# CONTROLLED AND PROGRAMMED DRUG DELIVERY SYSTEMS: GELS

Ph.D. thesis
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# 1. Introduction

Gels are special substances consisting of a three-dimensional network that immobilises the liquid phase. In the pharmaceutical industry, hydrogel systems dominate research thanks to their water content, biocompatibility and versatility (Figure 1). However, traditional hydrogels have several limitations, particularly when it comes to using lipophilic active ingredients with low water solubility. For this reason, my doctoral research focused on developing alternative, non-hydrogel-based gel systems, primarily oleogels and emulgels, which offer new possibilities for local, programmed drug delivery.

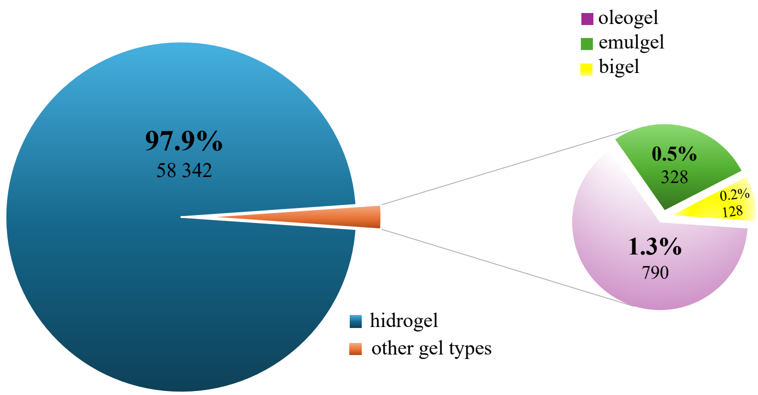


*Figure 1: Mentions of different gel types*
*The interval for the PubMed database searches was between 2013 and 2025. The search was performed on March 6, 2025. Without aiming for completeness, we also conducted searches for a few additional gel types. Hydrogels are mentioned significantly more often than other gel types*

# 2. Objectives

Upon examining the issue of the widespread use of hydrogels in pharmaceutical gel systems, I discovered an opportunity to conduct my doctoral research, aiming to explore the untapped potential of oleogels and emulgels. I set out to formulate new pharmaceutical gels that were biphasic with the hopes of overcoming the challenge of inadequate lipophilic gels in the pharmaceutical industry.

In the beginning phases of my PhD, I started working with on emulgels that were designed to be administered intravaginally. With emulgels being the ideal dosage form for lipophilic drugs and being patient-centered, they provided the needed versatility for optimal patient compliance.

I focused on the thermoresponsive and amphiphilic behavior of poloxamer based gels. Poloxamer 407, a widely studied member of this group, exhibits a temperature-dependent sol-to-gel transition that makes it ideal for formulations designed to be liquid at room temperature and to gel at body temperature.

Creating an emulsion-type gel that could efficiently administer clotrimazole, a popular antifungal medication with low water solubility, for the treatment of vulvovaginal candidiasis (VVC) was one of the main objectives. Many women around the world suffer from VVC. Current therapies are frequently bothersome or inconvenient, and they don't always guarantee the best possible drug delivery or patient comfort.

In order to improve drug retention and provide sustained release at the vaginal mucosa, I set out to create a heat-sensitive emulgel formulation that takes advantage of the advantageous rheological characteristics of gels as well as the solubility benefits of emulsions. In order to reduce discomfort, I tried to set an ideal the viscosity, stability, drug release properties, and overall sensory experience by adjusting the poloxamer and oil phase compositions.

Another significant aspect of my work focused on the rheological methodology itself. Recognizing the importance of precise rheological characterization in formulation development, I compared traditional rotational rheometer measurements with an emerging microfluidic viscosity technique. This newer method offers rapid, accurate viscosity measurement with minimal sample volume, particularly beneficial for heat-sensitive and low-viscosity systems.

# 3. Methods

## 3.1. Formulation and evaluation of clotrimazole containing emulgels

The emulgels were formulated by dissolving the chosen active ingredient – clotrimazole – in oleic acid and then adding it to the previously made poloxamer based thermoresponsive hydrogel system. The gelling agents used were poloxamer 407 (PLX407) and poloxamer 188 (PLX188), dissolved in cold distilled water under stirring and refrigerated for full solubilization and micellization. Hydroxypropyl methylcellulose (HPMC) was added in some formulations to increase mucoadhesion.

