BULETINUL INSTITUTULUI POLITEHNIC DIN IAŞI
Publicat de
Universitatea Tehnică „Gheorghe Asachi” din Iaşi
Volumul 71 (75), Numărul 2, 2025
Secţia
CHIMIE şi INGINERIE CHIMICĂ
DOI: 10.5281/zenodo.15617924

RHEOLOGICAL BEHAVIOUR OF SOME GELS BASED ON DICLOFENAC

BY

LOREDANA CHELEA[1], CONSTANȚA IBĂNESCU[1] and MARICEL DANU[1,2,*]

[1]“Gheorghe Asachi” Technical University of Iaşi, “Cristofor Simionescu” Faculty of Chemical Engineering and Environmental Protection, Iaşi, Romania
[2]“Petru Poni” Institute of Macromolecular Chemistry of Iaşi, Romania

Received: April 15, 2025
Accepted for publication: May 25, 2025

Abstract. The delivery of pharmaceuticals to the skin is possible using two methods: topical and transdermal. In the context of topical administration, the drug is intended to act at the skin level, and it is commonly employed in the treatment of skin diseases. Transdermal administration achieves systemic delivery, when the skin is a barrier, not a target. The objective of the present study is to characterize the rheological behavior of drug carriers in topical administration. To this aim, the rheological measurements of several commercial diclofenac containing gels were performed.

The present study demonstrates the application of rheological measurements in the characterization of pharmaceutical products. The viscoelastic properties could be successfully correlated with the end-use properties, such as applicability, processing behavior, storage, and thermal stability.

Keywords: viscoelastic properties, structural stability, gel strength, diclofenac, rheology.

---

[*]Corresponding author; *e-mail*: maricel.danu@academic.tuiasi.ro

1. Introduction

Skin is the largest and most accessible organ of the body. Topical delivery of drugs is a method of local or systemic delivery. In local delivery, drug-containing formulations are applied to the skin to treat dermatological conditions such as acne, psoriasis, and eczema. In systemic drug delivery, drugs are applied to the skin to be delivered to the systemic circulation. Topical delivery systems offer several advantages over oral and parenteral delivery methods, including the circumvention of first-pass metabolism, the prevention of gastrointestinal irritation, and non-invasive drug delivery to a specific site of action, enhanced patient compliance, and ease of application (Washington *et al.*, 2000; Baibhav *et al.*, 2011; Shiva Prasada and Mutta, 2021; El-Setouhy and El-Ashmony, 2010).

A variety of pharmaceutical products (ointments, creams, and pastes) has been used for the purpose of topical drug delivery. However, these formulations often exhibit a high degree of adhesiveness, which can result in patient discomfort upon application. Consequently, transparent gels have emerged as a prevalent component in both cosmetic and pharmaceutical preparations. The gels formation entails the entrapment of drugs within a substantial quantity of aqueous or hydrophilic liquid, thereby establishing a colloidal network. These gels are particularly well suited for water-soluble drugs, as opposed to hydrophobic drugs, which pose significant challenges in their incorporation into aqueous gel bases (Baibhav *et al.*, 2011; Shiva Prasada and Mutta, 2021; Hamed *et al.*, 2015).

Diclofenac, a nonsteroidal anti-inflammatory drug, is widely used as a painkiller in rheumatoid arthritis due to its analgesic and anti-inflammatory effects. This drug is available in different salt forms (sodium, potassium, and diethyl amine). The sodium and diethyl amine salts are commonly used in topical administration (the diclofenac sodium in gel, the diclofenac diethyl amine in emulgels), whereas the potassium salt is most frequently used in oral administration (Fini *et al.*, 2012; Goh and Lane, 2014; Trivedi *et al.*, 2022; Altman *et al.*, 2015; Hamed *et al.*, 2020).

When diclofenac is orally administered, it can cause local mucosal irritation and undergo extensive first-pass metabolism. However, studies have demonstrated that these adverse effects can be mitigated by topical administration of the drug. The rate of penetration of the skin is directly proportional to the lipid solubility of the drug. Diclofenac diethyl amine, a more lipophilic salt of diclofenac, is characterized by higher solubility (Washington *et al.*, 2000; Baibhav *et al.*, 2011; Hamed *et al.*, 2015; Goh and Lane, 2014).

The objective of the present study is to characterize the rheological behavior of drug carriers in the context of topical and transdermal administration. The study focused on the rheological properties, determinant for enhancing drug penetration through the skin.

