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FORMULATION AND RHEOLOGICAL CHARACTERIZATION OF EMULSION TYPE GELS AS DRUG DELIVERY SYSTEMS

PhD thesis

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AI	Artificial Intelligence
AO	Almond Oil
API	Active Pharmaceutical Ingredient
CLZ	Clotrimazole
DAD	Diode Array Detector
HLB	Hydrophilic-Lipophilic Balance
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropyl Methylcellulose
IPN	Interpenetrating Polymer Network
JO	Jojoba Oil
LA	Lactic Acid
LLOQ	Lower Limit of Quantification
MCT	Medium Chain Triglycerides
OA	Oleic Acid
PEG	Polyethylene Glycol
PEO	Polyethylene Oxide
PLX188	Poloxamer 188
PLX407	Poloxamer 407
PPO	Polypropylene Oxide
QC	Quality Control
RSD	Relative Standard Deviation
SO	Sunflower Oil
ULOQ	Upper Limit of Quantification
USP	United States Pharmacopoeia
UV-Vis	Ultraviolet-Visible Spectroscopy
VVC	Vulvovaginal Candidiasis

1. INTRODUCTION

Gels are complex colloidal systems comprising a liquid phase structure by a gelling agent [1]. The gel matrix is a three-dimensional network, which immobilizes the dispersed liquid, creating an intermediate state between solid and liquid phases. This duality arises because: the solid-liquid network prevents liquid flow through percolation forces, while the entrapped liquid plasticizes the matrix, preventing structural collapse via osmotic stabilization [2, 3].

In the past few years, the interest in gels and various gel-forming polymers has exploded and the research into them has increased significantly. The exponential growth in gel research over the past decade reflects their transformative potential across industries. Hydrogels in particular, they have emerged as the unequivocal frontrunners. They stand out in this field, attracting attention not only for their wide range of applications, but also for their many beneficial properties. These beneficial possessions, such as their high water content, biocompatibility and versatility, allow hydrogels to play a noticeable role in many fields, not only in pharmacy but also in medicine, biomedicine, cosmetics and environmental protection [4, 5].

The popularity of hydrogels is not only due to their applicability mentioned above, but also to the fact that they are relatively easy to control and can be tailored to different needs. In addition, advanced technologies allow the development of newer and newer types, further expanding the possibilities. This dynamic development and versatility make hydrogels one of the most promising and popular branches of gel chemistry [6, 7].

The latest breakthroughs in hydrogel technology include the development of self-healing hydrogels [8], the advancement of conductive hydrogel variants for low impedance neural interface [9], and the use of AI models in hydrogel development [10]. These innovations not only enrich materials science but also accelerate the advancement of personalized medical therapies and smart drug delivery systems.

While hydrogels dominate the research landscape, alternative gel systems hold untapped potential despite their limited representation (Figure 1).

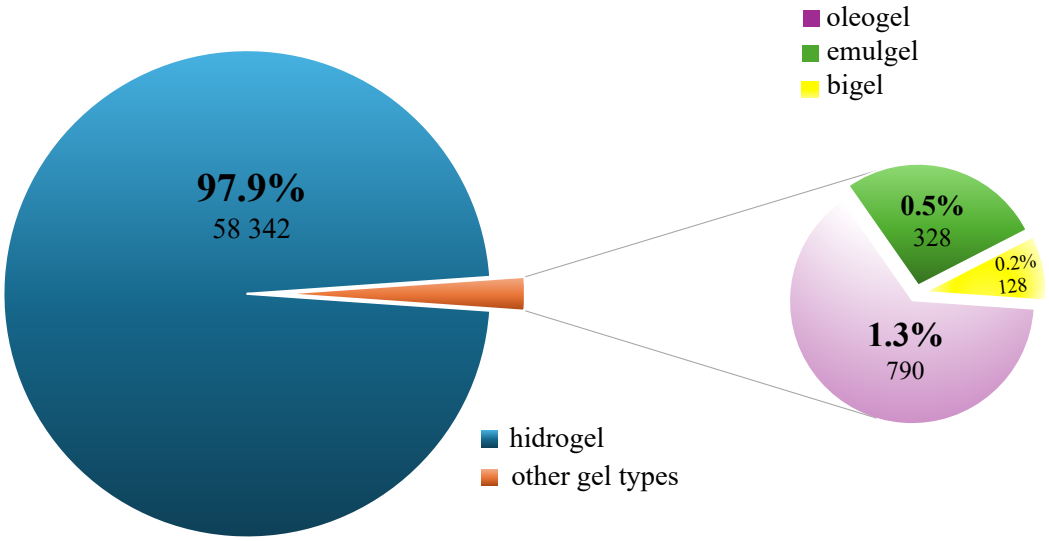

Figure 1: Mentions of different gel types

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. It is evident that hydrogels are mentioned significantly more often than other gel types. Among the gel types shown in the figure hydrogels account for 97.9% of mentions, oleogels represent 1.3%, emulgels constitute 0.5%, while bigels make up only 0.2%.

Despite the current dominance of hydrogels in the literature, non-aqueous gels possess significant pharmaceutical technological potential. The solubility of lipophilic active ingredients in oleogels, as well as the combined hydrophilic and lipophilic nature of emulgels and bigels can offer alternative solutions to the limitations of hydrogel-centered therapies, such as transdermal delivery of water insoluble active ingredients.

Based on the above, the primary objective of my doctoral research was to explore alternative gel systems capable of functioning as viable substitutes for hydrogels in pharmaceutical applications, with a focus on designing controlled and programmable drug delivery platforms. This investigation concentrated on understanding gel types – including mainly oleogles and emulgels – to address limitations inherent in hydrogel-based formulations, particularly for liphophilic and dual-phase therapeutics. My research not only expands the pharmaceutical toolkit beyond hydrogel dominance but also

provides a rheology-driven paradigm for gel design, bridging the gap between material science and drug delivery system formulations.

1.1. Gels

1.1.1. History

The first mention of gels in the scientific literature dates to 1861. Thomas Graham, a 19th century British chemist, defined them as slowly diffusing substances. He classified dispersions made of starch, gelatine, albumin and supersaturated inorganic solutions into this group. At the time, the molecular structure of these substances was still unknown, It was not until much later, in 1920, that Hermann Staudinger, a German organic chemist, developed the polymer theory, which demonstrated that long-chain macromolecules can form three-dimensional networks [11]. The classification of gels was initiated by P.H. Hermans in 1949 [12], and later refined in 1974 by Paul John Flory, an American Nobel Prize-winning chemist [13]. From the mid 20th century, the research on gels, particularly hydrogels, experienced a significant boom across multiple fields. Simultaneously, sol-gel technology also advanced: Ebelmen discovered a new method of gel formation in 1846, which by 1980 had laid the foundation for modern materials science [14]. Nowadays gels span disciplines from molecular biology to nanotechnology, through biomedicines and pharmaceutics driven be their exceptional and stimuli-responsive properties (Figure 2) [15, 16].

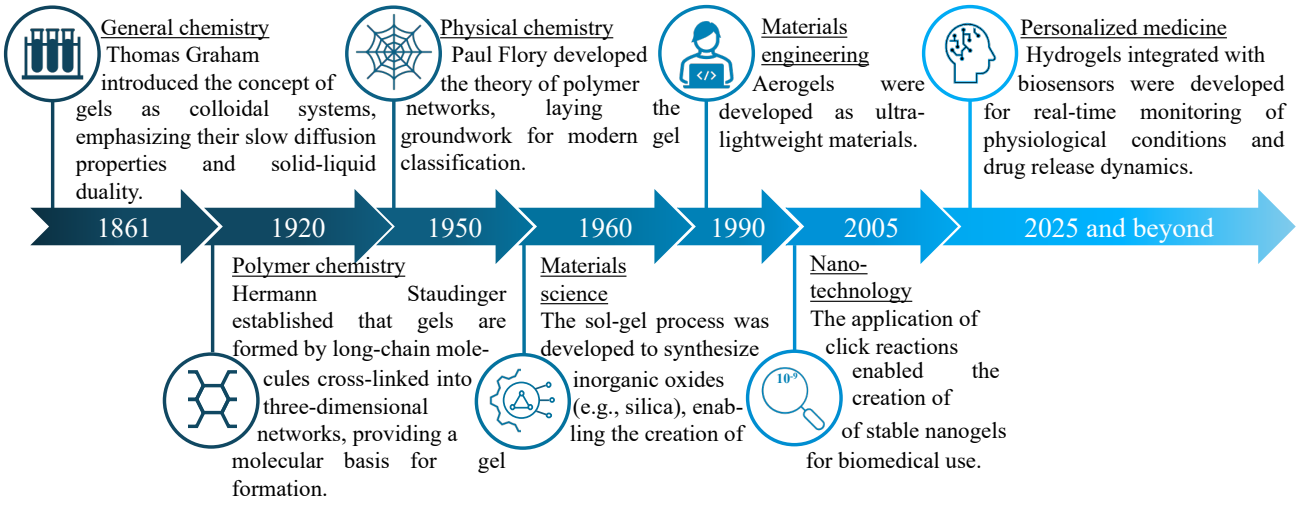

Figure 2: The history of the evolution of gels

The timeline of key milestones in the scientific development of gels, illustrating major breakthroughs across chemistry, materials science, nanotechnology, and biomedical applications.

1.1.2. Classification

There is no consensus in the literature regarding the classification of gels, as they can be categorized based on various criteria. In the following, I have conducted the classification based on the most found criteria in the literature, supplemented by my own insights (Figure 3).

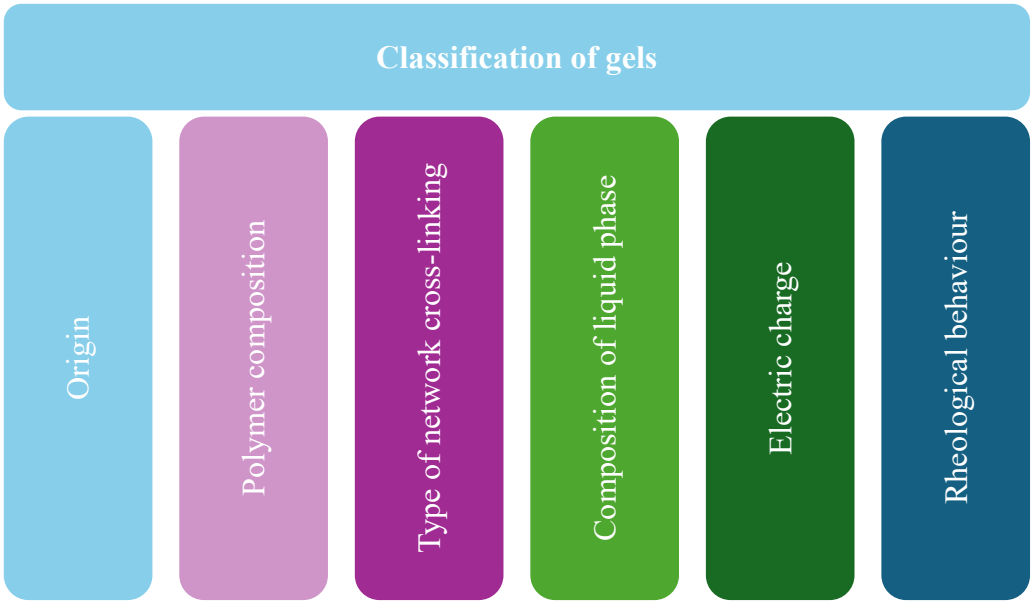

Figure 3: Classification of gels

Main criteria for the classification of gels, including their origin, used gelling agents, type of network, liquid phase composition, electric charge and rheological behaviour.

1.1.2.1. Origin

Gels can be classified according to their origin as natural or synthetic gels. Natural gels are typically formed by macromolecular gelators, such as gelatine, collagen, agar, starch, and gellan gum. These gelators build three dimensional networks primarily through physical cross-linking mechanisms [17]. The natural gelators are cost-effective, biodegradable and eco-friendly, however their mechanical strength is questionable and they can vary from batch to batch because of their natural origin [17, 18].

In contrast, synthetic gels are constructed from polymers such as polyacrylamide, poly(ethylenglycol), polyvinyl alcohol and other various copolymers. These synthetic gelators can be cross linked either physically or chemically, which also can be a sub-group during the classification of gels. With chemical cross-linking the gels will have improved mechanical strength and stability. Unlike the natural gelators, synthetic gels offer precise control over network architecture, porosity, and responsiveness to external stimuli, like pH, temperature, or ionic strength. These properties enable the designee of smart or stimuli responsive gels for specific applications, including controlled drug delivery, tissue engineering. Meanwhile some of these synthetic gels lacking the inherent biocompatibility and biodegradability of natural gels [19, 20].

1.1.2.2. Polymer composition

The classification of gels based on their polymer composition can either form a separate categorization system or be used to further subdivide gels that have already been grouped into broader categories.

Homopolymer gels are composed of a single type of monomer unit repeated throughout the polymer network. A classic example is polyacrylamide hydrogel, which is widely used in electrophoresis and as a superabsorbent material. These gels have uniform network structure and predictable swelling behaviour [1, 21].

Copolymer gels are created by combining two or more different types of monomers, which are copolymerized to form a network with specific physical and chemical properties. A good example is PEG-co-poly(lactic acid) hydrogel: this material blends the biodegradable quality of poly(lactic acid) and the biocompatible and hydrophilic nature of PEG, resulting in hydrogels with adjustable mechanical strength and degradation rates. They have a tuneable structure – such as controllable hydrophilicity, charge density, or sensitivity to external stimuli – copolymeric gels offer great versatility in areas like drug delivery, tissue engineering, and biosensing [16, 22, 23].

A further level of structural complexity is found in multipolymer or interpenetrating polymer network (IPN) gels. IPN gels are consist of two or more independent polymer network that are physically entangled but not covalently bonded to each other. The networks may be formed sequentially or simultaneously, resulting in synergic properties that are not attainable with single polymer gels [24].

1.1.2.3. Type of network cross-linking

It is again evident that this group can stand as an independent category, but it may also serve as a subgroup within broader classification frameworks. The two main categories based on the type of the network cross-linking are physical gels and chemical gels. Physical gels are formed through non-covalent interactions such as hydrogen bonding, ionic interactions, van der Waals forces and hydrophobic interactions [25].

Chemical gels, on the other hand, are formed by covalent bonds creating a permanent three-dimensional network. This covalent cross-linking imparts greater mechanical stability and durability to the gel. A common example of a chemically cross-linked gel is polyacrylamide gel, widely used in electrophoresis and biomedical applications due to its robustness and stability [26, 27].

1.1.2.4. Composition of the liquid phase

One of the most fundamental and widely used criteria for classifying gels is the nature of their liquid phase, or dispersion medium. In this context, gels are generally divided into hydrogels and organogels (oleogels) [28].

Hydrogels are three-dimensional polymeric networks that absorb and retain large quantities of water, often exceeding 90% of their total mass, while maintaining their structural integrity. This water content imparts hydrogels with unique physicochemical properties such as flexibility, biocompatibility, and the ability to mimic natural tissues, making them highly attractive for biomedical, pharmaceutical and tissue engineering applications [29, 30].

In contrast, organogels (or oleogels) are formed when the liquid phase is an organic solvent or oil, structured by a suitable organogelator. Organogels are particularly valuable for the encapsulation and delivery of lipophilic active agents, and find applications in pharmaceuticals, cosmetics, and food technology [31, 32].