The formulations were then subjected to a series of evaluations including physical appearance, sol-gel transition temperature, viscosity, mucoadhesion, spreadability, microstructure observation, and in vitro drug release studies (Figure 2).

Drug release was measured using vertical diffusion cells with cellulose acetate membranes separating donor and receptor compartments, and via paddle dissolution apparatus (Hanson SR8+) using phosphate buffer-ethanol mixture as a release medium. Quantification was performed using HPLC coupled with Vis detection or with UV-Vis Spectrophotometer, and release kinetics were analyzed according to the Higuchi model.

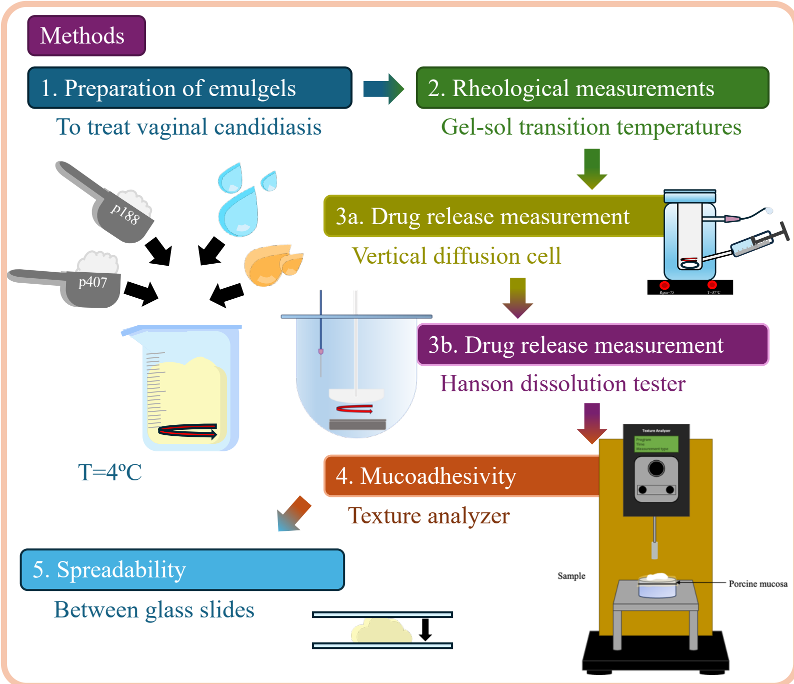


*Figure 2: Experimental workflow for the development and characterization of emulgels intended for vaginal drug delivery The process includes: (1) preparation of emulgel bases using PLX407 and PLX188 at low temperature adding the OA, (2) rheological measurements to determine sol-gel transition temperatures, (3) drug release studies using both vertical diffusion cells and Hanson dissolution testers, (4) evaluation of mucoadhesive properties, and (5) assessment of spreadability.*

## 3.2. Rheological methodology

The rheological properties of commercially available pharmaceuticals were investigated using two different measurement methods - a conventional rotational rheometer (Kinexus Pro+, Malvern Instruments Ltd., UK) and a microfluidic rheometer (FluidicamTM RHEO, Formulaction, France). The products are listed in the table below (Table I).

*Table I: Overview of commercially available pharmaceutical products*
*The table summarizes the dosage form, route of administration, API, viscosity-modifying excipients (if present), and intended clinical indication of each product*

| Dosage form | Route of administration | API | Viscosity modifying excipient | Indication |
|---|---|---|---|---|
| **Gel** | Vaginal | Acidum lacticum, Glicogen | Methyl-hydroxy-propyl-cellulose (MHPC) | Bacterial vaginosis, Candidiasis |
| **Gel** | Topical | Sodium hyaluronate | Carbomer | Wound care |
| **Solution** | Eyedrop | - | Polysorbate 80 | Lubricant |
| **Klysma (solution)** | Rectal | Diazepam | Propylenglycol | Seizure resolution |
| **Injection** | Intramuscular/ intravenous | Metamizole-sodium | - | Painkiller |
| **Excipient** | Subcutaneous | - | - | Lubricant for implants |
| **Medical device-gel** | Oral | - | Carragenan | Lubricant for solid dosage forms |

The aim of the study was to investigate the viscosity, flow behaviour of different dosage forms (gel, solution, injection, klysma, eye drop, implant lubricant, oral gel) and the comparability and applicability of the two measurement methods in drug technology development and quality control.

