ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

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«27» august 2021 y.

METHODICAL DEVELOPMENT OF INDEPENDENT WORK OF STUDENTS (IWS)

Course 5 Faculty Pharmaceutical

Course Biopharmacy

Topic №2 **«Biopharmaceutical and physicochemical aspects of suspensions and emulsions. Release and bioavailability of drugs from these dosage forms.»**

Methodical recommendations on IWS developed by:
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Methodical recommendations of IWS were discussed at the methodical meeting of the department
«27» august 2021 y.
Protocol № 1

Odesa - 2021

Topic: "Biopharmaceutical and physicochemical aspects of suspensions and emulsions. Release and bioavailability of drugs from these dosage forms. " - 6 years

Objective: To deepen knowledge in the method of studying the pharmaceutical availability of drugs from suspensions and emulsions.

Basic concepts: Heterogeneous system, suspension, emulsion.

Plan

I. Theoretical questions for the lesson:

Liquid heterogeneous dispersed systems. Absorption of drugs used in the form of emulsions and suspensions takes place mainly in the upper part of the small intestine, because for absorption from the stomach they do not have sufficient solubility in water. The liquid state of these drugs promotes their rapid penetration into the site of absorption, increases the secretion of the gastrointestinal tract and stimulates peristalsis. The rapid transition from the stomach to the intestine is hindered by the high content of lipids in the emulsions and the increased viscosity of the emulsion and suspension systems. The excipients contained in these dosage forms interact with the intestinal membrane and, as a rule, improve its permeability.

Physico-chemical properties important for the release and transport of the drug substance from emulsions and suspensions are expressed by the following equations.

For the diffusion of soluble drug substance from the conductor is really:

$$Q = 2 \cdot C_0 \sqrt{\frac{Dt}{\pi}}.$$

Diffusion of the suspended drug substance from the conductor proceeds depending on:

$$Q = \sqrt{(2 \cdot C_0 - C_s) \cdot C_s \cdot D \cdot t}.$$

Diffusion of the emulsified drug substance from the conductor can be established by the equation:

$$D \to D_e = \frac{D_1}{V_1 + P \cdot V_2} \left(1 + 3V_2 \frac{P \cdot D_2 - D_1}{P \cdot D_2 - 2D_1}\right).$$

The Stokes-Einstein diffusion constant has the form:

$$D = \frac{R \cdot T}{N_A \cdot 6 \cdot \pi \cdot \eta \cdot r},$$,where

Q - released substance
C_s -solubility
P -distribution coefficient
N_A -Avogadro's number
D, D1, D2 -diffusion coefficient

η — viscosity
r — the radius of the molecule
C_0 — initial concentration
t — time
R — gas constant
V_1, V_2 — phase volume 1.2
T — absolute temperature
D_e — effective ratio

From the above equations it is seen that the absorption of drugs from oral emulsions and suspensions is affected by surface size, viscosity, surface tension, surfactants, which dissolves the ability of the components of the dispersion medium and the formation of complexes.

Viscosity. In emulsions, the viscosity of the oil increases:

- when using a narrower oil;
- when dissolving in it higher fatty alcohols and acids, emulsifier T-2, monoglycerides;
- with increasing molecular weight of the oily medium.

The viscosity of the aqueous medium increases with inclusion

to the composition of oil / water emulsions (m / v) gelling excipients: derivatives of cellulose and alginic acid, various polysaccharides.

The high viscosity of the dispersion medium is considered to be a factor that slows down the diffusion of the drug in the membrane, which is manifested in a slow absorption. The maximum concentration of the drug in the blood in this case reaches the initial value relatively later, and incomplete absorption may occur. A clear decrease in the DB with increasing viscosity was proved by the example of sodium salicylate, nitrofurantoin, salicylic acid, and others. In contrast to these drugs, thiamine and riboflavin from the system with higher viscosity are absorbed as well as from non-viscous solutions, obviously because in the mechanism of their absorption the active element predominates over the diffusion one.