2. Materials and Methods

2.1. Materials

The four commercially available diclofenac-based gels (Table 1) were used for the rheological characterization: DF_10, V_11.6, V_23.2, D_10.

Table 1
Composition of the gels

Components	DF_10	V_11.6	V_23.2	D_10
Diclofenac sodium	x			x
Diclofenac diethyl amine		x	x	
Diethyl amine		x	x	
Isopropyl alcohol		x	x	
Purified water	x	x	x	x
Carbomer 980	x		x	x
Carbopol 974 P		x		
Liquid paraffin wax		x	x	
Propylene glycol		x	x	
Triethanolamine	x			

2.2. Methods of analysis

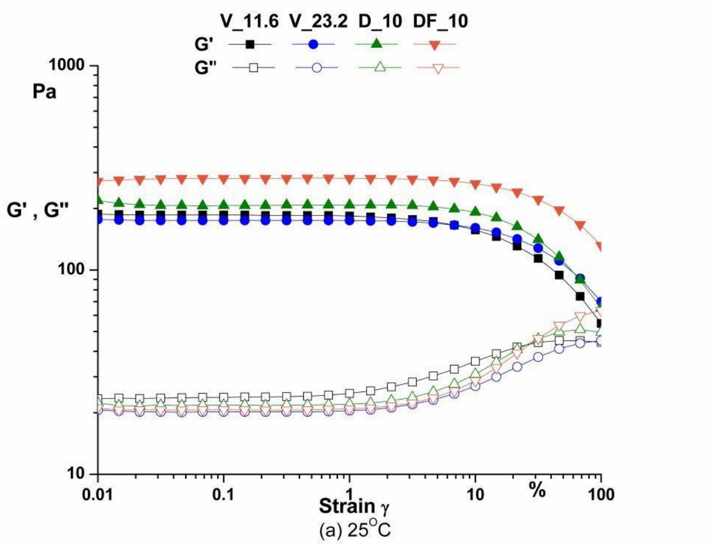
Rheological tests were conducted using a Physica MCR 501 modular rheometer (Anton Paar, Austria). The serrated parallel-plate geometry, with a diameter of 50 mm, was selected as the measuring system. The samples were subjected to heating using a Peltier system (Ibănescu *et al.*, 2010; Danu *et al.*, 2012).

The amplitude sweep is a method used to determine the limit of the linear viscoelastic range. In this experiment, the oscillation frequency is maintained at a constant value of 10 rad/s, while the oscillation amplitude (γ) is systematically varied from 0.01 to 100%. The limit of the linear viscoelastic range is determined by the maximum deformation that the sample can withstand before its structural integrity is compromised. The frequency sweep constitutes a widely utilized standard test in rheological characterization of gels. In this test, a sinusoidal strain with a constant amplitude in the linear viscoelastic range (γ = 1%) is applied, and the oscillation frequency is varied (between 0.1 and 100 rad/s). The flow curve was determined within the shear rate range of 0.01-100 s^{-1}. All measurements were carried out at constant temperatures of 25°C and 37°C. The oscillatory time test was performed at a constant shear strain (γ = 1%) and constant temperature (25°C) for a duration of 25 minutes.

3. Results and Discussions

Rheological characterization of pharmaceuticals is a valuable tool for understanding various aspects of pharmaceutical processes and products. This characterization provides insights into the viscoelastic behavior of the system, facilitating the evaluation of raw materials and final products. Additionally, it aids in understanding manufacturing processes such as mixing, pumping, packaging and filling. Furthermore, this characterization can elucidate the influence of specific process parameters on the quality of the final product. It enables the assessment of the efficiency of use of a pharmaceutical product, including factors such as application to the skin, adhesion to the skin, and removal from a tube or container (Hamed *et al.*, 2015; Lucero *et al.*, 2016).

A **strain sweep** test (Fig. 1: (a) 25°C, (b) 37°C) at a frequency of 10 rad/s was performed to determine the linear viscoelastic region, from which an appropriate strain was selected for the subsequent oscillatory tests. The viscoelastic properties of the gels were evaluated by recording the evolution of the dynamic moduli, G' and G". The storage modulus (G') provides insights into the solid-like (elastic) behavior of the sample, while the loss modulus (G") offers information about the liquid-like (viscous) behavior (Danu *et al.*, 2012; Simionescu *et al.*, 2013).