In all cases, the samples were tested in their original, unopened form, without dilution, within their expiry date. With the rotational rheometer, a cone-plate or plate-plate geometry was used, depending on the viscosity of the formulations, and the measurement temperature was adapted to the dosage route (e.g. vaginal gel: 37 °C, wound healing gel: 32 °C, eye drops: 34 °C). The measurement ranges were adapted to the conditions of use of the formulations: the shear rate range was between 0.1 and 10 000 $s^{-1}$. For the microfluidic rheometer, the sample volume was 1-2.5 ml, the measurement time was 3-6 min/min, and the shear rate range was 100-10 000 $s^{-1}$ (up to 100 000 $s^{-1}$ for low viscosity solutions). In all cases, the viscosity of the reference solutions was chosen according to the values provided by the manufacturer.

# 4. Results

## 4.1. Evaluation of clotrimazole containing emulgels

### *4.1.1. Rheological behavior of the poloxamer hydrogels*

I investigated the effect of different poloxamer ratios and the addition of hydroxypropyl-methylcellulose on the gelation temperature of hydrogels. During the experiments, I observed that increasing PLX188 raises the initial viscosity of the gel measured at low temperatures, while the viscosity measured at high temperatures decreased compared to those without PLX188, meaning that PLX188 narrows the temperature-dependent viscosity range. The gel transition temperature increases with increasing PLX188, which is advantageous as it brings it closer to body temperature (Figure 3).

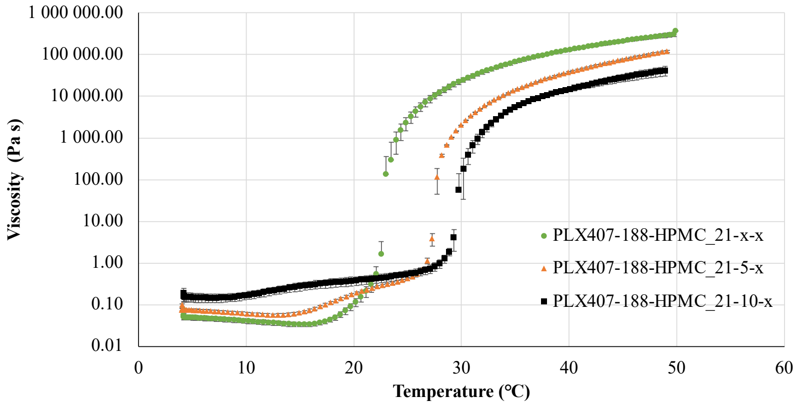


*Figure 3: 21% by weight PLX407 and 0%, 5% and 10% PLX188 and 0% HPMC containing hydrogen sol gel transition temperature*

HPMC (hydroxypropyl methylcellulose) was also added to the gels at different concentrations to improve the mucoadhesive properties of the formulation. However, based on the results, the amount of HPMC did not significantly affect either the viscosity or the gel formation temperature (Figure 4).

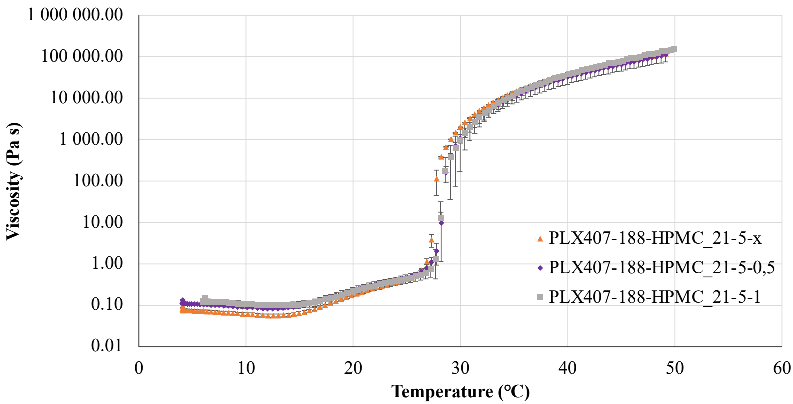


*Figure 4: 21% by weight PLX407 and 5% PLX188 with increasing amount of HPMC (0%, 0.5% and 1%)*

### *4.1.2. Rheological behavior of emulgels*

When oleic acid was added to the poloxamer-based hydrogel, immediate gel formation was observed. The final emulsion gels (emulgels) thus exhibited a stable structure at the moment of preparation and continued to show a consistent viscosity profile at both low and high temperatures, which may be beneficial in the long term in terms of the stability of the preparation. The presence of HPMC, intended to increase mucoadhesiveness, did not significantly affect viscosity values, but resulted in a slight improvement in flow properties (Figure 5).