In addition to hydrogels and oleogels, emulgels represent an increasingly important and popular type of gel that combine the properties of emulsions and gels in a single system. They are created by incorporating an emulsion – typically oil-in-water (O/W) or water-in-oil (W/O) – into a gel matrix. This unique structure allows emulgels to carry both hydrophilic and lipophilic active ingredients at the same time. The gel not only helps stabilize the emulsion and prevent phase separation, but also gives the formulation favourable rheological characteristics, like better spreadability and controlled release of active compounds. Thanks to these benefits, emulgels have become widely used in pharmaceutical products and transdermal drug delivery systems, offering better skin absorption and improved patient comfort compared to ointments [33, 34].

Beyond the main categories, there are several specialized types of gels with unique structures and applications. Bigels represent hybrid sytems that combine both hydrogel and oleogel phases, enabling the simultaneous delivery of hydrophilic and lipophilic substances [35, 36]. Xerogels are formed by drying gels to remove most or all their liquid content, resulting in rigid, porous material that still preserves much of the original network structure [37].

1.1.2.5. Electric charge

Gels can also be categorized based on their electrical charge, which plays a crucial role in determining how they interact with their surroundings, what active ingredient can they deliver and what applications they are best suited for [19].

Non-ionic gels don't have charge in their matrix. Their inert nature is advantageous in biomedical applications where minimal interaction with biological components is desired. Ionic gels can be divided into two sub-groups: cationic and anionic gels. Anionic gels, such as alginate, often contain carboxylate or sulphate groups, while cationic gels, like chitosan gels, include ammonium or amine groups. These gels can interact strongly with oppositely charged molecules [38].

The ion distribution in an amphoteric gel is symmetric, they contain both positive and negative charges within the same polymer network [39]. Zwitterionic gels have repeating units that simultaneously contain both positive and negative charges, but the overall molecule remains electrically neutral. These materials exhibit exceptional resistance to protein adsorption and biofouling, making them highly biocompatible. As a result, zwitterionic gels are particularly useful in biomedical applications requiring non-fouling surfaces, such as biosensors, implant coatings, and advanced wound dressings [40-42].

1.1.2.6. Rheological behaviour

Gels can be classified according to their rheological behaviour, which show their mechanical response under stress and their suitability for certain applications [19]. These rheological behaviours (shear-thinning, thixotropic, viscoelastic, etc.) are determined by the gel's properties, like internal structure, type of cross-linking, response to external forces and critic [43-45].

Since rheology is a distinct scientific discipline, gels can be classified into several subgroups based on their rheological behaviour. In this dissertation, rheology will be discussed in detail in a separate section later.

1.1.3. Significance of gels

Thanks to their unique structure and high fluid content, gels play a significant role across various fields of science, technology, and industry. Their three-dimensional network makes them suitable carriers for a wide range of active substances, which may be

hydrophilic or lipophilic depending on the liquid phase [46-48]. In medicine and pharmaceutical sciences, gels facilitate targeted and programmed drug delivery, enabling localized therapies and reducing side effects [49]. Certain types of hydrogels have gained particular popularity due to their biocompatibility, tuneable mechanical properties, and resemblance to biological tissues, making them widely used in wound care, tissue engineering, and regenerative medicine [49, 50].

Beyond healthcare, gels are also key materials in food science, where they are used to improve texture, stability, and consumer acceptability [51]. In environmental protection, their high absorption capacity makes them suitable for water purification and pollutant removal [52, 53].

Thanks to their adaptability – from smart, stimulus-responsive hydrogels to multiphase bigels and emulgels – various gel systems continue to drive innovation in sensing technologies, nanotechnology, and advanced manufacturing. As a research progresses, the precise design and tuning of gel properties is enabling the emergence of new functionalities, further increasing their importance in both traditional and emerging technologies [48, 54].

1.1.4. Growing interest in alternative gel types

Despite the longstanding dominance of hydrogels, recent years have seen growing research and industrial interest in the development of non-hydrogel-based gels, such as oleogels, emulgels and bigels. This trend stems from the recognition of the limitations of hydrogel-centric approaches and the increasing demand for personalized drug formulations [55].

Olegels – oil-based systems structured with organogelators – are gaining popularity for the delivery of lipophilic active ingredients, as they can effectively dissolve such compounds and enhance skin penetration [56]. Emulgels, which combine the advantages of emulsions and gels, enable the simultaneous delivery of both hydrophilic and lipophilic drugs while providing controlled drug release [57]. Bigels, hybrid systems that unite hydrogel and oleogel phases, further expand formulation possibilities by enabling the co-delivery of active ingredients with differing solubilities. Additionally, their mechanical properties and drug release profiles can be finely tuned, making them versatile platforms for advanced drug delivery applications [35].

In recent years, nanogels and nanoemulgels have come to the forefront due to their ability to protect sensitive active pharmaceutical ingredients (APIs), deliver them in a targeted manner and respond to environmental stimuli [58]. For the pharmaceutical industry, these alternative gel types offer not only cost-effectiveness and improved patient comfort, but also enhanced compliance with regulatory expectations, particularly through the use of natural, biodegradable components [56].

The latest advances in formulation science and materials engineering – such as AI assisted gel design and the development of smart gels – are further expanding the application potential of these alternative gel systems [59]. These innovations aim not only to overcome the limitations of hydrogel-cantered therapies but also to open new directions in personalized treatments, combination formulations, and sustainable pharmaceutical development. As a result, the research and optimization on non-hydrogel-based gel systems has become an integral part of modern pharmaceutical technology, contributing significantly to the expansion of therapeutic options and the creation of next-generation drug delivery platforms [60].

1.2. Rheology

1.2.1. Introduction into rheology

Rheology is the science of the flow and deformation behaviour of materials, which studies how different materials – e.g. pharmaceutical liquids, gels, etc. – respond to external forces, and how their shape or flow properties change over time and under different conditions [61].

Materials can exhibit purely elastic, purely viscous, or a combination of these, viscoelastic behaviour. Rheological analysis characterizes these responses by relating stress (force per unit area) to strain (deformation) or strain rate (rate of deformation). Behaviours such as shear thinning, shear thickening, yield stress, and thixotropy are quantified through rheological functions, which form the basis for process design, product performance, and quality control across industries – including pharmaceutical industry, where dosage forms like gels, creams, and suspensions rely on well-defined flow properties to ensure stability, application performance, and controlled drug release [62].

1.2.2. Basic concepts

To understand the science of rheology, it's necessary to introduce the fundamental concepts and models, as these are used to describe and interpret the deformation and flow behaviour of different materials – including pharmaceutical preparations. Among the most common parameters used to characterize rheological properties are the shear rate (G [s^{-1}]), which is the quotient of the velocity difference and the distance between two layers moving relative to each other, and the force per unit area, known as shear stress (τ [Pa] or [N/m^2]). Viscosity (η [$Pa\ s$]) is defined as the ratio of these two quantities [63].

1.2.2.1. Deformation types and models

Deformation is a physical change in which the shape or size of a material changes under the influence of an external force. The type and extent of deformation depend on the material and the type and magnitude of the load applied to it. Deformations are classified into three main groups based on their behaviour over time: elastic, viscous, and viscoelastic deformation [63, 64].

During elastic deformation, the material deforms under the influence of an external force acting on it but regains its original shape after the force is removed. This behaviour can be described by Hooke's law, which states, that there is a linear relationship between stress and strain. This type of deformation is characteristic for example, of solid materials such as metals under low loads or of spring like material models [65, 66].

Meanwhile during viscous behaviour, the deformation of the material is irreversible: it doesn't return to its original shape even after the force is removed. The behaviour can be described based on Newton's law [44].

Most of the semi-solid materials, such as creams, gels, ointments are neither purely elastic nor purely viscous, but exhibit a combination of the two, known as viscoelastic behaviour. In such materials, the deformation is partly reversible and partly permanent [63]. Various mechanical analogies are used to characterize the behaviour of viscoelastic materials, such as:

- Maxwell model: a spring and a dashpot connected in series (suitable for modelling immediate elasticity and long-term continuous flow),
- Kelvin-Voigt model: a spring and a dashpot connected in parallel (suitable for modelling short-term viscoelastic responses),

- Burgers model: a combination of the two above, used to characterize complex time-dependent responses [67].

1.2.2.2. Complex rheological behaviour

Most real materials, especially semi-solid and viscous systems (gels, creams, suspensions) used in pharmaceutical applications, exhibit complex rheological behaviours that deviate from ideal (pure elastic or viscous) models. The description of these behaviours is essential for formulation, manufacturing, storage, usability, and drug delivery [68].

In shear thinning materials, viscosity decreases as shear rate increases. This behaviour is common in gels, creams, emulsions, as it facilitates easier spreading or injection, and after the application the material sets and regains its higher viscosity [69]. Shear thickening or dilatant materials increase their viscosity with increasing shear rate. This is a rarer phenomenon but can be observed in certain suspensions or highly filled disperse systems [70]. Yield stress is a characteristic of materials that only begin to flow after a certain minimum stress (the yield stress) is exceeded. Below this threshold, the material behaves as a solid; above it, it flows like a liquid. Such behaviour can be seen in pastes, ointments, some gels, and emulsions [71]. These complex rheological behaviours are shown below (Figure 4).

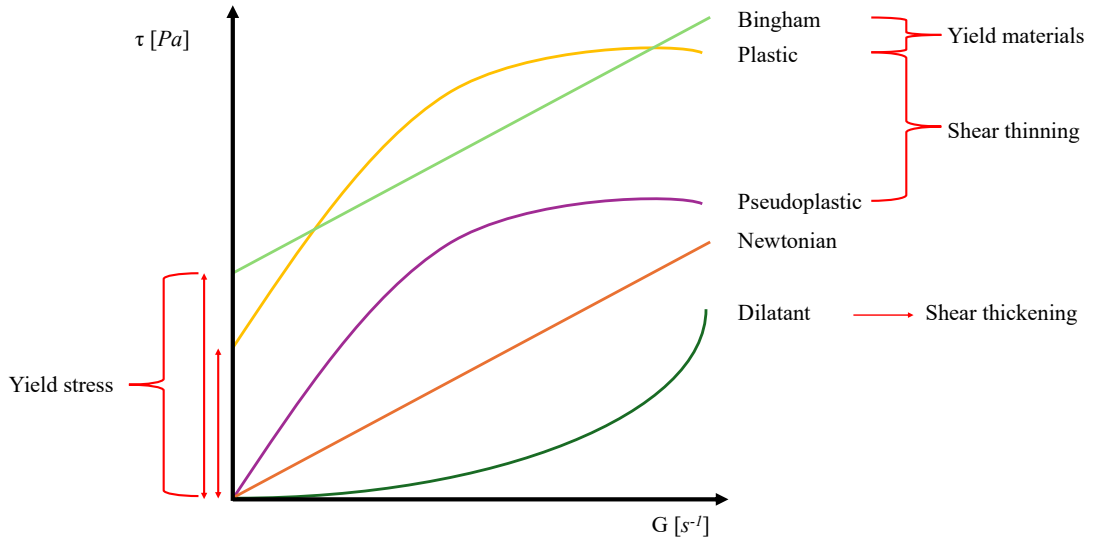

Figure 4: Schematic representation of flow behaviour in different types of rheological materials

Newtonian fluids have constant viscosity (linear curve). Pseudoplastic (shear-thinning) materials show decreasing viscosity with shear rate, while dilatant (shear-thickening) ones show increasing viscosity. Plastic materials (e.g., Bingham) require a yield stress before flow begins. These behaviours are crucial in formulating and processing pharmaceutical semi-solids.

1.2.3. Rheological measurement methods

Mapping the rheological properties is essential for understanding the flow and deformation behaviour of pharmaceutical systems. The choice of measurement method and measuring device directly affects the reliability and relevance of the data [72]. Without being exhaustive, the most used viscosimeters are:

- Rotational viscosimeters: frequently used conventional rheometers, mainly for measuring the rheological properties of gels, creams and other structured liquids. These instruments can be operated in controlled shear stress or shear rate mode, allowing the recording of flow curves and viscosity profiles, but usually on a lower shear rate [62, 73].
- Oscillating viscosimeters: there are rotational viscosimeters that have an oscillating mode, during which both storage and loss modulus can be determined, providing information on the viscoelastic behaviour and

structural integrity of the materials under test. However, a disadvantage of some of the oscillating and rotational types of viscosimeters is that they require a large sample size for measurement [73, 74].

- Capillary viscosimeters: capillary viscosimeters include the Ostwald, Ubbelohde and Canon-Fenske types. The measurement is based on measuring the flow time per unit volume of liquid through a glass capillary. They are generally used to measure samples of lower viscosity [75].
- Falling ball viscosimeters: the measurement of viscosity is based on the falling velocity of a ball dropped into the measured substance [76].
- Microfluidic viscosimeters: a new, innovative measurement method that determines the viscosity of a sample by measuring the relative flow rate of a reference material and the sample flowing through a microfluidic chip [77, 78].

Among the previously listed rheological measurement methods, microfluidic viscosimeters are offering a modern, efficient way to assess the viscosity of pharmaceutical samples. Unlike conventional rotational devices, these systems require only a very small amount of sample and are capable of delivering accurate results across a broad range of shear rates (Figure 5).

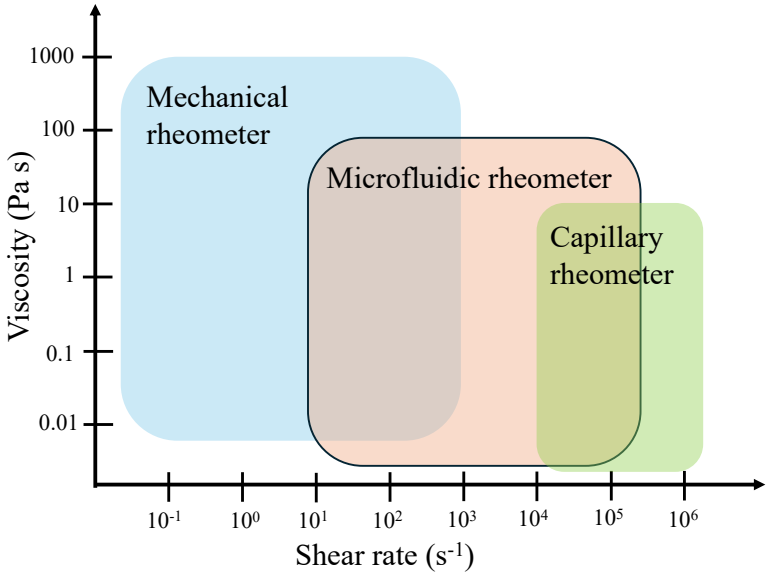

Figure 5: Schematic comparison of the operational ranges of mechanical (rotational), microfluidic and capillary rheometers for viscosity measurements as a function of shear rates [78]

Mechanical rheometers (blue) are suitable for low to moderate shear rates [79]. Microfluidic rheometers (red) bridge the gap between the shear ranges of mechanical and capillary rheometers, enabling measurements at lower viscosities and extend the accessible shear window [78, 80]. Capillary rheometers (green) are optimized for high shear rate applications with lower viscosity fluids, but typically operate over narrower viscosity range [81].

The principle of microfluidic rheometers is based on co-flowing a test sample alongside a reference fluid inside a microchannel. Due to the narrow geometry of the channel, the two fluids flow in parallel without mixing, maintaining a stable interface between them. Two different microfluidic chips with different gap diameters can be used based on the character of the measured sample (Figure 6).