(a) 25°C

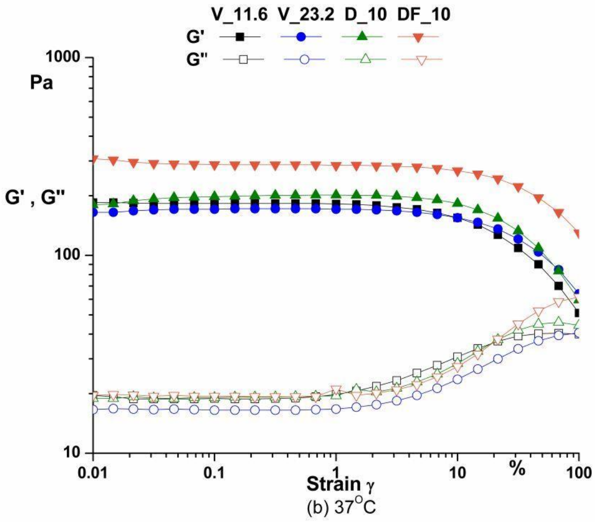


Fig. 1 – Amplitude sweep of the analyzed gels at two different temperatures: (a) 25°C and (b) 37°C.

The type and concentration of active principle (diclofenac sodium or diclofenac diethyl amine) do not influence the rheological properties of the studied samples. The amount of stabilizer in the tested samples (Carbomer 980 or Carbopol 974) was dosed in such a way that the samples exhibited rheological behavior corresponding to a gel-type product. A slight increase in the elastic component (storage modulus G') was observed in the DF_10 sample, attributable to the presence of triethanolamine, as a surfactant and emulsifier. The variation of dynamic moduli with deformation revealed the existence of viscoelastic materials with predominantly gel (solid) character (G' > G").

The experimental data obtained enabled the determination of the limit of the linear viscoelastic domain for all analyzed samples as 1% (γ_{LVE} = 1%), at both temperature of 25°C and 37°C. Within this linear viscoelastic domain, the dynamic moduli G' and G" are independent of strain, and the structural integrity of the samples remains uncompromised. This region is denominated as the linear viscoelastic region (LVR), wherein any disruption to the microstructure is instantaneously restored. The storage modulus (G') exhibits a significantly higher magnitude compared to the loss modulus (G"), indicating that the microstructure of the gels is highly organized. For all samples, a substantial decrease in the storage modulus (G') was observed within the strain range of 5 - 15%, suggesting the occurrence of gel destructions at higher strains. Subsequent oscillatory rheological tests will be conducted within the linear viscoelastic region at a 1% strain value to further investigate the mechanical behavior of these materials (Hamed *et al.*, 2015; Hamed *et al.*, 2020; Krishnaiah *et al.*, 2014).

In the **frequency sweep** tests, storage modulus (G’) and loss modulus (G”) were measured at a constant strain (γ_{LVE} = 1%) over a frequency range of 0.1-100 rad/s.

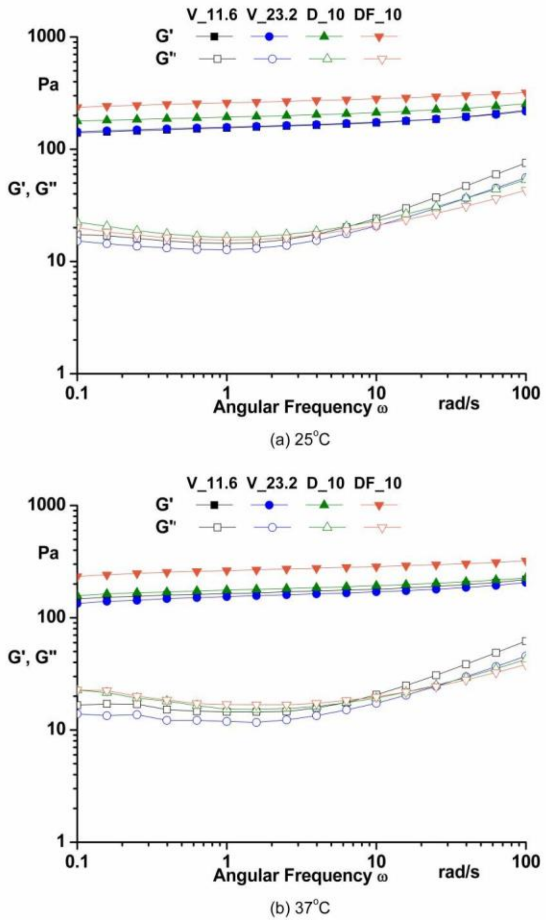
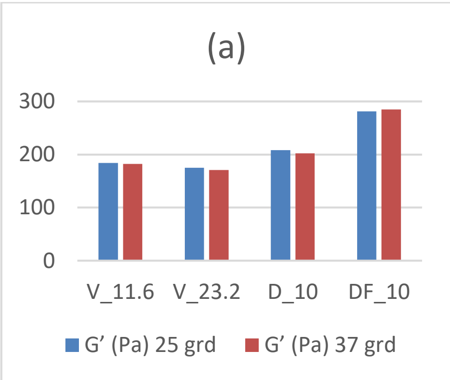


Fig. 2 – Frequency sweep for gel samples at two different temperatures: (a) 25°C and (b) 37°C.