A

B

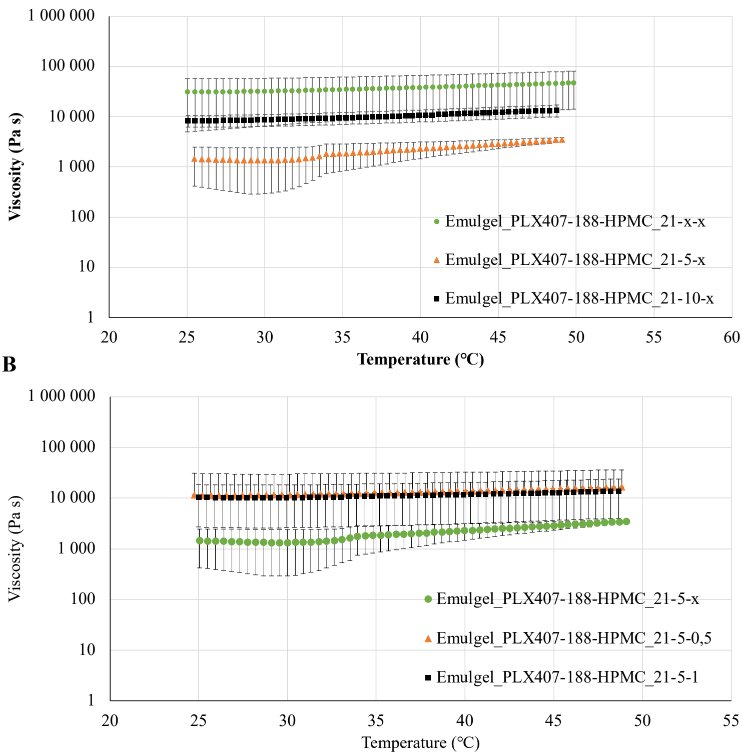


*Figure 5: Emulgels with 21% PLX407 and increasing amount of PLX188 content (A); emulgels with 21% PLX407, 5% PLX188 and increasing amount of HPMC content*

### *4.1.3. In vitro release studies*

During the vertical diffusion cell experiments, it was observed that increasing the concentration of PLX188 and HPMC resulted in faster release of the active ingredient. At the same time, clotrimazole dissolved in oleic acid showed a continuous but slower release profile from the formulations. The data obtained by multiplying the values thus show the expected active ingredient release over the entire internal surface of the vagina (Figure 6).

The results of both studies (Vertical diffusion cell and Hanson SR8+ Paddle apparatus) confirmed that increasing concentrations of PLX188 and HPMC accelerate drug release. The higher concentration of PLX188, due to its high HLB value, may facilitate the release of poorly soluble, lipophilic active ingredients from the gel matrix. Slower drug release can also be explained by the high concentration of PLX407, as its reversible heat-sensitive gel-forming properties can form a diffusion barrier at body temperature, slowing down release. Although both poloxamers and HPMC are capable of gelation, their gel-forming mechanisms are different. Poloxamers form gels in the form of micelles, while HPMC forms gels through swelling. This different water-binding mechanism can cause the gel matrix to loosen, which can also contribute to faster drug release