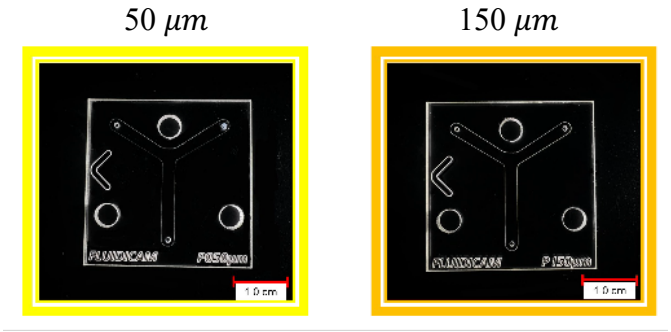

Figure 6: Microfluidic chips with different gap diameters [78]

The chip used for the measurement can be chosen according to the characteristics of the samples to be measured.

The exact position of this interface depends on the relative viscosities of the fluids and their flow rates and is detected optically by a built-in camera system. Since the viscosity of the reference fluid is known, the system calculates the viscosity of the sample based on how the interface shifts under controlled flow conditions (Figure 7) [82].

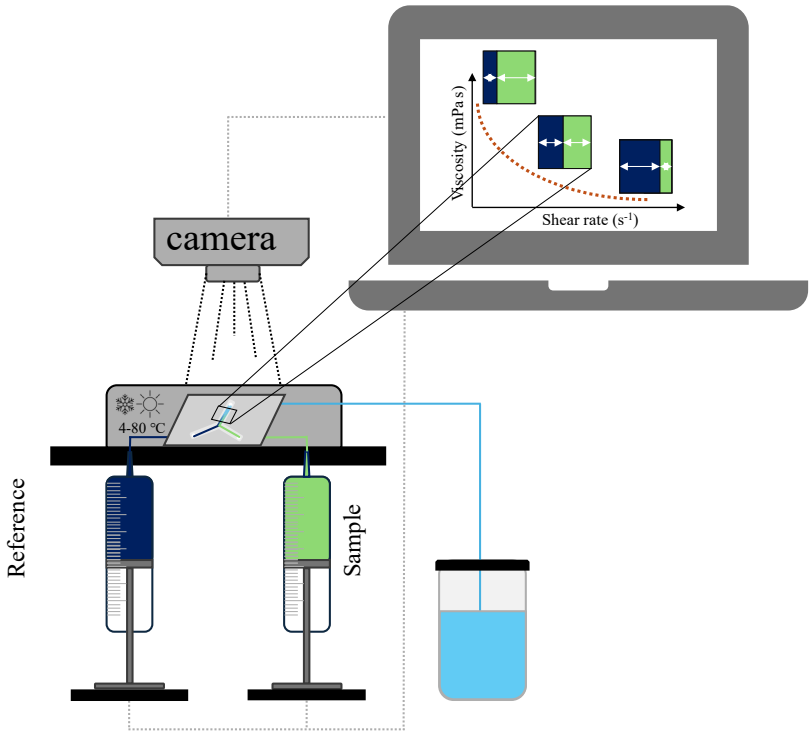

Figure 7: Schematic illustration of a microfluidic viscosimeter [78]

The equipment has a dual-syringe system for the reference and sample, temperature-controlled measurement system, camera-based on-line observation, and computer assisted analysis of viscosity.

The technique is particularly useful in pharmaceutical applications, where working with small sample volumes, temperature-sensitive materials, or complex formulations are often necessary.

1.2.4. The role of rheology in gel development

The rheological properties of gels play a key role in their successful formulation as they have a direct impact on stability, usability, user experience and drug delivery. Rheological measurements also provide information on the internal structure, mechanical strength, elasticity, and shape retention of gels. By varying the formulation parameters, rheological properties can be tailored to adapt the gel to the needs of the desired application. Rheological analyses allow the identification of formulation variations between batches and can be predict the long-term stability of gels, such as susceptibility to syneresis, phase separation or structural degradation during storage or application [62, 83].

The viscoelastic and flow properties of gels influence the diffusion and release rate of the active substance. Finally, sensory properties such as texture, lubricity, adhesion are closely related to rheological parameters. Optimising these increases patient acceptability, comfort, and patient compliance [62, 83].

Advanced rheological characterisation enables the design of stimulus-sensitive gels (e.g., temperature-sensitive gels, pH-sensitive gels) with properties that adapt to environmental changes, thus allowing controllable and programmable drug delivery [84].

Rheology forms a bridge between materials science and pharmaceutical technology, enabling the informed design, optimisation, and quality assurance of gel-based drug forms. Through rheological studies, the structure, processability, stability, drug delivery and user experience of gels can be controlled and improved [83].

2. OBJECTIVES

2.1. Objectives in the formulation of gels

My research is based on the recognition of the dominant position of hydrogels and the growing scientific interest in alternative gel types, focusing on the mapping of the pharmaceutical application of non-aqueous gel systems – primarily oleogels and emulgels. The aim of my work is to expand the pharmaceutical toolbox beyond hydrogels by developing lipophilic and two-phase systems.

In the first year of my PhD studies, I summarized the work I had started during my undergraduate training, focusing on oleogels for topical use [85]. After that, I started to shift my focus to other gel types and indications. The choice fell on in-situ formulating emulgels for vaginal use. In the first steps of the work, I mapped the rheological properties of poloxamers and poloxamer compositions with different ratios serving as the basis of emulgels, and then examined how the rheological properties were affected by the addition of different oils to the hydrogel base.

Poloxamers are triblock copolymers consisting of a central hydrophobic polypropylene oxide (PPO) and two hydrophilic polyethylene oxide (PEO) blocks in a PEO-PPO-PEO structure. These triblock copolymers have amphiphilic properties that make them highly attractive for pharmaceutical applications [86]. Poloxamer 407 is the most widely studied member of the poloxamer family. Its thermoresponsive properties are particularly valuable, as it exists in aqueous solution as a sol at lower temperatures and as a gel at higher temperatures, depending on its concentration [87].

One of the main objectives of my doctoral thesis was to develop alternative non-hydrogel-based drug delivery systems that offer a more advanced approach to pharmaceutical technology beyond the dominance of hydrogels, especially for lipophilic or biphasic therapeutic needs. The focus of the research was on an emulsion type gel formulation, the development of which was driven by its suitability for the topical treatment of vulvovaginal candidiasis (VVC).

Vulvovaginal candidiasis, most caused by Candida albicans, is a recurrent and often taboo infection affecting a significant proportion of woman, causing irritation, itching, discomfort, and inflammation of intimate regions. The disease is not only physically but

also psychologically burdensome for patients, while currently available forms of medication such as suppositories, tablets, capsules, or creams are often uncomfortable to use, can cause irritation, and do not provide adequate drug delivery or patient comfort. Clotrimazole (CLZ) is one of the most widely used topical antimicrobials, but its water solubility is extremely low, making it particularly challenging to formulate, especially for target areas where local but well-controlled drug delivery is required.

The aim of my research was to create an emulsion-type dosage form that combines the favourable rheological properties of gels with the solubility of emulsions, and thus may be suitable for the efficient delivery of CLZ through the vaginal mucosa. The chosen gelling agents, in particular the heat-sensitive poloxamers, allow the formulation to be in a liquid state at the time of administration and then convert to a gel at body temperature, thus facilitating retention and prolonged release. By using different poloxamer compositions and oil phases, the aim was to optimise the viscosity, stability and drug release properties of the formulations while minimising the feeling of discomfort.

During the research, rheological measurements were performed to investigate the mechanical properties of the formulations in detail, as well as in vitro drug release studies under different conditions (e.g., vertical diffusion cell, paddle apparatus, different pH values and solvent compositions) to ensure that the formulation approximates as closely as possible the vaginal environment. My aim was also to develop a formulation that not only delivers the active ingredient efficiently, but also meets the physiological requirements of the vaginal environment – for example, it does not negatively affect the natural pH or microbial balance.

Overall, therefore, my objective was to develop an innovative, well-tolerated, heat-sensitive, emulsion typed gel for the effective, convenient, and patient-friendly treatment of vaginal candidiasis that not only offers a technologically advanced approach, but also has the potential to improve patient compliance and quality of life.

2.2. Objectives in rheological method development

During my doctoral thesis, I focused on the rheological investigation of gel-based formulations, as these properties are essential for the stability, applicability, and drug release profile of the formulations. The main objective of my research was to develop and

characterise alternative non-hydrogel type systems with a focus on their rheological behaviour and its relevance in pharmaceutical technology.

During the development of the gels, I have systematically investigated the rheological properties of samples of different compositions to explore how the poloxamer concentrations, the type and proportion of oil phase and the presence of different excipients affect the structure and mechanical behaviour of the gel network. I considered it particularly important to analyse the temperature-dependent rheological responses, as the temperature sensitivity of poloxamer-based systems is a key issue in drug formulation: these gels exhibit a sol-gel transition, i.e., they are liquid in lower temperatures and turn into gels at body temperature [88].

The other main line of research focused on the methodological development of rheological assays and the evaluation of their application in pharmaceutical technology. The aim was to compare measurements performed with conventional rotational rheometers with a new microfluidic-based viscosity measurement technique and to explore their advantages, limitations, and specific applications in the pharmaceutical industry, especially for semi-solid dosage forms.

The use of microfluidics has made it possible to determine the viscosity of the formulations in a small, rapid, and precise way, and to study in detail the effect of different environmental parameters such as vaginal pH and electrolyte concentration. The resulting data have helped to provide a more accurate picture of the conditions under which the formulations retain their structure and the extent to which their viscosity varies in real application environments.

My intention was also to demonstrate that microfluidic methods can be effectively applied as a modern tool for rheological characterization in drug development, especially where sample volume is limited, speed of measurement is critical, or accurate monitoring of environment-dependent changes is of paramount importance.

This technique allows fast and accurate rheological characterisation of small sample volumes, especially in low viscosity or heat sensitive systems. I compared the results obtained with two types of viscometers and highlighted the relative advantages and disadvantages of the methodologies based on these comparisons [78].

3. MATERIALS AND METHODS

3.1. Materials

3.1.1. Materials used to prepare gels

Poloxamer 407 (Pluronic F-128; PLX407) and poloxamer 188 (Kolliphor P188; PLX188) were used as the gelling agents in the preparation of hydrogel and emulgel bases. These systems can undergo reversible sol–gel transitions triggered by temperature changes, making them especially advantageous for vaginal drug delivery applications. Poloxamers are widely used in pharmaceutical technology due to their favourable physicochemical and biological properties. In addition to their temperature-sensitive gelation behaviour, they exhibit excellent biocompatibility and low toxicity profiles, which are crucial for mucosal applications [89-91]. Moreover, their amphiphilic structure allows them to act not only as gelling agents but also as effective emulsifiers, enabling the incorporation and stabilization of lipophilic active pharmaceutical ingredients [92]. These characteristics make poloxamer-based systems highly suitable candidates for the development of safe and effective vaginal formulations [90].

To optimize the emulgel formulations, we tested a variety of oils incorporated at different concentrations into the poloxamer-based hydrogel matrix. The oils selected for this study included jojoba oil (JO), medium-chain triglyceride (MCT) oil, sunflower oil (SO), almond oil (AO), and oleic acid (OA). These oils were chosen due to their widespread use in pharmaceutical applications, as well as their varying fatty acid profiles and potential for solubilizing lipophilic drugs.

We varied the oil content in the formulations to explore how different oil types and concentrations impacted the gel's structure and overall properties. These oils differ in terms of their viscosity, polarity, and solubilization capacity, which can influence the stability of the emulsion and the drug-release characteristics. Among the oils tested, oleic acid was the most promising, as it demonstrated excellent solubility for CLZ and formed stable systems when incorporated into the poloxamer matrix [93].

Clotrimazole, a widely used antifungal agent, was used as the model active pharmaceutical ingredient (API) due to its poor water solubility and proven efficacy

against Candida albicans. Additional excipients, including hydroxypropyl methylcellulose (Pharmacoat 606, HPMC) were used to increase mucoadhesivity (Table I) [94].

Table I: Materials used to prepare the emulgels

Abbreviation	Name	Role	Purchased
PLX407	Pluronic F-128	Gelling agent	Sigma-Aldrich
PLX188	Kolliphor P188	Gelling agent	Sigma-Aldrich
HPMC	Pharmacoat 606	Mucoadhesivity	Shin-Etsu Chemical Co.
CLZ	Clotrimazole	API	Molar Chemicals Kft.
OA	Oleic Acid	lipophilic phase	Sigma-Aldrich
JO	Jojoba oil	lipophilic phase	Ellemental S.R.L.
MCT	Middle chain triglyceride	lipophilic phase	Nutricia
AO	Almond oil	lipophilic phase	Neuston Healthcare Kft.
SO	Sunflower oil	lipophilic phase	Molar Chemicals Kft.

3.1.2. Materials used for rheological tests

In addition to the formulated emulgels and hydrogels, a selection of commercially available pharmaceutical and medical products was also tested rheologically (Table II). These products were used during the microfluidic rheological measurement to explore how the method performs across different dosage forms and viscosities, and to assess its potential applicability in pharmaceutical technological formulation processes.

The products represented a wide range of administration routes, including vaginal, topical, oral, rectal, ophthalmic, and injectable forms. Our goal was to cover both liquid and semi-solid systems with varied composition and rheological behaviour.

All samples were used as received, without any modification or dilution, and measurements were performed within their expiration dates. The inclusion of these products allowed us to test the microfluidic viscosimeter across a broad spectrum of viscosities and textures, and to observe how the method responds to real-word pharmaceutical formulations with varying structural properties.

Table II: Overview of commercially available pharmaceutical products
The table summarizes the dosage form, the administration route, active pharmaceutical ingredient, viscosity-modifying excipients (if present), and intended clinical indication of each product [78, 95-101]

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

3.2. Methods

3.2.1. Preparation of hydrogel and emulgel formulations

Hydrogels were prepared by dispersing appropriate quantities of PLX407 and PLX188 in cold distilled water (4 °C) under magnetic stirring at 300 rpm [102]. The preparations were refrigerated for 24 hours to allow complete dissolution and micellization. For preparations that also contained HPMC, HPMC was added to the distilled water together with the gelling agents.

For the preparation of the emulgels, the selected oils were incrementally incorporated into the preformed hydrogel base under continuous mixing using an Ultra-Turrax homogenizer (IKA-WERK GmbH & Co. KG; Staufen, Germany). The mixture was homogenized at 3000 rpm for 2 minutes, with the process consisting of alternating 1-minute mixing periods followed by 15-minute cooling intervals to maintain the appropriate gel temperature. In the case of the API containing formulations, the required amount of CLZ was previously dissolved in the OA before adding it to the hydrogel base. For each emulgel, exactly 30 grams were prepared.

In some cases, I adjusted the pH of the prepared emulgels to vaginal pH (3.8-4.2) [103]. During the preparation of these, I added lactic acid (LA) from Molar Chemicals Kft. (Halásztelek, Hungary) drop by drop to the formulation.

The sequence of experiments with gels selected for vaginal use is shown in the figure below (Figure 8).