In the frequency sweep, the storage modulus (G') is indicative of the sample elastic behavior, providing insights into its structural stability and strength, also known as "stiffness." The loss modulus (G") is associated with the viscous behavior of the sample, also referred to as "flexibility."

As illustrated in Fig. 2 (a) 25°C and (b) 37°C, the frequency dependence of the dynamic moduli G' and G" at 25°C and 37°C for diclofenac gels is demonstrated. The observation that the storage modulus (G') exceeds the loss modulus (G") indicates the presence of mechanical and structural stability in the analyzed samples. The high values of the storage modulus indicate the presence of a stable internal network of forces within the samples, which proves the compositional homogeneity of the studied gels (the components did not separate). The absence of an intersection point between the dynamic moduli further substantiates the hypothesis of mechanical and structural stability, thereby confirming that the studied gels do not exhibit a sticky texture (Hamed *et al.*, 2015; Hamed *et al.*, 2020).

The structural strength of the gel can be determined by the numerical value of G' (Fig. 3a) and by the significant difference between G' and G" (Fig. 3b), indicating the existence of a strong gel for a high value of the ΔG parameter (Chenite *et al.*, 2001).



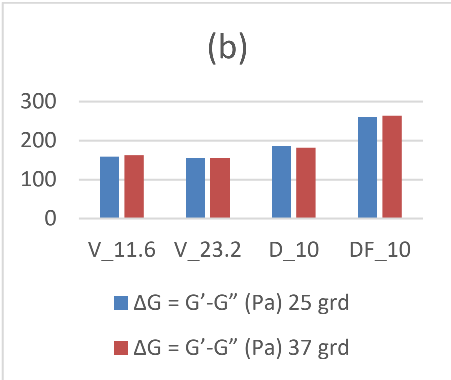


Fig. 3 – The G' (a) and ΔG (b) values for analyzed gels.

The application of the Carreau-Yasuda model (Table 2) to the frequency sweep results enables the calculation of zero shear viscosity, η_0, and infinite shear viscosity, η_∞. A high zero shear viscosity is indicative of a high average molecular weight and increased mechanical stability of the sample.

Table 2

Rheological parameters calculated from the Carreau - Yasuda model

Carreau – Yasuda model:

$$y = \frac{y_0 - y_{inf}}{((l + lambda \cdot x)^a)^{(l-n)/a}} + y_{inf}\ ,\ y_0 - y_{inf} > 0$$

Sample name	25ºC		37ºC	
	zero shear viscosity, η_0 [Pa·s]	infinite shear viscosity, η_∞ [Pa·s]	zero shear viscosity, η_0 [Pa·s]	zero shear viscosity, η_∞ [Pa·s]
V_11.6	18137	0.5114	9183.4	0.3685
V_23.2	2024.8	0.3813	11484	0.2904
D_10	1705.9	0.8484	3144.1	0.2237
DF_10	8052.4	0.1895	17851	0.1610

The **flow curves** were recorded at 25°C and 37°C in the shear rate range of 0.01–100 s^{-1}. As illustrated in Fig. 4, the viscosity of the samples decreased with increasing shear rate, indicating shear-thinning behavior at both temperature. This phenomenon is a typical response observed in gel-type materials and can be attributed to the gradual disintegration of the three-dimensional network of the gels with increasing shear rate. It is noteworthy that all the samples exhibited high viscosity values at low shear rates and low viscosity values at high shear rates. This phenomenon results in prolonged skin contact time and a reduction in the potential for irritation after use. The correlation between low viscosity and high fluidity is well-documented, and it ensures easier handling, faster distribution over a larger surface area, more efficient mixing, and better flow of the product from the tube (Walicka *et al.*, 2019).

