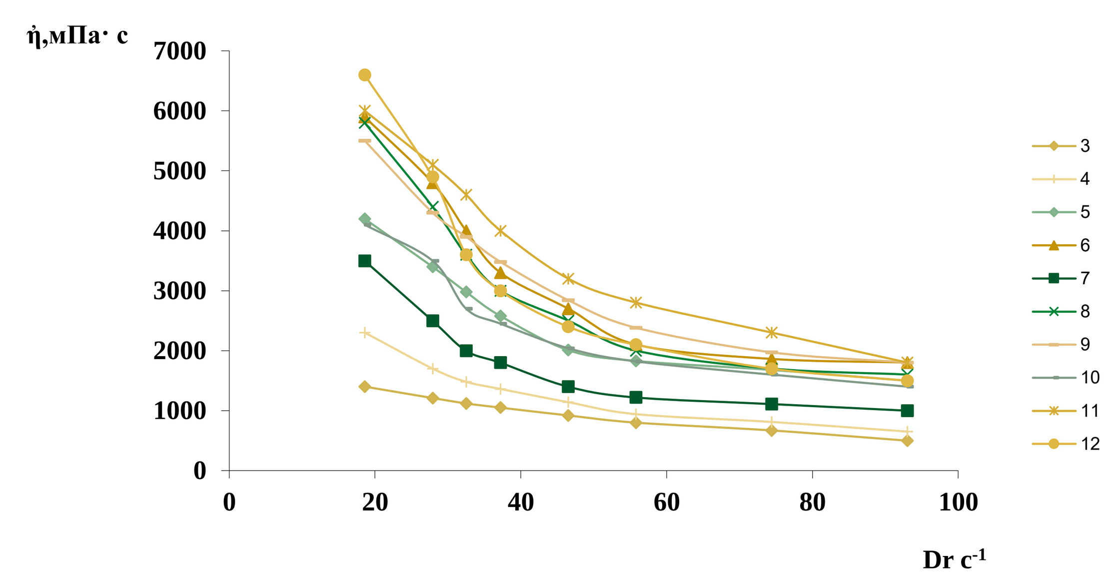


Figure 4 Dependence of the structural viscosity of model samples on shear rate (Dr) at a temperature of 20 ° C

To study the extrusion properties of the bases, a dynamic rarefaction coefficient was calculated, which has average values of 69. High Kd values indicate the possibility of a better application of drugs during mechanical grinding, which characterize better rarefaction in the mixing mode, better distribution of APIs made in the base, and easy filling of tubes, which confirms the graph of viscosity versus shear rate.

Based on the research results of physico-chemical and organoleptic characteristics bases containing Span 80 from 6 to 10% and Span 60 from 4 to 6% and 50% corn oil were selected for the further study.

CONCLUSIONS

The developed emulsion bases of the first and second kind with different concentrations of emulsifiers mixture and correspondingly consistent properties can be used as the basis for the preparation of dermatological drugs and protective cosmetics, for the prevention of age-related skin changes and other.