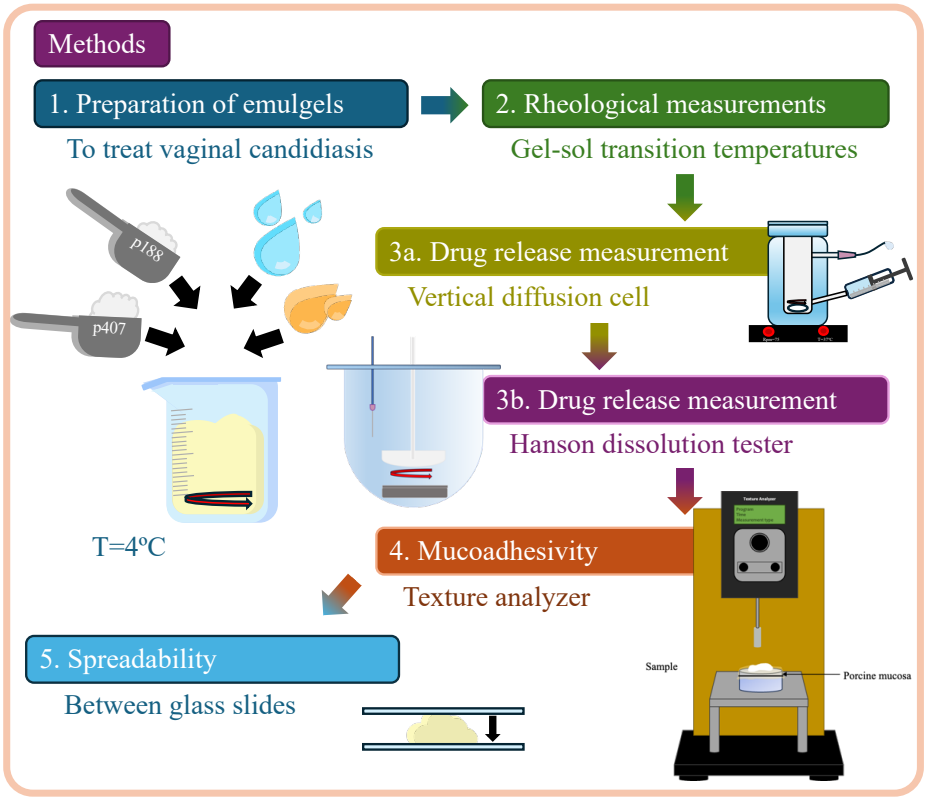

Figure 8: Experimental workflow for the development and characterization of emulgels intended for vaginal drug delivery [104]

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.

3.2.2. In vitro release and diffusion studies

Diffusion through a membrane from the emulgel formulations was studied using vertical diffusion cells. The formulations were loaded into the donor compartment, separated from the acceptor phase by a cellulose acetate membrane that had been previously impregnated with the release medium itself [105]. The receptor compartment was loaded with 7.5 mL of phosphate buffer at pH 4.5 mixed with 35% ethanol to enhance the solubility of CLZ [106-110]. The system was maintained at 37 °C to replicate physiological conditions. Samples were collected at specific time points (0.5, 1, 2, 3, 4, 5, 6, and 24 hours) and

analyzed using UV-Vis spectroscopy after HPLC separation. Three replicates were performed for each preparation.

The chromatographic analysis was carried out using an Agilent Series 1100 liquid chromatography system (Agilent Technologies, Santa Clara, CA, USA). The separation of clotrimazole was performed on a Phenomenex® Luna C18(2) column (4.6 mm × 250 mm, 5 μm particle size, 100 Å pore size; Torrance, CA, USA). The column and autosampler were both maintained at 25 °C throughout the measurements. A 5 μL sample volume was injected, and isocratic elution was conducted at a flow rate of 2 mL/min using a mobile phase composed of acetonitrile and water in a 70:30 (v/v) ratio. Detection was achieved using a UV diode array detector (DAD) set to 210 nm. Quantification of clotrimazole was based on an external calibration curve, prepared by diluting a stock solution into seven concentration levels, each measured in duplicate at the start of the run. The calibration demonstrated excellent linearity, with an R^2 value of 0.9997. The lowest and highest points of the curve established the lower limit of quantitation (LLOQ) and upper limits of quantitation (ULOQ), respectively. Precision and accuracy were evaluated within a single day by analyzing five replicates of quality control (QC) samples at low and high concentrations. Accuracy was expressed as the percentage of the nominal concentration, while precision was reported as relative standard deviation (RSD). Both parameters satisfied the acceptance criterion of ±5%.

In the second in vitro release experiment, the formulations were placed into metal ointment cells, which were separated from the release medium by a cellulose acetate membrane. The dissolution medium consisting 500 mL of a pH 4.5 phosphate buffer–ethanol mixture (65:35 v/v), was kept at a temperature 37 ± 0.5 °C. Release testing was conducted using the USP paddle method on a Hanson SR8 Plus dissolution apparatus (Hanson Research, Chatsworth, CA, USA) at a stirring speed of 50 rpm. Samples (5 mL) were withdrawn at predefined intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hours) and analysed spectrophotometrically at 205 nm. The withdrawn volume was replaced with fresh medium to maintain sink conditions. Each formulation was tested in triplicate (n = 3).

To evaluate drug release kinetics, the Higuchi model was applied to the average release data obtained during the first 8 hours of testing. According to this model, the amount of drug released is directly proportional to the square root of time, expressed by the equation:

$$Q = K_H \times \sqrt{t}$$

where Q represents the cumulative drug released per unit area (mg/cm²), K_H is the Higuchi release constant, and t denotes time in hours [104].

3.2.3. Rheological characterizations of emulgels for vaginal use

The rheological properties of the tested emulgels were analyzed using a Kinexus Pro+ rotational rheometer (Malvern Instruments Ltd., UK) equipeed with a CP4/40 cone-plate geometry (gap: 0.15 mm). Measurements were taken at a constant shear stress of 1 Pa over a temperature range of 5 to 50 °C. The study focused on determining the sol-gel transition temperature and temperature-dependent viscosity of hydrogels containing varying ratios of poloxamer 407 (PLX407) and poloxamer 188 (PLX188), as well as emulsion gels derived from these hydrogels. Three parallels were measured.

3.2.4. Mucoadhesive measurement

The mucoadhesive properties were evaluated using a CT3-4500 texture analyzer (AMETEK Brookfield, USA) on fresh porcine mucosal tissue. A 1 g of gel was applied onto the membrane, after which the TA5 cylindrical probe was pressed into the gel for 2 seconds. The maximum force required to detach the probe from the gel was then recorded. All of the measurements were conducted at room temperature, three times from each gel.

3.2.5. Spreadability

In the spreading test, 1 g of gel was placed between two glass plates and 120 g of weight was placed on the upper plate (n=3). After 1 minute, the spreading diameter was measured. The measurement was made at room temperature.

3.2.6. Microstructural investigation

For the microstructural examination, emulsions containing an oil phase stained using Sudan III dye were observed under a digital microscope (Keyence Corp., Osaka, Japan).

3.2.7. Rheological characterization of commercially available products

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 (Fluidicam^{TM} RHEO, Formulaction, France). 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.

All preparations were tested in at least three replicates to ensure accuracy and reproducibility. The configuration parameters of the devices are shown in the tables below (Table III, Table IV).

Table III: Setting parameters of Kinexus Pro+ [78]

Measurement set-up for each of the pharmaceutical products tested: a summary of the measurement geometry used with the rotational rheometer, the shear rate range (s-¹) and the test temperature (°C).

Liquid and Gel-Based Dosage Forms	Used Geometry	Shear Rate Range (s^{-1})	Temperature (°C)
Vaginal gel	Cone–Plate	10^{-1} to $1 \cdot 10^{4}$	37
Wound gel	Cone–Plate	10^{-1} to $5 \cdot 10^{3}$	32
Eyedrop	Plate–Plate	10^{-1} to $1 \cdot 10^{4}$	34
Klysma	Plate–Plate	10^{-1} to $5 \cdot 10^{3}$	37
Injection	Plate–Plate	10^{-1} to $1 \cdot 10^{4}$	37
Lubricant	Cone–Plate	10^{-1} to $5 \cdot 10^{3}$	37
Oral gel	Cone–Plate	10^{-1} to $5 \cdot 10^{3}$	37

Table IV:Setting parameters Fluidicam RHEO [78]

Summary of the settings used for viscosity measurements with a microfluidic rheometer for different pharmaceutical preparations.

Liquid and Gel-Based Dosage Forms	Microchip Channel Diameter (µm)	Shear Rate Range (s^{-1})	Temperature (°C)	Reference Sample Viscosity (mPa·s)
Vaginal gel	150	$1 \cdot 10^{2}$ to $5 \cdot 10^{3}$	37	500
Wound gel	150	$1 \cdot 10^{2}$ to $5 \cdot 10^{3}$	32	500
Eyedrop	50	$5 \cdot 10^{2}$ to $1 \cdot 10^{4}$	34	5
Klysma	50	$5 \cdot 10^{2}$ to $3.5 \cdot 10^{4}$	37	5
Injection	50	$1 \cdot 10^{3}$ to $1 \cdot 10^{5}$	37	5
Lubricant	50	$5 \cdot 10^{2}$ to $1 \cdot 10^{4}$	37	5
Oral gel	150	$1 \cdot 10^{2}$ to $5 \cdot 10^{3}$	37	500

4. RESULTS

4.1. Physical appearance of the gels for vaginal use

The physical appearance of hydrogels and emulgels based on poloxamer is influenced by multiple factors, including the gel base composition, the type and proportion of oil phase, and the use of various additives.

Freshly prepared PLX-based hydrogels are homogeneous and uniform in consistency, with an opalescent or slightly translucent appearance depending on the amounts and ratios of poloxamer and other additives (Figure 9).

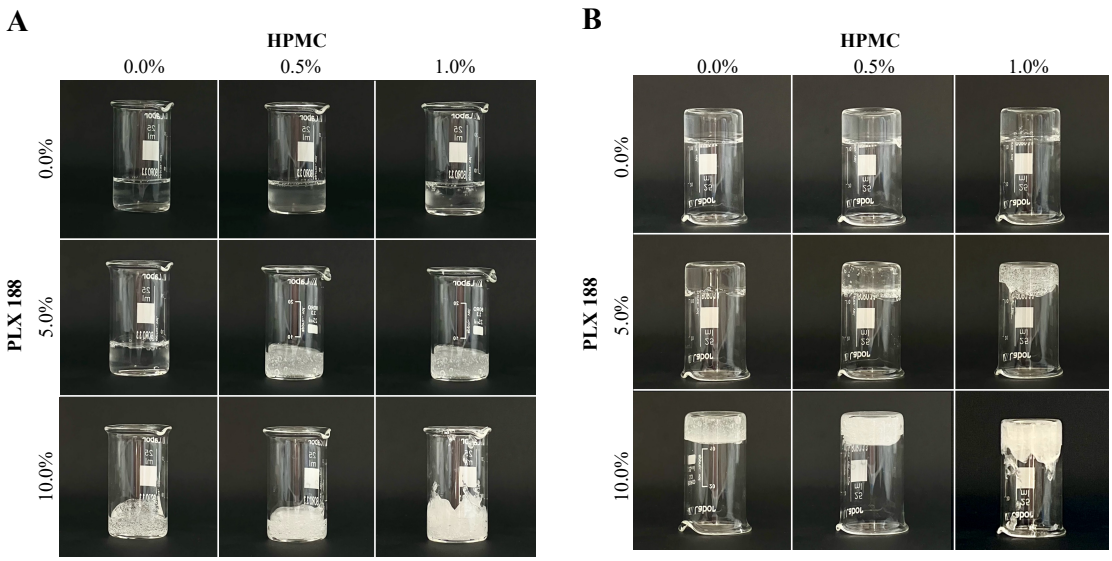

Figure 9: Hydrogels containing 21% PLX407 and varying amounts of PLX188 and HPMC [104]

It can be seen that increasing amounts of HPMC and PLX188 make the gels opaquer. The images were taken at room temperature, at which point the gels had already taken on their gel structure.

In the case of emulgels, the incorporation of the oil phase may result in a slightly yellowish or milky hue, depending on the oil, but the preparations remain homogeneous (Figure 10).

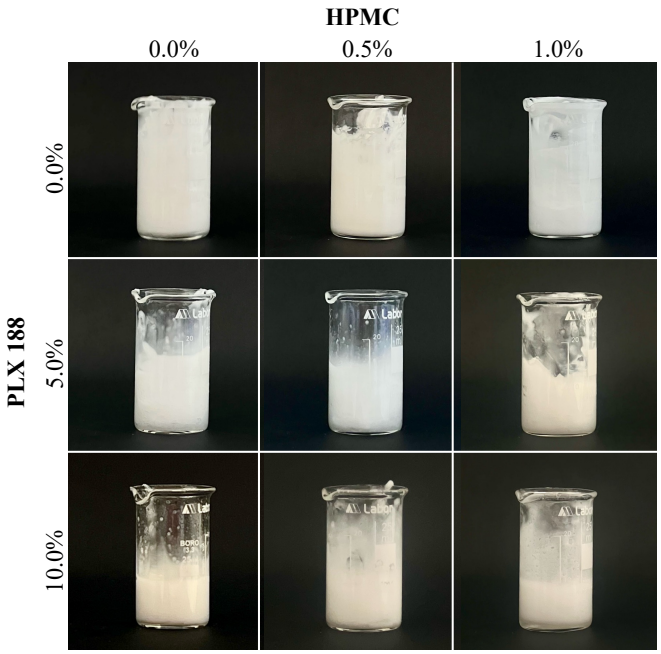

Figure 10: Emulgel containing 30% OA at room temperature [104]
The prepared emulsions have a milky, ointment-like consistency. The amounts of PLX188 and HPMC differ in the gels.

4.2. Rheological measurements of the gels

4.2.1. Rheological measurement of the different hydrogels

At the beginning of my research, I first mapped the effect of the amount of my main gelling agent, PLX407, on the sol-gel transition temperature. Several types of hydrogels containing different percentages of PLX407 were prepared, and their gelation temperatures are shown in the figure below (Figure 11).

The Figure 11. shows that there is no significant difference between the gelation temperatures between the gelation temperatures of different hydrogels whose concentrations differ by only 1%, but the gelation temperatures of gels containing higher amounts of PLX407 (25% and 27% by weight) are visibly lower.

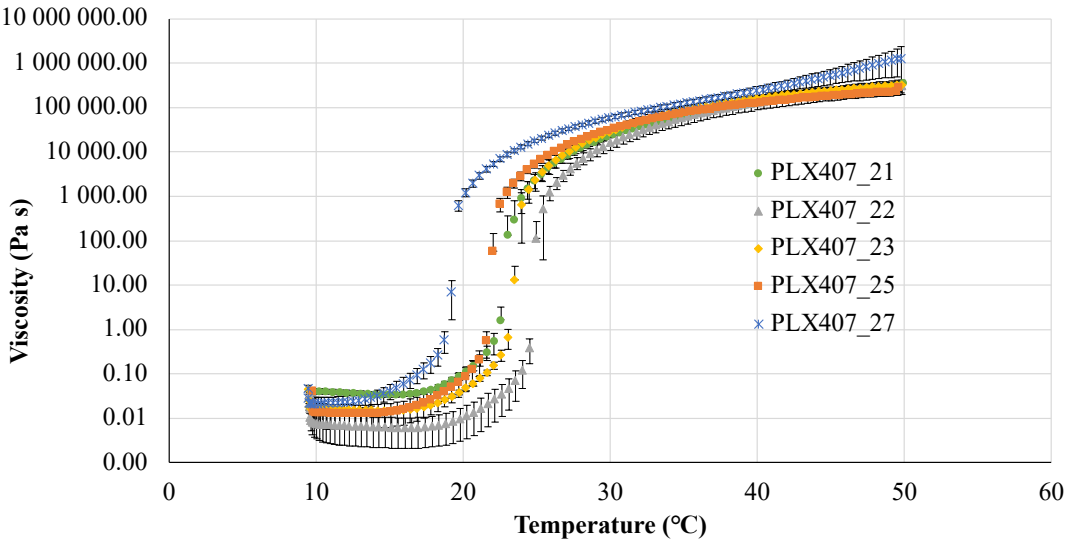

Figure 11: Sol-gel transition temperatures of PLX407 containing hydrogels

In the next part of my work, I looked at how PLX188 and HPMC affect gelation temperature.