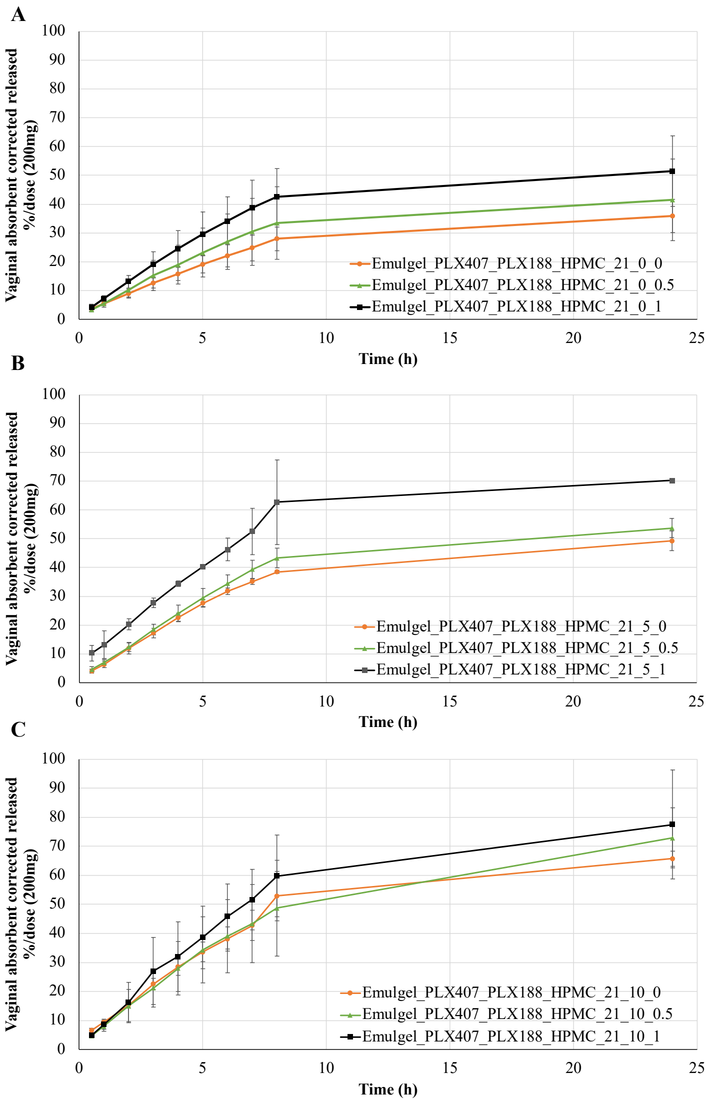


*Figure 6: Released CLZ corrected with the average vaginal size; PLX188 amount 0% (A); 5% (B) and 10% (C)*

### *4.1.4. Spreadability*

The mucoadhesion test was performed using a Texture Analyzer. The bottom tray of the device was covered with porcine mucosa to simulate natural mucosa, and then an equal amount of each formulation was placed on the surface of the mucosa. The geometry of the analyzer was then immersed in the gel, where it remained in contact with the sample for 2 seconds, and then began to be pulled upward. During the lifting process, the device recorded the force required to detach it from the gel. The less force required for detachment, the stronger the adhesion of the gel to the mucosa, i.e., the better the mucoadhesive properties observed. The measurement data shows, that increasing amount of HPMC clearly increased the mucoadhesion. The emulgel, which didn't contain HPMC neither PLX188 exhibited the least adhesion (Table II)

*Table II: Force needed to detach the emulgels from the mucosa (g). All of the gels were containing 21% PLX407, they were only differing in the amount of PLX 188 (0%, 5% and 10%) and HPMC (0%, 0.5% and 1%)*

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| **PLX 188** | **0.0%** | | | **5.0%** | | | **10.0%** | | |
|---|---|---|---|---|---|---|---|---|---|
| **HPMC** | **0.0%** | **0.5%** | **1.0%** | **0.0%** | **0.5%** | **1.0%** | **0.0%** | **0.5%** | **1.0%** |
| **Force *(g)*** | 71.17± 7.28 | 9.33± 0.76 | 5.67± 0.29 | 7.00± 1.32 | 5.83± 0.29 | 4.25± 0.35 | 5.67± 0.76 | 5.50± 0.50 | 4.83± 1.75 |

### *4.1.5. Spreadability*

The results of the area measurements were in good agreement with the observations from the mucoadhesion measurements. The emulsifying gels with higher PLX188 content covered a significantly larger area when placed between two glass surfaces. However, phase separation was also observed in the gels with the highest PLX188 content, raising questions about the physical stability of the formulations.

### *4.1.6. Microstructural investigation*

On the figure below (Figure 7) the first image shows a sample containing 21% poloxamer 407 without any additional polymers. The second image corresponds to the mid-range formulation, which includes 21% poloxamer 407, 5% poloxamer 188, and 0.5% HPMC. In both of these samples, no visible oil droplets can be observed at the given magnification. In contrast, the third image reveals clear phase separation, which is noticeable not only under the microscope but also to the naked eye. This sample contains 21% poloxamer 407, 10% poloxamer 188, and 1% HPMC.