It is not easy to specify the effect of viscosity on the database, because the viscosity affects the peristalsis of the gastrointestinal tract, and, in addition, substances that achieve high viscosity, often change the pH, dielectric characteristics and osmotic pressure of the liquid medium. , forming complexes and precipitates with many substances (especially polysaccharides).

Surfactants. The effect of surfactants on the absorption is manifested in the fact that they change the permeability of the membrane, improve surface wetting, thereby affecting the solubility and dissolution rate.

The best wetting is achieved by a small amount of surfactant, which is sufficient to accelerate the dissolution of many hydrophobic substances. When associated with a surfactant molecule, the active substance approaches the site of absorption, resulting in an increase in this factor. This mechanism is confirmed by the addition of sorbimacrogel Oleat to cholesterol, phenacetin, spironolactone and others.

Surfactants affect the membrane by dissolving and releasing phospholipids (lysolecithin), which changes the structure of the membrane, which becomes extremely permeable.

The effect of surfactants on absorption is manifested not only in increasing the wettability of the surface and changing the absorption properties of membranes, but also in the ability to solubilize hydrophobic substances. As a result of the transition of less soluble substance into solution increases, on the one hand, its DB, and on the other - the substance is fixed in the micelles, which complicates its diffusion to the site of absorption. This phenomenon occurs when the surfactant concentration exceeds the critical micelle concentration (CCM). The micelles form a second, accumulating on the solubilized substance colloidal phase. Absorption is slowed down because the micelles form a kind of accumulation of the active substance, from which, under stationary conditions, it is released by kinetics of pseudo-zero order. This is true, for example, for salicylic acid, but not for ethanol, which is not retained in the micelles.

The solubility of the components of the dispersion medium. To improve the degree of dispersion in liquid heterogeneous systems in most cases for technological reasons add ethanol, sorbitol, glystyrene, propylene glycol, dimexid, etc. These substances accelerate and increase the absorption, first, by dissolving part of the suspended matter , and secondly, due to its high lipophilicity facilitate the passage of drugs across the membrane.

The size of the surface. In suspensions, the surface size depends on the size of the dispersed particles. Properly formulated, in terms of the rate of absorption of drugs, the suspension is between the solution and the tablet, because the substance is not yet dissolved, but the phase of release (decomposition) and wetting is absent.

The particle size of the suspended drug particles is often a decisive factor for dissolution and absorption. By grinding the particles, the solubility of the drug increases slightly, and the dissolution rate increases significantly. Acceleration of dissolution promotes faster absorption, although it proceeds according to the laws of diffusion.

Reducing the particle size has its limits not only in terms of technology, but also in terms of database. For example, when taking trimethoprimsulfamethoxazole with a particle size of 12 and 6 nm, the difference was still determined, while at a value of 5 and 3 nm it was absent. The reason for this was the poor wettability of very small particles of the drug substance.

To ensure a high database, it is not the size of the particles that is crucial, but their effective surface, which depends on the interaction between the particle size and the surface tension of the dispersion medium. This phenomenon also explains why the absorption of drugs containing more mucous substances is slower than from the tablet.

Emulsions are characterized by a large surface area of the dispersing phase. However, this advantage is largely paralyzed by the very slow transport of the drug (diffusion) to the membrane.

The advantage of emulsions is that the drug substance in the internal phase is not exposed to gastric juice. In addition, the oily drug associated with food fat molecules can enter the systemic circulation through the lymph. For example, the absorption of vitamin A from fat systems is explained. Absolute absorption of insulin and macromolecular compounds (IUD) was achieved from water / oil (i / m) systems.

Suspensions. If in the technology of solutions the main issue is the solubility of the drug substance, then in the technology of suspension production - thermodynamic stability. The development of theoretical and practical issues of stabilization of pharmaceutical suspensions is associated primarily with the study of adsorption processes by various methods, which allow to obtain a number of parameters that characterize not only the surface area of the drug, but also its degree of filler, specific surface area and others.