The temperature-dependent gelation of aqueous solutions of PLX407 is a result of the dehydration of the copolymer polypropylene oxide (PPO) block [111]. This property allows the gelation temperature of poloxamer-based gels to be controlled by adding another poloxamer—a type with a different polyethylene oxide (PEO) and PPO ratio—to the system. The addition of PLX188 increases the total poloxamer concentration, thereby improving the mechanical stability of the gel; at the same time, the gel formation temperature can also be influenced by modifying the PEO/PPO ratio.

During the experiments, it was found that increasing the concentration of PLX188 led to higher "initial viscosity" of the gels, which was the viscosity measured at lower temperatures. Conversely, the viscosity at elevated temperatures decreased compared to formulations lacking PLX188. Based on this, it can be said that the addition of PLX188 narrows the temperature-dependent viscosity range. Based on the gel formation temperatures shown below (Figure 12), it can be concluded that with increasing proportions of PLX188, the sol-gel transition occurred at higher temperatures, which is advantageous from a pharmaceutical technology point of view as it is closer to body temperature.

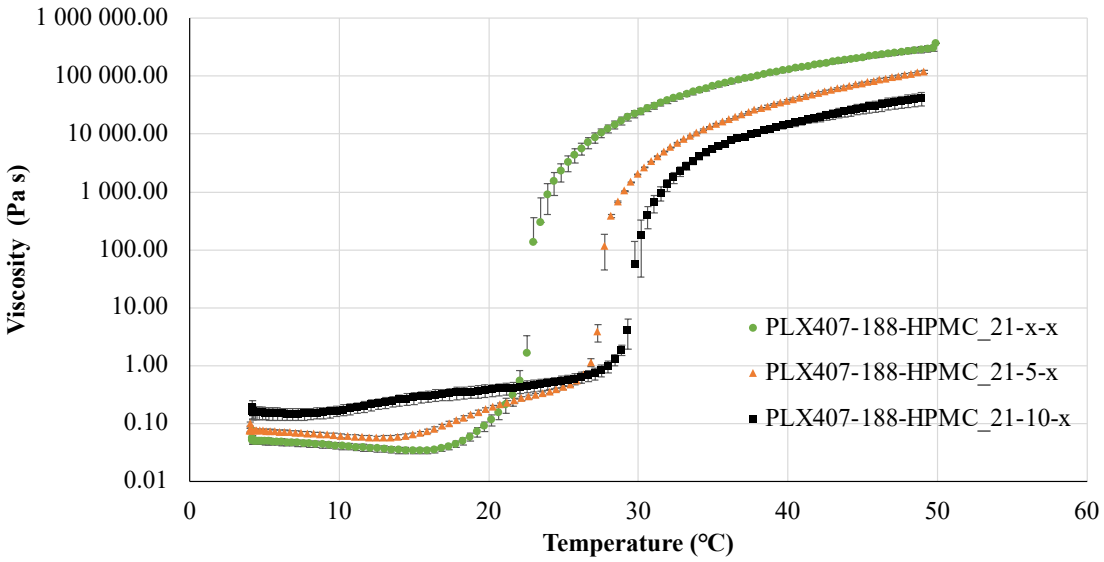

Figure 12: 21% by weight PLX407 and 0%, 5% and 10% PLX188 and 0% HPMC containing hydrogen sol gel transition temperature [104]

HPMC (hydroxypropyl methylcellulose) was also added to the gels at different concentrations to improve the mucoadhesive properties of the formulation. However, the results indicated that the concentration of HPMC had no visible impact on either the viscosity or the temperature at which gelation occurred (Figure 13).

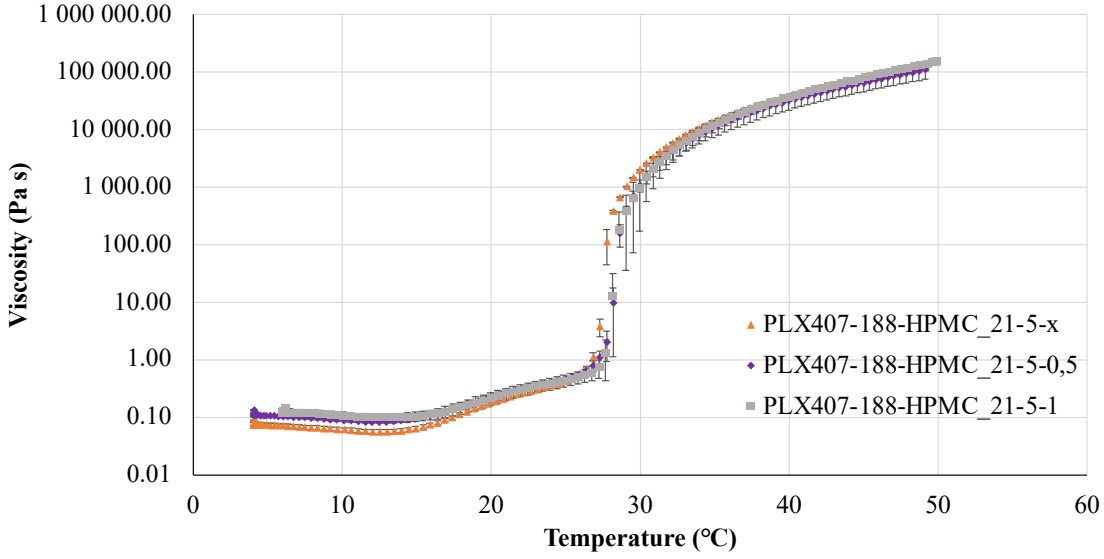

Figure 13: 21% by weight PLX407 and 5% PLX188 with increasing amount of HPMC (0%, 0.5% and 1%) [104]

4.2.2. Rheological measurement of the emulgels made with different oils

As a continuation of my work, I aimed to explore how different oils, added in different quantities – in 30, 40, and 50 percent – affect hydrogel bases. To do this, we added sunflower, almond, jojoba, and MCT oils to the hydrogels separately, and then, after selecting the model active ingredient, we also tried oleic acid.

By adding SO, AO, JO, and MCT at low temperatures, we obtained slow-flowing, viscous, sol-like, milky white or pale-yellow liquids, which thickened under the influence of higher temperature, increased their viscosity, and reached a gel state.

The initial viscosity of the emulgels made from each oil was higher than that of hydrogel in all cases, but the characteristic sol-gel transition temperature was still visible. Although the viscosity curves flattened out compared to the hydrogels, the gelation temperature was not as pronounced.

In general, it can also be said that adding larger amounts of oil increased the initial viscosity value in the case of SO, AO, JO, and MCT. However, the final viscosity value after gelation was lower than that of the hydrogel (Figure 14).

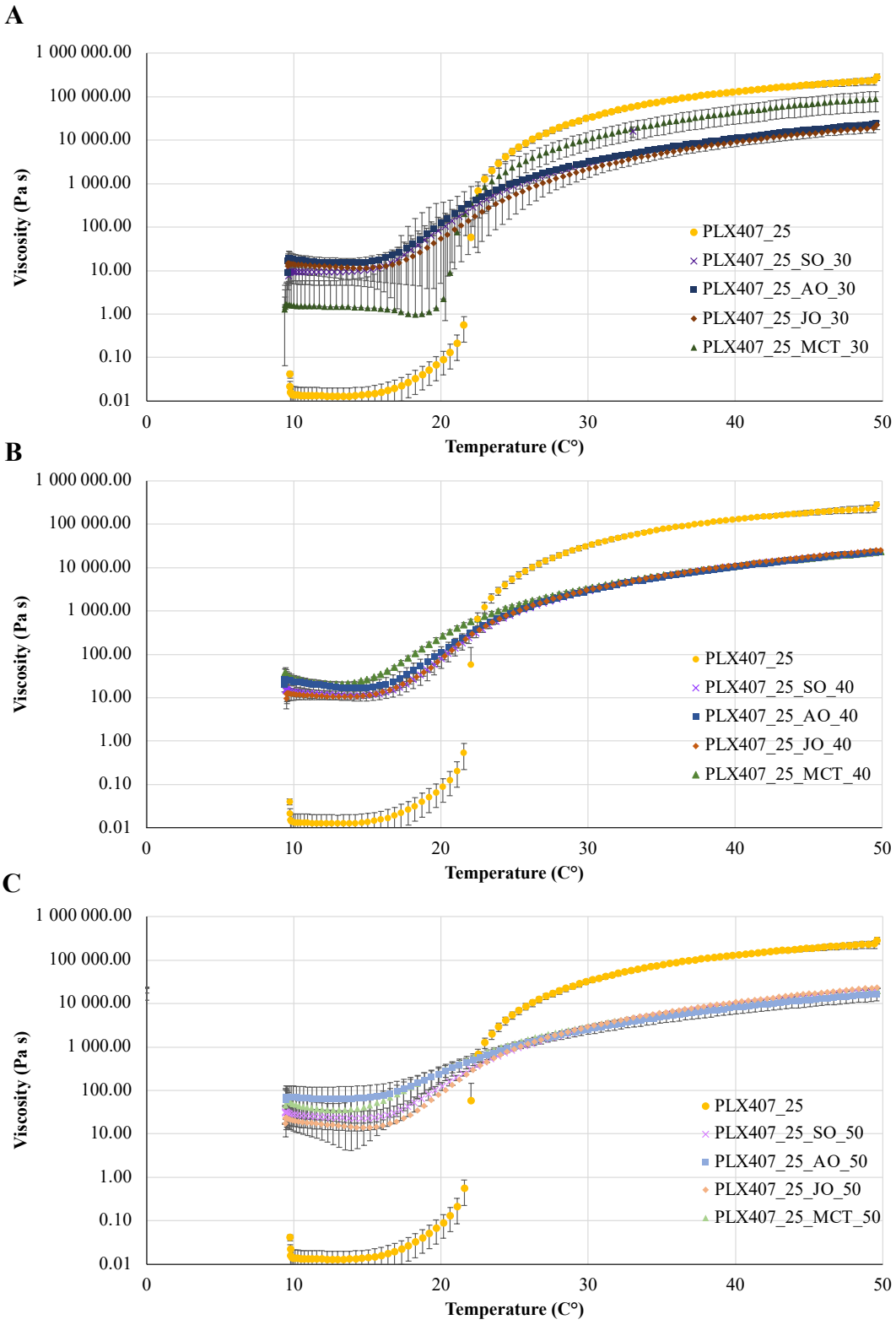

Figure 14: 30% of various oils added to PLX407 hydrogel with a concentration of 25% (A); 40% of various oils added to PLX407 hydrogel with a concentration of 25% (B) and 50% of various oils added to PLX407 hydrogel with a concentration of 25%

4.2.3. Rheological measurement of certain emulgels after pH settings

In some cases, I adjusted the pH of the emulgels to between 3.8 and 4.2 and examined how the pH change affected the rheological properties of the gels, thereby concluding what changes might occur in the gel structure during physiological use (Figure 15).

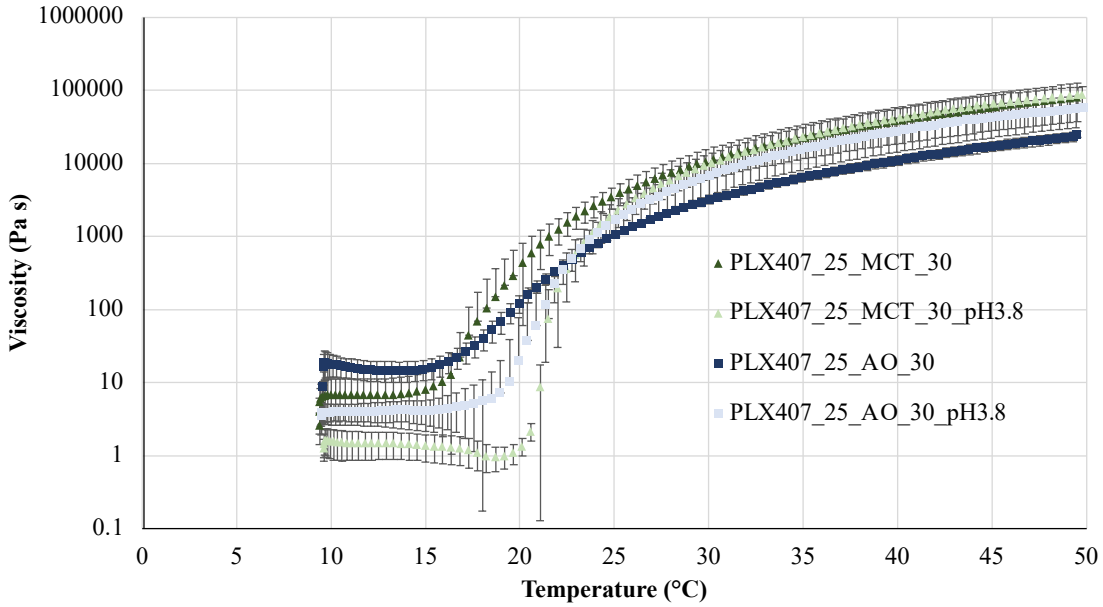

Figure 15: Viscosity curves of MCT and AO emulgels before and after decrease their pH value to vaginal pH

Lowering the pH by adding lactic acid reduced the initial viscosity of the gel at low temperatures in both cases tested. At body temperature there was no significant change in viscosity.

4.2.4. Rheological measurement of the gels for vaginal use

During the experiments, I finally chose oleic acid as the lipophilic phase, as the solubility of the selected model active ingredient in oleic acid is outstanding. I chose the hydrogel containing the smallest amount (21%) of poloxamer in order to prepare the further samples. The addition of oleic acid can aid maintaining the balance of the vaginal microflora, thus promoting the vaginal health [112]. Because of the solubilityof CLZ in OA, the entire intended dose of the drug is already present in dissolved form in the final preparation. However, due to the relatively high melting point of OA (approximately 12 °C), special care must be taken during its processing [113].

When oleic acid was added to the poloxamer-based hydrogel, immediate gel formation was observed. The final emulsion gels (emulgels) demonstrated a stable structure at the immediately after preparation and maintained a consistent viscosity profile at both low and high temperatures, which could contribute to the long term stability of the formulation.

The presence of HPMC, intended to increase mucoadhesiveness, did not significantly affect viscosity values, but resulted in a slight improvement in flow properties. Due to the high melting point of oleic acid, a distorting effect occurred in measurements performed at very low temperatures. The viscosity of the emulsions remained virtually unchanged with temperature changes, so no classic sol-gel transition was observed, unlike in pure poloxamer, and PLX407-SO, PLX407-AO, PLX407-JO and PLX407-MCT systems (Figure 16).