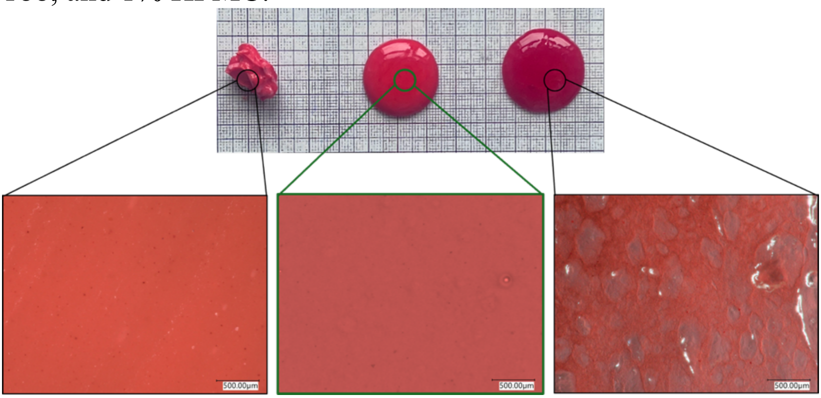

*Figure 7: Evaluation of the stability of certain emulgels with digital microscope*

## 4.2 Evaluation of clotrimazole containing emulgels

### *4.2.1. Microstructural investigation*

The Kinexus Pro+ is a high-precision rotational rheometer capable of performing various viscosity measurements in both rotational and oscillatory modes. However, it only provides reliable results in a limited shear rate range, especially at low or very high ranges. In contrast, the Fluidicam™ RHEO is a microfluidic-based measurement system that has been specifically developed for testing across a wide shear rate range and is particularly well suited for modelling situations such as injection, spraying, or even 3D printing. The accuracy of the Fluidicam device is particularly evident at higher shear rates, and the applicable shear rate range is determined by the type of microscale chip used and the rheological properties of the sample.

For low-viscosity liquid formulations (e.g., eye drops, enemas, injections), the microfluidic meter provided accurate measurements even in a wider shear rate range, detecting slight shear-thinning behaviour, while the reliability of the rotational rheometer was limited at very low or high shear rates (Figure 8). When measuring the viscosity of semi-solid dosage forms (e.g., wound healing gel, oral gel, vaginal gel), both instruments gave nearly identical results, with a difference of no more than 0.5 Pa·s in the biologically relevant shear range (1–1000 $s^{-1}$). Thanks to its low dispersion, the microfluidic meter allows for more reliable and faster evaluation. Overall, microfluidic viscosity measurement is an efficient and precise solution for the rapid characterization of pharmaceutical formulations, especially for small sample volumes and wide shear rate ranges (Figure 9).