These issues are especially important in the preparation of suspensions with hydrophobic drugs, for which it is advisable to possibly large hydro-phylization of the surface. It is carried out using surfactants, which dramatically reduce the absolute amount of wetting.

1. Biopharmacy: textbook / edited by: Borisyuk IY, Fizor NS, Akisheva AS Odessa, ONMedU, 2020. - pp. 69-72.

Questions for self-control

1. Stabilization of emulsions.
2. Pharmaceutical factors, their importance in drug technology.
3. .Influence of physicochemical state of drug substance on its pharmaceutical and bioavailability.
4. The main tasks of biopharmacy at the present stage and their role for practical health care.
5. Pharmaceutical factors influencing the therapeutic efficacy of drugs.
6. Physical state of medicinal and excipients in dosage forms and their effect
7. on the rate of release and absorption of drugs.
8. The use of different degrees of dispersion of drugs to create drugs with different bioavailability.
9. The concept of polymorphism.
10. The effect of crystal structure and polymorphism of drugs on the therapeutic activity of drugs.
11. Influence of the nature of the solvent, solubility, degree of viscosity and pH of the medium on the absorption of drugs.

12. The degree of purity of the drug and its effect on pharmacotherapy.
13. Dependence of therapeutic activity of drugs on the type and quality of packaging.

Approximate tasks for the study of theoretical material

1. Make a dictionary of basic concepts on the topic
2. Fill in the orientation card for self-preparation of the student using the literature on the topic :

№ WITH	**The main tasks**	**Instructions**	**Answers**
1.	What determines the release and resorption of the drug from the suspension.	Give an explanation	The release and resorption of drugs from suspensions is largely determined by the concentration of surfactants. And the principle: the more, the better - does not always justify itself. For example, it has been shown that better release and resorption of norsulfazole are observed from a suspension with 0.001% sucrose mono-laurate than from a suspension with a higher concentration of this surfactant. Therefore, it is of interest to study the creation of methods for selecting the amount of surfactants, in particular, using the value of the surface tension, measuring the absorption coefficient of ultrasound, and others.
2.	The stability of the emulsions that affect it.	Give an explanation	The stability of emulsions depends on the nature of the emulsifier, the dispersion medium and the oil phase, the ratio between oil, water and emulsifier, the method of preparation of the emulsion, the method of introduction of the emulsifier (surfactant, Navy, etc.). Depending on the objectives, emulsions should either promote

			the rapid and complete release of drugs, or provide a prolongation of their action.

II. Practical work (tasks) that will be performed in class:

Task1

To establish the influence of the degree of dispersion of streptocide on the process of its release from ointments by the method of "agar plates".

III. Test tasks for self-control

http://info.odmu.edu.ua/chair/drugs technology / Tests Step-2 on the following topics: Technology of preparation of aqueous and non-aqueous solutions. Evaluation of the quality of solutions

IV. Individual tasks for students on the topic of the lesson

Prepare a presentation (abstract): Features of liquid dosage forms

List of recommended reading

Main:

. 1. Біофармація : підруч. для студентів закл. вищ. освіти / О. І. Тихонов [та ін.] ; за ред. О. І. Тихонова. – 2-ге вид., перероб. і допов. – Харків : НФаУ: Золоті сторінки, 2019. – 224 с

2. Настанова СТ-Н МОЗУ 4242-7.1:2005 «Лікарські засоби. Настанова з клінічних досліджень. Дослідження біодоступності та біоеквівалентності» - Київ, 2018.

3. Настанова СТ-Н МОЗУ 4242-7.1:2005 «Лікарські засоби. Настанова з клінічних досліджень. Дослідження біодоступності та біоеквівалентності» - Київ, 2018.

4. Настанова СТ-Н МОЗУ 42-7.2:2018 Лікарські засоби дослідження біоеквівалентності. – Київ, 2018. – 77 с.