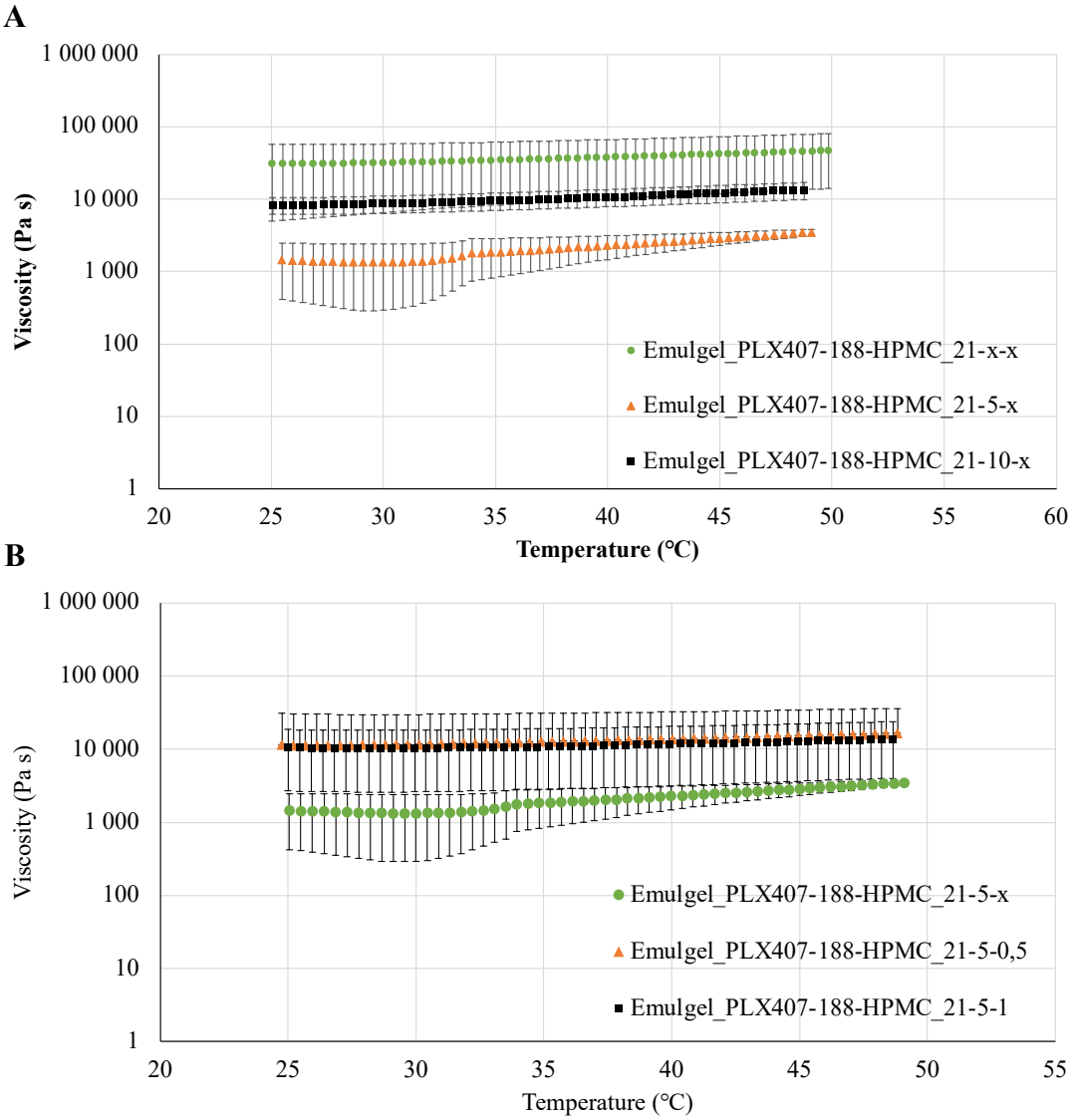

Figure 16: Emulgels with 21% PLX407 and increasing amount of PLX188 content (A); emulgels with 21% PLX407, 5% PLX188 and increasing amount of HPMC content

Based on viscosity measurements, emulsions containing 5% PLX188 showed the lowest viscosity values. The reason for this is presumably that phase separation did not yet occur at this concentration, while the higher PLX188 content already influenced micelle formation and thus the structure of the gel network, leading to a decrease in viscosity [114-116]. At a PLX188 concentration of 10%, phase separation became visible, which probably resulted in some of the OA "leaking" out of the gel during the rheological measurement while the measuring geometry was rotating. As a result, the device measured the gel base (hydrogel) rather than the emulsion phase.

4.3. In vitro release studies

4.3.1. Vertical diffusion cell

During the study of the drug release, the quantity of clotrimazole released from the vertical diffusion cell was quantified relative to the membrane surface area, expressed in mg/cm². The cellulose acetate membrane used had a surface area of 1.77 cm². It was observed that increasing the concentrations of PLX188 and HPMC accelerated the release of the active compound, whereas clotrimazole dissolved in oleic acid exhibited a steady but slower release profile from the formulations (Table V).

Table V: Released CLZ per unit area (mg/cm²) [104]

Samples 1A-C is for the emulgels containing 21% PLX407, 0%PLX188 and from A to C, increasing amount (0%, 0.5%, 1%) of HPMC. Samples 2A-C are containing 21% PLX407, 5% PLX188 and increasing amount (0%, 0.5% and 1%) of HPMC. 3A-C are composed of 21% PLX407, 10% PLX188 and 0%, 0.5% and 1% of HPMC.

Sample	Time (h)									
	0.5	**1.0**	**2.0**	**3**	**4**	**5**	**6**	**7**	**8**	**24**
1A	0.15±0.04	0.22±0.05	0.36±0.06	0.49±0.07	0.62±0.09	0.76±0.12	0.88±0.15	0.98±0.17	1.11±0.16	1.42±0.13
1B	0.13±0.02	0.22±0.02	0.40±0.09	0.60±0.21	0.75±0.27	0.92±0.34	1.07±0.38	1.21±0.46	1.32±0.50	1.64±0.56
1C	0.17±0.04	0.29±0.04	0.52±0.08	0.76±0.18	0.97±0.24	1.17±0.30	1.35±0.33	1.53±0.38	1.69±0.38	2.04±0.48
2A	0.16±0.03	0.25±0.05	0.47±0.08	0.68±0.07	0.90±0.06	1.09±0.05	1.26±0.05	1.39±0.04	1.52±0.02	1.95±0.14
2B	0.18±0.04	0.28±0.04	0.49±0.06	0.73±0.08	0.96±0.11	1.17±0.13	1.36±0.12	1.56±0.13	1.71±0.14	2.13±0.13
2C	0.41±0.12	0.64±0.40	0.97±0.60	1.23±0.85	1.50±1.13	1.70±1.30	1.96±1.46	2.20±1.57	2.77±1.82	2.80±0.47
3A	0.26±0.03	0.38±0.02	0.61±0.04	0.90±0.08	1.13±0.11	1.33±0.13	1.51±0.16	1.70±0.21	2.10±0.34	2.60±0.10
3B	0.18±0.01	0.32±0.07	0.59±0.23	0.84±0.26	1.11±0.36	1.36±0.45	1.55±0.50	1.71±0.53	1.93±0.65	2.89±0.41
3C	0.19±0.00	0.34±0.07	0.65±0.27	1.07±0.46	1.27±0.47	1.53±0.43	1.82±0.45	2.05±0.41	2.37±0.56	3.07±0.74

Since the amount of active ingredient released per unit surface area may not always have direct clinical relevance, the measured values were multiplied by the estimated total

surface area of the vagina. To calculate the average body cavity area, we used a cylindrical model open at both ends, where the average depth was taken as 7.57 cm and the width as 4.67 cm, which led to calculated surface area of 111.01 cm² (Figure 17). Nevertheless, it is important to note that individual anatomical differences can be significant [117].

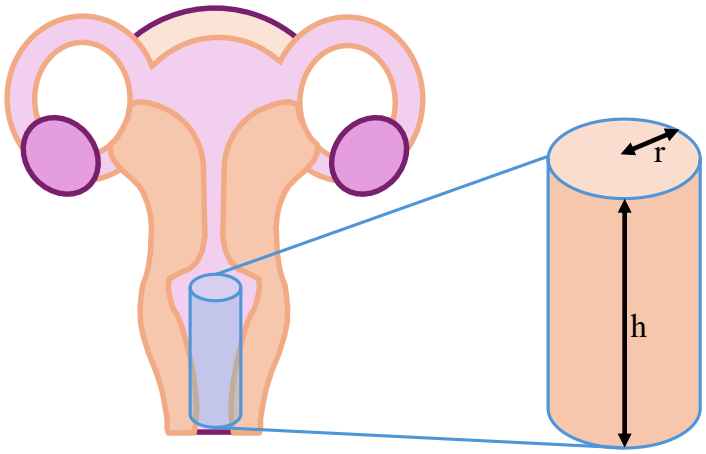

Figure 17: Average vaginal size calculation based on the area of a cylinder with two open ends [104]

The 'h' represents the depth of the body cavity while 'r' is the radius of it.

The data obtained by multiplying the values thus show the expected active ingredient release over the entire internal surface of the vagina (Figure 18). Considering that most commercially available vaginal preparations contain approximately 5 g per single dose, we adjusted the clotrimazole content of our formulations accordingly: each 5 g of gel contained 200 mg of clotrimazole, which corresponds to the active ingredient content of standard single-dose vaginal treatments [118-120]. Based on the dissolution profiles, the formulations may even be suitable for the gradual release of larger doses (e.g., 500 mg) within 24 hours [121].

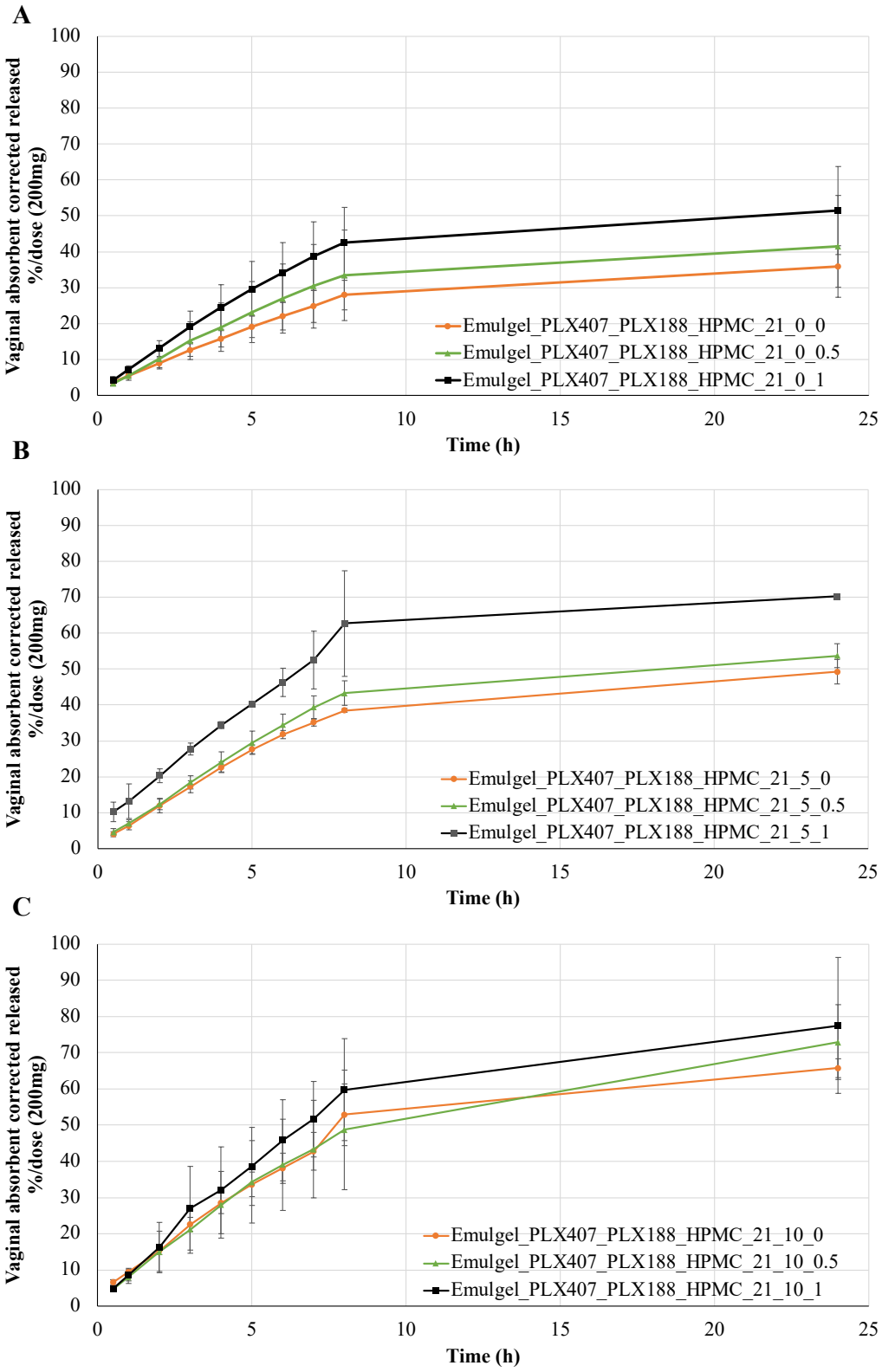

Figure 18: Released CLZ corrected with the average vaginal size [104] PLX188 amount 0% (A); 5% (B) and 10% (C)

4.3.2. Hanson SR8+ apparatus

The data obtained used the Hanson SR8+ dissolution tester equipped with paddles were also regulated to the membrane surface area. In this case, the surface area of it was 11.24 cm², which is larger than that of the membrane used in the vertical diffusion cell, and the sample volume and solvent volume were also larger. Nevertheless, the results obtained from the two measurement methods showed a very similar pattern, and the final values obtained are well comparable with each other (Figure 19).

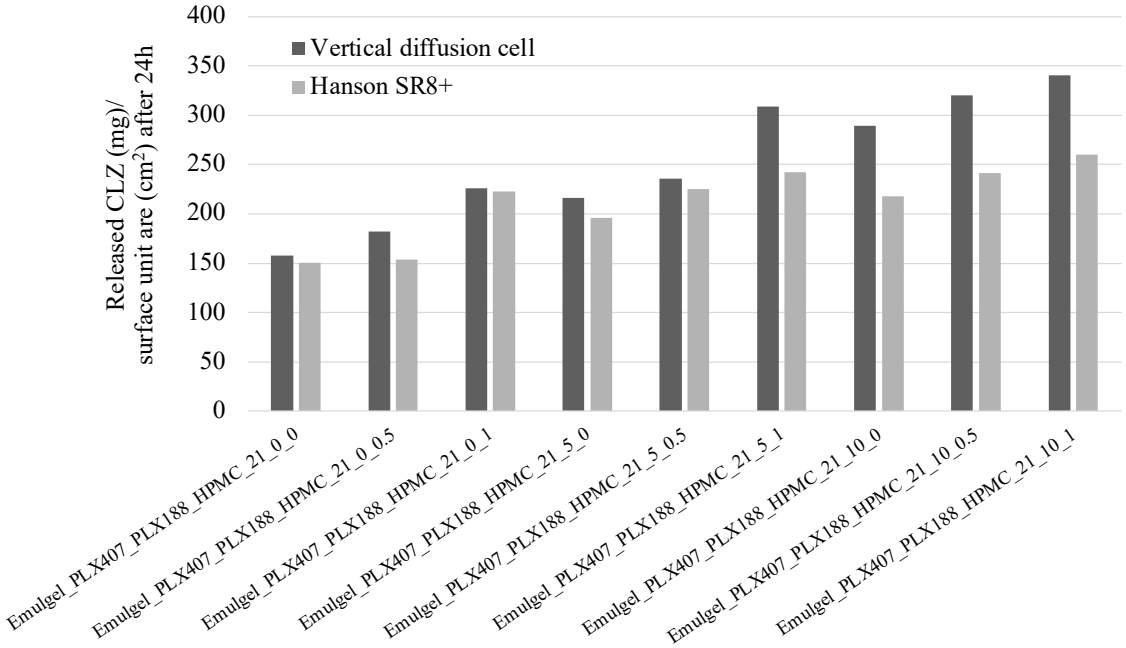

Figure 19: Comparison of the two different method [104]
Released CLZ per surface unit area over 24 hours

The findings from both studies confirmed that higher concentrations of PLX188 and HPMC lead to an accelerated release of the drug. The increased amount of PLX188, attributed to its high HLB value, likely enhances the release of poorly soluble, lipophilic active ingredients like clotrimazole from the gel matrix [122]. At the same time, 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 [123]. 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 [124, 125].

