The rheological properties of basic components of pharmaceutical ointments and creams

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INTRODUCTION

The ointment is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (oil 80% - water 20%) with a high viscosity, that is intended for external application to the skin or mucous membranes. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired. The ointment is typically consist of two/three parts: ointment base (in majority), active ingredients (pharmaceutical formulas) and other chemical agents. Depends on the type of base, the following forms of ointments are found:

- **Ointment solutions** – where the drug substance are dissolved in the medium (ointment base). In the ointments of this type, the drug substance may be dissolved in a hydrophobic or hydrophilic substrate;

- **Ointments emulsions (creams)** – this type is contained with several substances, which are not immiscible each other. The emulsion is most often formed by the substrate components and the therapeutic substance is dissolved in the aqueous or oily phase. In medicine, both oil / water emulsions and water / oil emulsions are used. The most stable emulsions are obtained by combining the ingredients into warm and vigorous stirring;

- **Slurry ointment** – in this type of ointment, the active molecules are insoluble in any component of the substrate. There systems are always at least two phases (if the substrate is uniform it is one phase and the substance is suspended - the other). It is also possible to suspend the solids in the emulsion medium and then multiphase. If the solid constitutes more than 40% of the ointment, then the ointment is called a paste. Production of ointment suspensions consists in grinding a very fine powdered active substance (particle size should not exceed 90μm) with the medium. Preferred, though not necessary, is the homogenization of the preparation procedure.

Therefore, the ointment base have the largest part in the finished product and directly influence on the speed and depth of penetration and transportation of medical substances. They play a role like as a carrier, wherein the active substances are placed, and should not have an own therapeutic effect, or interact with the drug contained therein, and should be stable from a physicochemical point of view. The different types of ointment bases are:

- **Lipophilic substrates** (mixture of hydrocarbons, for example paraffin, petrolatum, natural fats, vegetable fats, olive oil, sunflower oil, lard, cod-liver oil, isopropyl myristate, isopropyl palmitate);

- **Absorption substrates, anhydrous** (lanolin, cetyl alcohol, cholesterol, waxes);
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- Absorption substrates, hydrated (mixture of vaseline, lanolin and water);
- Creams (water-repellent creams: water/oil and hydrophilic creams oil/water emulsion);
- Hydrophilic substrates (hydrogels, glycerine ointment, polyoxyethylene gels (PEG)).

In addition, the ointment bases must have a suitable consistency, which affects the rheological properties such as the yield point and plastic viscosity (spreadability) as well as adhesion to the skin or mucous membranes. Due to pasty consistency they belong to the category of non-Newtonian fluids, so their instruments should be used absolute instruments – rheometers.

THEORETICAL ASPECTS OF RHEOLOGY

Most materials behave in such a way that they have a combination of viscous and elastic response under stress or deformation. Among real liquids Newtonian and non-Newtonian fluids can be distinguished. Viscosity is one of the rheological parameters which can characterise liquids. By measurement of the viscosity versus shear rate one can classify the liquid into a particular group. If the viscosity decreases vs. the shear rate the liquid has shear thinning properties, and when the viscosity rapidly increases, the shear thickening or dilatancy effect is observed. Rheological classification of liquids is presented in **Figure 1**

![](Image)

**Figure 1** Rheological classification of liquids.
The shear thickening effect appears in suspensions of various concentration and morphology of the solid phase. The shear thickening of fluids can be explained by a few theories, the most popular being the clustering theory. According to its main assumption, the particles at low shear rates are prevented from aggregation by repulsive and Brownian forces. With an increase in the shear rate, hydrodynamic forces also increase and particles form chains, blocking the flow of the fluid. The next potential explanation of the dilatancy phenomenon is the Order – Disorder Transition (ODT) theory, which claims that the spherically shaped particles exist in ordered arrangement before the shear thickening effect takes place and transfer to a disordered state under the action of mechanical shear [2].

Thixotropy is a form of time dependent behaviour describing a material whose viscosity decreases over time while it is subjected to shearing forces. After some time the material recovers completely to its original state. Thixotropy should not be confused with rheopexy, a rare phenomenon, (rheopexy is also time dependant, but the viscosity increases with time).

One of the most useful methods for determination the thixotropy or antithixotropy behaviour of liquids is the Thixotropy/Antithixotropy loop, which is presented in Figure 2.

![Figure 2. Algorithm of shear rate changes and hysteresis loop resulted from shear rate.](image)

The area and shape of the hysteresis loop depends on the type of material, the history of the sample before shearing, maximum shear rate and guided speed measurement. The hysteresis loop can also be determined by the shear rate change algorithm with its constant value, in the time interval from $t_1$ to $t_2$ (Figure 3).
Figure 3. Algorithm of shear rate changes with constant rate of shear in the range $t_1$ to $t_2$.