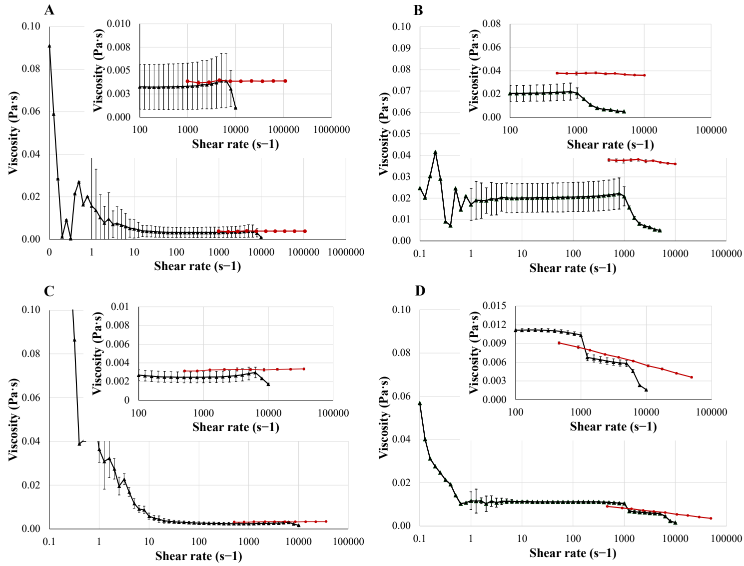


*Figure 8: Viscosity curves of the liquid dosage forms*

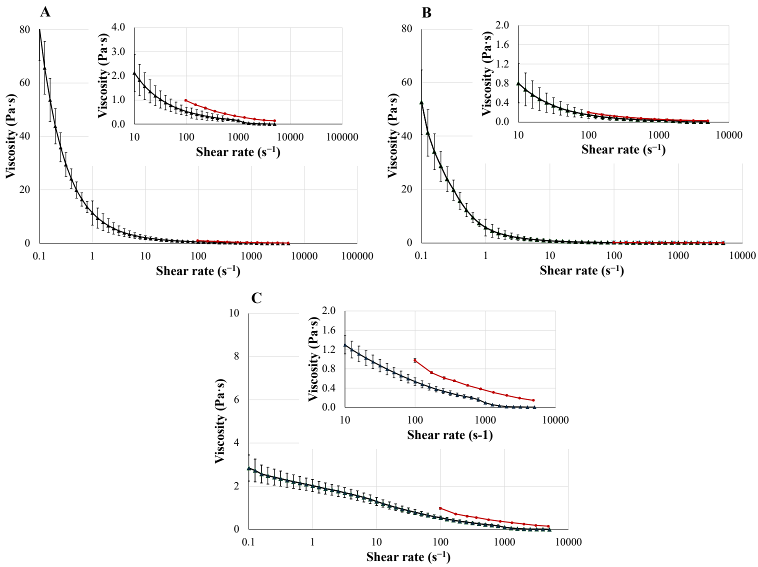


Figure 9: Viscosity curves of gel-based drug formulations

# 5. Conclusions

As a result of the research conducted during this thesis, the pharmaceutical technology factors that enable the development and application of alternative, non-hydrogel gel systems in modern drug formulation were identified. Based on the results, it can be said that poloxamer-based emulsions and microfluidic rheological measurement methods offer significant advances in the implementation of personalized, programmable drug delivery.

Key findings include:

- Formulation flexibility and customization: By adjusting the ratios of PLX407, PLX188, and HPMC, the gel network structure, viscosity, and drug release kinetics can be precisely modulated.
- Mucoadhesion and local retention: The incorporation of HPMC enhances the mucoadhesive properties of the gels, thereby increasing local residence time and improving drug delivery efficiency.
- Innovative measurement methods: Microfluidic rheology enables rapid viscosity assessment across a wide shear range using minimal sample volumes. This technology is especially advantageous for heat-sensitive or scarce samples. The results closely match those of conventional rotational rheometers, with the added benefits of faster data acquisition and reduced variability.
- Controlled and programmable drug release: In vitro studies demonstrated the capability of the developed emulgels to sustain clotrimazole release over 24 hours, supporting both small and larger single-dose applications. The content of poloxamers and HPMC

affects the release rate according to the Higuchi kinetic model.

- Physical stability and application suitability: The use of oleic acid improves the solubility of the chosen lipophilic active agent and contributes to the long-term stability of formulations. Appropriate poloxamer compositions and HPMC content ensure physical stability and a patient-friendly consistency.

Overall, poloxamer-based emulgels represent promising alternatives for local delivery of lipophilic drugs. Microfluidic rheology offers a valuable tool in modern pharmaceutical development and quality control, notably for semi-solid and liquid dosage forms. Further in vivo investigations are necessary to evaluate clinical applicability, long-term stability, and patient compliance. Continued development of microfluidic rheology, including the capacity to analyze complex biological matrices and combined physicochemical parameters, may open novel research and application avenues.

## 6. Bibliography of the candidate's publications

**Publications related to the thesis:**

**Vilimi Z**, Pápay ZE, Basa B, Orekhova X, Kállai-Szabó N, Antal I. Microfluidic Rheology: An Innovative Method for Viscosity Measurement of Gels and Various Pharmaceuticals. Gels. 2024 Jul 16;10(7):464. doi: 10.3390/gels10070464.

**Vilimi Z**, Király M, Barna ÁT, Pápay ZE, Budai L, Ludányi K, Kállai-Szabó N, Antal I. Formulation of Emulgels Containing Clotrimazole for the Treatment of Vaginal Candidiasis. Gels. 2024 Nov 12;10(11):730. doi: 10.3390/gels10110730.

**Publications not related to the thesis:**

Budai L, Budai M, Fülöpné Pápay ZE, **Vilimi Z**, Antal I. Rheological Considerations of Pharmaceutical Formulations: Focus on Viscoelasticity. Gels. 2023 Jun 7;9(6):469. doi: 10.3390/gels9060469.

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