The kinetics of clotrimazole release over the initial 8 hours were assessed using the Higuchi model. Based on the correlation coefficients (r) indicating the strength of the fit, the data followed the Higuchi equation well, as even the lowest r value was 0.9847. The results clearly show that the concentration of additional polymers added to PLX407, especially PLX188 and HPMC, significantly affects the slope of the Higuchi model, i.e., the rate of drug release: higher polymer concentrations resulted in steeper curves and faster release (Table VI).

Table VI: Kinetic analysis of the dissolution data based ont he Higuchi model [104]

Parameter	**Emulgel_PLX407_PLX188_HPMC**	**Emulgel_PLX407_PLX188_HPMC**	**Emulgel_PLX407_PLX188_HPMC**	**Emulgel_PLX407_PLX188_HPMC**	**Emulgel_PLX407_PLX188_HPMC**	**Emulgel_PLX407_PLX188_HPMC**	**Emulgel_PLX407_PLX188_HPMC**	**Emulgel_PLX407_PLX188_HPMC**	**Emulgel_PLX407_PLX188_HPMC**
K_H	38.012	45.697	58.297	53.294	58.385	82.579	67.834	66.286	78.351
Correlation coefficient (r)	0.9907	0.9876	0.9881	0.9882	0.9862	0.9917	0.9882	0.9877	0.9847

4.4. Mucoadhesion measurements

The mucoadhesion assessment was conducted using a Texture Analyzer, where porcine mucosa was placed on the instrument's bottom tray to replicate natural mucosal tissue. Equal amounts of each formulation were then applied onto the mucosal surface for testing. 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 phase, the device measured the force needed to separate it from the gel. A lower detachment force indicates stronger adhesion of the gel to the mucosal surface, reflecting

improved mucoadhesion properties. The emulgel, which didn't contain HPMC neither PLX188 exhibited the least adhesion (Table VII).

Table VII: 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%)

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

4.5.Spreadability

The results of the area measurements aligned well with the findings from the mucoadhesion tests. Emulsifying gels with higher PLX188 content spread over a substantially larger area when placed between two glass plates. However, formulations with the highest PLX188 concentration also exhibited phase separation, which raises concerns regarding their physical stability (Figure 20).

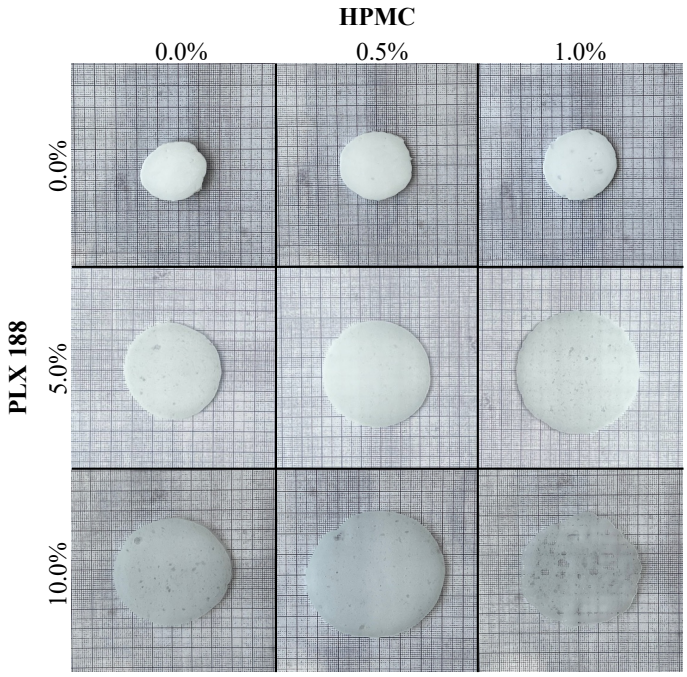

Figure 20: Spreadability studies of the emulgels with 21% PLX407 content and different amount of PLX188 and HPMC [104]

4.6. Microstructural investigation

To confirm the presence of phase separation and assess the physical stability of the gels, three selected formulations were examined microscopically (Figure 21). The gel containing only PLX407 proved to be stable at the microscopic level, with no phase separation observed. Its consistency, however, was unsatisfactory, as spreadability tests showed it was difficult to apply, making it less ideal for coating body cavities. In contrast, the emulgel containing 5% PLX188 and 0.5% HPMC demonstrated favourable spreading characteristics as well as good physical stability. No phase separation was detected in the formula, either with the naked eye or under a microscope, so this combination represents a favourable balance between stability and usability.

The third sample, containing 10% PLX188 and 1% HPMC, showed significant phase separation, which was clearly visible to the naked eye and confirmed by microscopic examination. This was also observed when the formulation contained a large amount of gelling agent, suggesting that excessive polymer concentration does not necessarily improve stability and may even have a destabilizing effect.

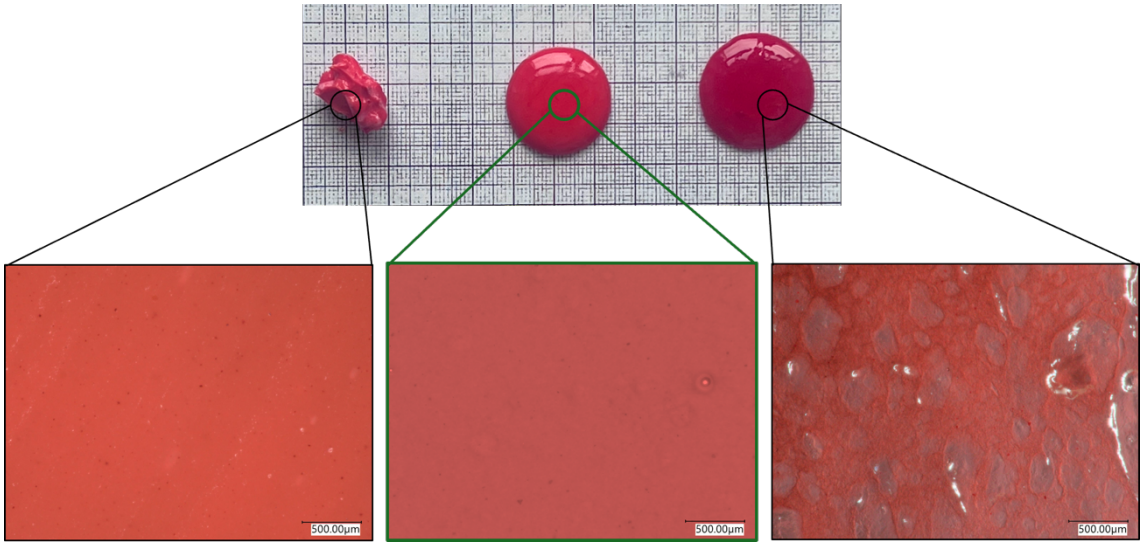

Figure 21: Evaluation of the stability of certain emulgels with digital microscope [104] The first image shows a sample containing 21% PLX407 without any additional polymers. The second image corresponds to the mid-range formulation, which includes 21% PLX407, 5% PLX188, and 0.5% HPMC. In both of these 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 composed of 21% PLX407, 10% PLX188, and 1% HPMC.

4.7. Rheological comparative measurement of different dosage forms

Presented below are the rheological test results of various liquid and gel dosage forms, which were conducted using a Kinexus Pro+ rotational rheometer alongside a Fluidicam™ RHEO microfluidic viscometer. By paralleling the two methods, we highlight their advantages and disadvantages, with regard to measurement time, sample quantity required, and reliability at different shear rate ranges.

The Kinexus Pro+ is a highly precise rotational rheometer capable of conducting viscosity measurements in both rotational and oscillatory modes. However, its accuracy is limited to a specific shear rate range, with less reliable results observed at very low or very high shear rates. 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. The figure (Figure 22) below shows the different dosage forms during the measurements.

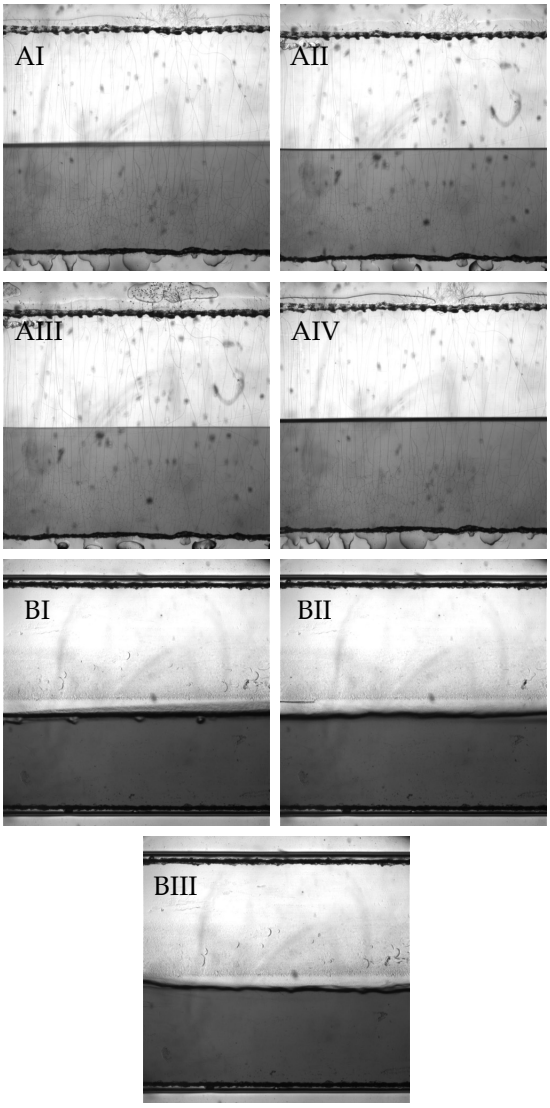

Figure 22: Comparing the results of measurements performed on the two types of plastic microfluidic chips [78]

Various liquid drug forms, such as injections (AI), lysmas (AII), eye drops (AIII), and lubricants (AIV), were examined in the smaller 50 µm microchip. In contrast, the larger 150 µm microchip was used to measure gel-based drug forms, such as wound treatment gel (BI), oral gel (BII), and vaginal gel (BIII).

4.7.1. Comparison of time and sample quantity

The data presented in the table below (Table VIII) clearly indicate that, for the same samples, the microfluidic measuring device completes measurements in significantly less time. Naturally, the measurement duration depends on the shear rate range selected for both instruments. With the Kinexus Pro+, a specific sample volume must be loaded and removed for each measurement. In contrast, the Fluidicam™ RHEO uses a preloaded syringe, enabling automatic, parallel measurements without the need to transfer the sample between tests.

In contrast, with a rotational rheometer, the measuring head and sample holder must be cleaned after each measurement, which can be time-consuming, especially with highly viscous gels.

Table VIII: Sample volume and measurement time required for different dosage forms [78]

Liquid and Gel-Based Dosage Forms	**Volume of Sample Used (mL)**		**Measurement Time (min)**	
	Kinexus Pro+	**Fluidicam™ RHEO**	**Kinexus Pro+**	**Fluidicam™ RHEO**
Vaginal gel	1.50	2.1	31 min ± 2 min	4 min 58 s ± 27 s
Wound gel	1.50	2.6	27 min ± 2 min	5 min 32 s ± 29 s
Eyedrop	1.19	1.2	48 min ± 4 min	3 min 12 s ± 12 s
Klysma	1.19	0.9	35 min ± 2 min	2 min 53 s ± 21 s
Injection	1.19	1.0	38 min ± 3 min	2 min 48 s ± 17 s
Lubricant	1.19	1.8	30 min ± 2 min	3 min 8 s ± 24 s
Oral gel	1.50	2.16	32 min ± 2 min	5 min 16 s ± 28 s

4.7.2. Liquid formulations

The viscosity measurement results for liquid drug formulations are presented below (Figure 23).

The tested eye drops, a low-viscosity product designed to alleviate eye irritation, contain polysorbate 80, a nonionic surfactant known to influence viscosity. Using a rotational

rheometer, the eye drops exhibited Newtonian behaviour within a shear rate range of 1 to 1000 s^{-1}. However, higher shear rates encountered in blinking (up to 28,000 s^{-1}) exceed the measurement capabilities of this device. Conversely, the microfluidic viscometer accurately measured viscosity at these elevated shear rates and revealed a slight shear-thinning behavior, which may be critical in optimizing ophthalmic formulation performance.

Diazepam Desitin® klysma is a rectally administered solution for the acute treatment of epileptic seizures. The main component affecting viscosity is propylene glycol, a safe and widely used solvent. The preparation exhibited Newtonian behaviour between 10 and 50,000 s^{-1} with both measuring devices, but below 10 s^{-1} the rotational rheometer was no longer reliable. During rectal administration, a typical shear rate of 10 to 100 s^{-1} can be expected, which can be used to model the practical behaviour.

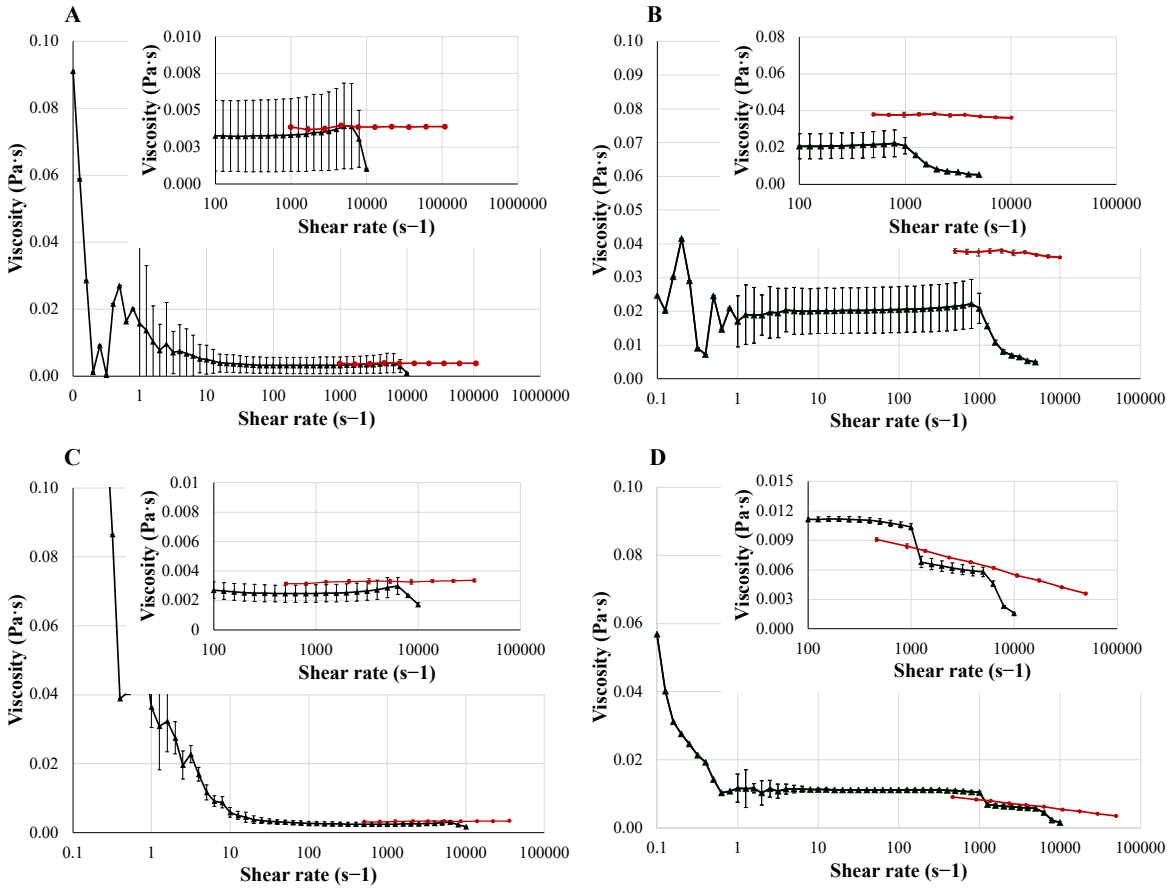

Figure 23: Viscosity profiles of the liquid dosage forms [78]

Two different instruments, the Kinexus Pro+ and the Fluidicam™ RHEO, were used to analyze the dosage forms. In the graphs, the black curve corresponds to the Kinexus Pro+ results, while the red curve represents data obtained from the Fluidicam™ RHEO. For each sample, an enlarged section of the viscosity curve is also displayed in the upper right corner of the graph, providing a closer look at specific ranges of interest. All the investigated dosage forms — including injection (A), lubricant (B), klysma (C), and eyedrop (D) — were measured three times, and each parallel measurement was performed on freshly-loaded samples to ensure accuracy and reproducibility.