Hysteresis loop resulted from shear rate changes.

The mobilotixotropy and chronotiotropy coefficients

The size and shape of the hysteresis loop were used by Green and Weltman [15] to determine the quantitative phenomena of thixotropy by determining coefficients chronotiotropy and mobilotixotropy (Figure 4). These coefficients are used for imaging effect thixotropy. Chronotropotropy ($B$) indicates the breakdown rate of the structure over time, at constant shear rate, while the mobilotixotropy ($M$) coefficient is a measure of thixotropic degradation caused by increasing shear rate, where:

The chronotropotropy coefficient is given by:

$$
B = \frac{\eta_1 - \eta_2}{\ln \frac{t_2}{t_1}}
$$

$\eta_1$ - viscosity [mPa · s], determined after time $t_1$,
$\eta_2$ - viscosity [mPa · s], determined after time $t_2$,
$t_1$ - shear time at the first maximum speed [min],
$t_2$ - shear time at second maximum speed [min].

The mobilotixotropy coefficient is determinate as follows:

$$
M = \frac{\eta_1 - \eta_2}{\ln \frac{\gamma_{max}^{1}}{\gamma_{max}^{2}}}
$$

$\eta_1$ - viscosity [mPa · s], determined at maximum shear rate $\gamma_{max}^{1}$
$\eta_2$ - viscosity [mPa · s], determined at maximum shear rate $\gamma_{max}^{2}$
$\gamma_{max}^{1}$ - first maximum shear rate [1 / s]
$\gamma_{max}^{2}$ - second maximum shear rate [1 / s]
The next experiment is the measurement of viscosity at constant shear rate. When the fluid is subjected to shear at constant speed, the viscosity of the material is decreased with the time of shear, which means that this material is destroyed. The curves of fluctuation of apparent viscosity over the time is given at Figure 5.

The last tool used for determining the thixotropy properties of liquids is the shear jump method. It consists of multiple application of step-varying shear speeds. It allows to determine the rheological parameters of a model that describes the thixotropic properties of the medium. Method jump shear consists of three stages. During the first stage the sample is sheared at constant speed (a time period from t0 to t1) (Fig. 6). This stage lasts as long as the viscosity of the fluid at time t1 reaches the equilibrium viscosity (Figure 6). This viscosity is a reference value during the second measurement step, on the basis of which can determine the degree of destruction of the fluid structure. The method also determines whether the sample of the same medium are the same rheological state, independent of the
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filling procedure of the rheometer. In the second step, the sample is sheared at a higher speed than in the first stage and in the time interval $t_1$ to $t_2$ can again reach the equilibrium viscosity at a given shear rate (Fig. 6). The shear rate in the third stage (time from $t_2$ to $t_3$) should be the same as in the first stage, allowing for the reconstruction of the liquid structure and its viscosity increase.

![Figure 6. The algorithm of shear rate changes and changes of viscosity of thixotropic fluid resulted from shear rate changes.](image)

This experiment allows the determination of a number of quantities that can be considered a measure of the thixotropic properties of the test liquid. These are: (1) the difference in viscosity between the initial viscosity at time $t_1$ and the viscosity at time $t_2$; (2) the time of complete restoration of the structure over time from $t_2$ to $t_3$; (3) the time of partial restoration of the structure, which may be several hours or even several days, and (4) the degree of structural restoration over a given period of time, which is important for practical reasons.

**EXPERIMENT PART**

During the exercise, the thixotropy properties of various base ointments will be determined. The measurement will be taken placed at two different temperature: (1) 20°C, which corresponds to the standard storage temperature and (2) 32°C, which corresponds to human skin temperature (typical application temperature), to show how the temperature will be influence on rheological properties of measuring liquids. The chosen ointment base are:

- Vaseline
- Combination of lard and glycerine
- Typical cream with the lanolin base
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- gelatin with different concentrations of the fillers

The rheological studies will be carried out using a rotary rheometer RM180 Prorheo with the cup-bob arrangement with different sizes (detailed information will be provided by the tutor). The apparatus will be connected with the PC to determine the thixotropy properties of measuring liquids. The basic measurements will be:

- Flow curves
- Thixotropy loop
- Thixotropy loop with the constant phase of shear rate
- Determination of mobilotixotropy and chronotiotropy coefficients
- Measurement of viscosity at constant shear rate
- Method of jump shear

All of above methods should be taken placed in two different temperatures and for all measuring ointment base, creams and other liquids. For one of temperature and liquid the system of measuring (cup-bob) will be changes for determined the appropriate architecture of system form chosen liquid.

The report should be consist of:

1. Short description of the proceeded work (all of measuring liquids and combinations)
2. All the of determined graphs for all combinations
3. Calculations (if needed)
4. Conclusions and interpreting the results (specially for used temperatures and type of measuring liquids and system of architecture the cup-bob)