The metamizole sodium injection, intended for pain relief and fever reduction, does not contain any components that modify viscosity. The sample displayed Newtonian behaviour; however, the rotational rheometer could not provide accurate measurements below a shear rate of 10 s^{-1}, whereas the microfluidic device yielded reliable data even at higher shear rates.

Macrogol 400 (PEG 400) is a low molecular weight lubricant used as a coating for implants and as an excipient in pharmaceutical formulations. Since the appropriate viscosity of lubricants is crucial for the function and biocompatibility of implants, microfluidic measurements are particularly useful for their precise evaluation.
In ranges where the measurements of the rotational rheometer were not reliable, the deviations were not plotted. In contrast, the measurements of the microfluidic viscometer showed low dispersion, thus allowing for a more accurate evaluation.

4.7.3. Semi solid formulations

The viscosity measurement results for gel-based dosage forms are presented below (Figure 24).

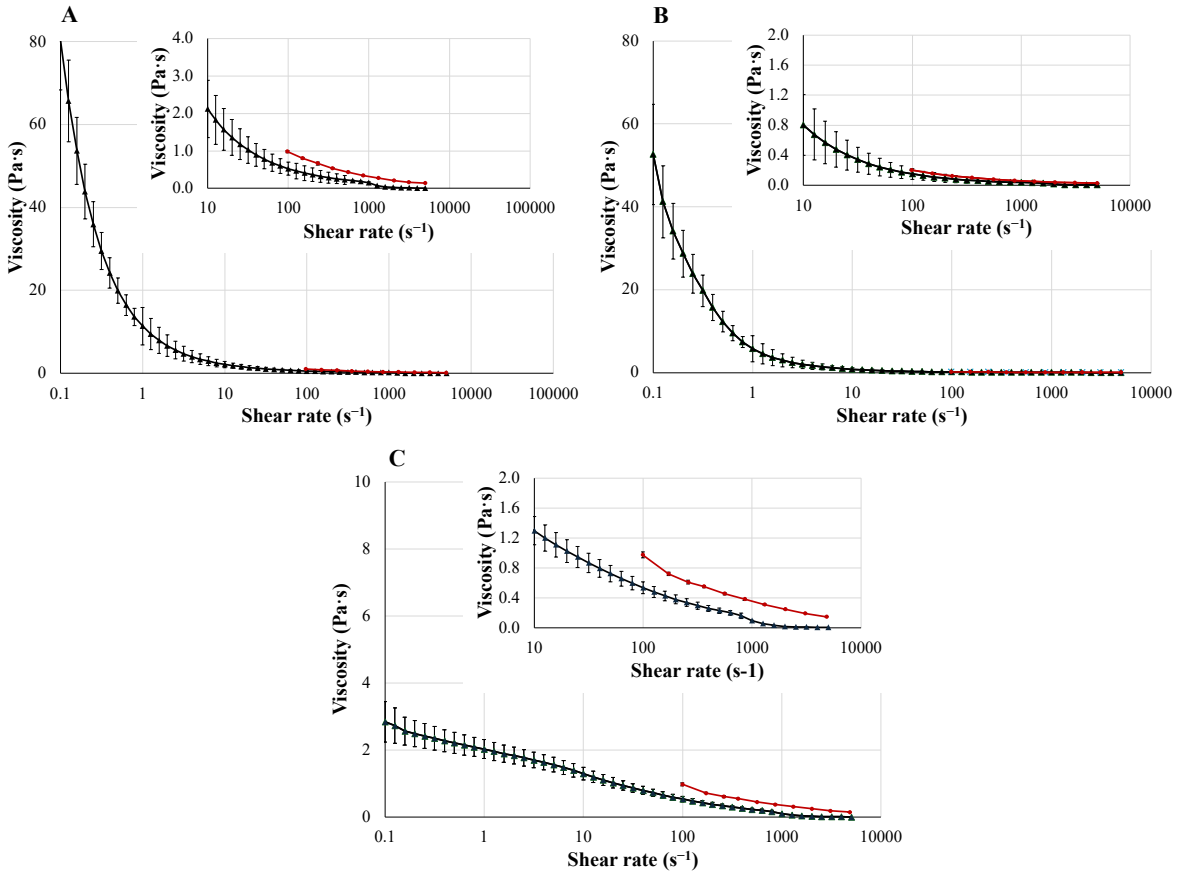

Figure 24: Viscosity profiles of gel-based drug formulations [78]

The black curve represents the measurements obtained with the Kinexus Pro+ rheometer, while the red curve corresponds to the data from the Fluidicam™ RHEO microfluidic viscometer. An enlarged view of selected sections of each viscosity curve is displayed in the upper right corner. All formulations were measured three times, with each parallel measurement performed on a freshly loaded sample. Wound healing gel (A); oral gel (B); vaginal gel (C).

The vaginal gel tested (Lactofeel®) contains lactic acid and glycogen, which help maintain a healthy vaginal pH, supporting the functioning of the natural microflora. Its gelling agent is methyl hydroxypropyl cellulose (MHPC), a widely used cellulose derivative. The measurements were taken in the range of 0.1–5000 s^{-1}, but the stable values were between 1–1000 s^{-1}, which well covers the biologically relevant shear rates of 0.01–100 s^{-1} occurring in the vagina. There was a maximum difference of 0.5 Pa·s between the results of the two measurement methods (rotational and microfluidic).

The main active ingredient of the wound treatment gel is hyaluronic acid, which promotes wound healing and retains moisture. The gelling agent is carbomer, which results in a well-spreading, film-forming hydrogel. The preparation exhibited pronounced shear-thinning behaviour, with a significant decrease in viscosity even at a small increase in shear rate. During application to the skin surface, a shear rate of around ~100 s^{-1} is typical. We obtained almost identical values with both devices, with a maximum difference of 0.5 Pa·s.

Gloup® oral gel is a medical device designed to aid in swallowing tablets, particularly for elderly individuals, children, or those who experience difficulty during swallowing. Its gelling agent is carrageenan, a natural polysaccharide. During swallowing, the shear rate is estimated to range between 10 and 50 s^{-1}. The gel's shear-thinning behaviour is beneficial, as the reduction in viscosity during swallowing helps facilitate the intake of solid dosage forms. The results obtained with the two measurement methods were practically identical.

In all cases, the dispersion of the microfluidic viscometer was negligible, thus ensuring a reliable and accurate evaluation.

5. DISCUSSION

The aim of the research was to develop and characterize alternative, non-hydrogel-based drug forms (with particular attention to rheological characterization). The research focuses on the applicability of emulsified gels for vaginal use, controlled and programmed drug release, and the applicability of various types of rheological measurements in pharmaceutical technology.

Based on the results, poloxamer-based hydrogels and emulsified gels can be successfully produced. Their properties can be greatly varied and controlled by changing the ratio of the components (gelling agents, other excipients, various oils). Stable gel systems have been formulated using multiple oils, and depending on the oil phase, active ingredients with different solubilities can be used, so that gels could be adapted to many indications with different emulgel formulations.

The addition of oleic acid not only favored the solubility of the selected lipophilic active ingredient, clotrimazole, but also contributed to the stability of the preparation and the maintenance of the balance of the vaginal microflora.

The use of HPMC as a mucoadhesive excipient clearly improved the mucoadhesion of gels intended for vaginal use, which is crucial in terms of longer local retention time and more effective drug delivery.

Various rheological tests can highlight many aspects of the usability of the prepared and tested gels. The effect of vaginal pH and temperature differences between storage and use can greatly influence the effectiveness of the preparations. Rheological tests help to provide insight into all of these factors.

In the case of more complex samples intended for vaginal use, rheological tests have shown that increasing the PLX188 content leads to an increase in the sol-gel transition temperature, resulting in gel formation closer to body temperature, thereby improving therapeutic efficacy. The viscosity of emulsions prepared with oleic acid proved to be temperature-independent, which may result in longer-term stability. Different poloxamer and HPMC ratios allowed for fine-tuning of the drug release kinetics; a higher PLX407 ratio resulted in slower release, while a higher PLX188 and HPMC ratio resulted in faster release.

The various poloxamers and HPMC affected each other's influence on the formation of the gel network. Altering the poloxamer composition produced gels with different strengths, which can be attributed to their varying molecular weights, HLB values, and the ratio of PPO to PEO blocks. Additionally, the presence of HPMC significantly impacted the final gel structure. While HPMC alone can form a gel by swelling, poloxamers gel through micelle formation. Consequently, these materials compete for the available water in the formulation or environment, which may lead to a reduction in gel consistency [114-116].

In vitro release studies have confirmed that the developed emulsions are capable of sustained release of clotrimazole over 24 hours, which may be appropriate for both lower (200 mg) and higher (500 mg) single doses. Based on kinetic analysis according to the Higuchi model, the poloxamer and HPMC content significantly influences the release rate.

Viscosity measurement is closely linked to the development of semi-solid dosage forms. In pharmaceutical technology, there is a need for the fastest and most accurate rheological characterization possible.

The use of the microfluidic rheology method has been a significant advance in the rapid measurement of the viscosity of dosage forms from small sample volumes. The method was particularly advantageous for low-viscosity, heat-sensitive, or low-volume samples, where the use of traditional rotational rheometers is limited. The results of the two measurement methods are comparable, but the microfluidic device provided lower dispersion and faster measurement, especially in higher shear ranges.

Microfluidic measurement allowed the behaviour of drug forms to be modelled under real-world conditions (e.g., injection, applicator administration, eye drops), where high shear rates occur. This approach may open up new perspectives in terms of drug technology development and quality control.

The results of this research are consistent with those reported in the international literature, which indicate that poloxamer-based hydrogels and emulgels are excellent for local drug delivery, especially in the treatment of vaginal candidiasis. The increasing focus on developing alternative gel systems, such as oleogels and emulgels, highlights the importance of this research. These systems address the limitations of traditional hydrogels, particularly regarding the solubility of lipophilic active ingredients and the

need for therapies involving multiple phases. Several studies emphasize the advantages of using microfluidic rheology, especially its speed, low sample requirements, and measurability over a wide shear range. The results of this research confirm that this method can be effectively applied in pharmaceutical technology development, especially for semi-solid and liquid dosage forms.

The tests were conducted under laboratory conditions in in vitro systems, therefore further in vivo studies are required to assess clinical applicability. Further research is also needed to evaluate long-term stability, patient compliance, and therapeutic efficacy. In connection with the above, it would be important to conduct further microbiological studies and, in the case of vaginal gels, to investigate the effect of electrolytes in vaginal fluid that meet the gels. Further development of microfluidic rheology, such as the simultaneous measurement of more complex biological samples or combined physical-chemical parameters, may also open up new avenues of research.

6. CONCLUSION

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.

The main findings of the research are as follows:

- Formulation freedom and customizability: By varying the ratio of PLX407, PLX188 and HPMC, the structure of the gel network, its viscosity, and the kinetics of drug release can be precisely controlled. This allows drug formulations to be tailored to therapeutic needs, such as achieving longer or shorter drug release times.
- Mucoadhesion and local residence time: The inclusion of HPMC substantially enhanced the mucoadhesive strength of the gels, which can lead to prolonged local retention and more effective drug delivery.
- Innovative measurement methods: Microfluidic rheology enabled fast viscosity measurements over a wide shear range from small sample volumes, which is particularly advantageous for heat-sensitive or low-yield samples. The results were comparable to those obtained with a conventional rotational rheometer, but the microfluidic method provided faster and less scattered data.
- Controlled and programmable drug release: In vitro release studies confirmed that the developed emulgels are capable of continuous release of clotrimazole over 24 hours, which may be appropriate for both smaller and larger single doses. Based on kinetic analysis according to the Higuchi model, the poloxamer and HPMC content influences the release rate.
- Physical stability and applicability: The use of oleic acid not only increased the solubility of the lipophilic active ingredient, but also contributed to the long-term stability of the formulations. With the appropriate poloxamer composition and HPMC content, the physical stability and user-friendly consistency of the formulations can also be ensured.

Based on the results of the research, it can be stated that alternative gel systems, especially poloxamer-based emulgels, may represent a promising alternative in local drug delivery, especially for lipophilic active ingredients. Microfluidic rheology can be an effective tool in modern drug development and quality control, especially for semi-solid and liquid dosage forms.

Following laboratory in vitro studies, further research is needed to evaluate clinical applicability, long-term stability, and patient compliance. Further development of microfluidic rheology, such as the simultaneous measurement of more complex biological samples or combined physical-chemical parameters, may also open up new avenues of research.

Overall, the objectives set out in the thesis were achieved: the development of alternative, non-hydrogel-type, lipophilic and two-phase drug forms, as well as the validation of microfluidic rheological methods for use in pharmaceutical technology. The results contribute to the expansion of the pharmaceutical technology toolkit and the development of personalized, programmable drug delivery systems, which may significantly improve therapeutic efficacy and patient comfort in the future.

7. SUMMARY

During the first year of my doctoral studies, I developed a comprehensive overview of the scientific and pharmaceutical significance of gels, with a particular focus on the types of gels available on the Hungarian market. In mapping and systematizing the gels available on the domestic market, I analysed in detail not only the physical and chemical properties of the different types (hydrogels, oleogels, emulgels, bigels), but also their pharmaceutical applications. I published the results of this work in a Hungarian-language paper, contributing to the expansion of the domestic literature.

After classifying the gels, I focused my research on the development of non-hydrogel-type alternative gel systems. I placed particular emphasis on the production of emulgels and oleogels and the investigation of their rheological stability, and drug release properties. During the development of poloxamer-based emulgels, I succeeded in creating formulations that were capable of effectively dissolving lipophilic active ingredients (e.g., clotrimazole) and releasing them in a controlled, programmable manner. I optimized the gel network structure and drug release kinetics by fine-tuning the ratio of poloxamers and HPMC, while improving the local residence time of the formulations by increasing mucoadhesion.

In vitro release studies of the developed systems confirmed that the emulsified gels are capable of continuous drug release for 24 hours, which is of paramount importance for personalized, patient-centered therapies. The use of microfluidic rheological measurement methods has made it possible to quickly test the viscosity of the formulations in a wide shear range from small sample quantities, which is particularly advantageous in modern drug development and quality control.

In summary, my work has succeeded in mapping and systematizing domestic gel types, as well as contributing to the expansion of the toolkit for personalized drug formulation through the development and rheological testing of new, alternative gel systems. The results lay the foundation for the future development of innovative, patient-centered therapeutic solutions that can significantly improve therapeutic efficacy and patient comfort.

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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.

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9.1.Other publications

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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