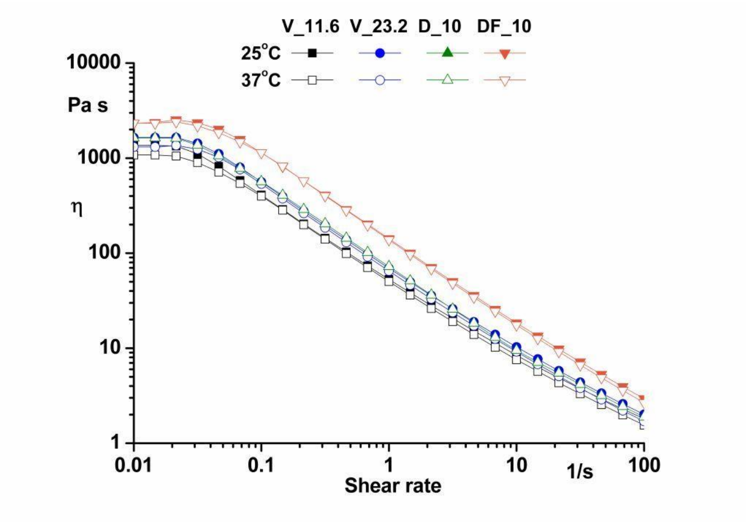


Fig. 4 – Flow curves at 25ºC and 37ºC for analyzed gels.

In conditions of low shear, gels exhibit elevated viscosity levels (1000 - 5000 Pa·s), thereby conferring a firm texture to the product. However, as the shear increases, the product's viscosity undergoes a rapid decrease, falling below 10 Pa·s. This allows for the product to be easily spread over a large surface area of the skin (Krishnaiah *et al.*, 2014).

In the range of shear rates 0.01-100 s^{-1}, the flow curves were processed with the Ostwald de Waele (Table 3), Herschel-Bulkley (Table 4) and Casson (Table 5) rheological models.

Table 3
Rheological parameters of the flow curves corresponding to the Ostwald de Waele model

Ostwald de Waele model $y = a \cdot x^b$; a – viscosity; b – flow index				
Sample name	25ºC		37ºC	
	a [Pa·s]	b	a [Pa·s]	b
V_11.6	37.969	0.335	34.746	0.322
V_23.2	49.306	0.302	46.367	0.279
D_10	45.771	0.306	14.799	0.271
DF_10	111.18	0.208	109.95	0.190

Table 4
Rheological parameters of the flow curves corresponding to the Herschel-Bulkley model

Herschel – Bulkley model $y = a + b \cdot x^p$; a – yield point; b – viscosity				
Sample name	25ºC		37ºC	
	a [Pa]	b [Pa·s]	a [Pa]	b [Pa·s]
V_11.6	40.878	13.389	39.633	11.432
V_23.2	53.655	16.394	52.434	13.127
D_10	63.539	8.791	52.659	11.011
DF_10	115.62	26.845	114.23	29.026

Table 5
Rheological parameters of the flow curves corresponding to the Casson model

Casson model $y^{1/p} = a + b \cdot x^{1/p}$; a – yield point; b – infinite shear viscosity				
Sample name	25ºC		37ºC	
	a [Pa]	b [Pa·s]	a [Pa]	b [Pa·s]
V_11.6	31.956	0.100	32.183	0.079
V_23.2	43.407	0.066	44.977	0.056
D_10	58.761	0.247	46.625	0.069
DF_10	103.35	0.024	104.18	0.017

Tables 3-5 reveal the independence of the yield point on temperature with the exception of sample D_10. However, it is influenced by the concentration of diclofenac in the sample, with a higher concentration resulting in a higher yield point value. Furthermore, the Ostwald de Waele rheological model demonstrates a decrease in viscosity and flow index with an increase in temperature. When plotting viscosity versus shear rate, it was observed that all gels had identical slopes in the lower viscosity range (Fig. 4). The gels exhibited a flow index *b* ranging from 0.2 to 0.3 (Table 4), indicative of uniform shear-thinning behavior across all gels. It is hypothesized that all samples will demonstrate analogous spreading behavior on the skin. A yield stress ranging from 10 to 100 Pa (parameter *a* in Tables 5 and 6) indicates a minimum force to initiate flow, and it is anticipated that the gels will be readily applicable to the skin and will spread there (Krishnaiah *et al.*, 2014; Pleguezuelos-Villa *et al.*, 2019).

The **time tests** were carried out in oscillatory regime at a constant strain value (γ = 1%), at a constant temperature of 25ºC, for 25 minutes. As illustrated in Fig. 5, the structural stability of the tested samples over time can be attributed, at least in part, to the presence of Carbomer 980 or Carbopol 974 components in their composition, which function as stabilizers.

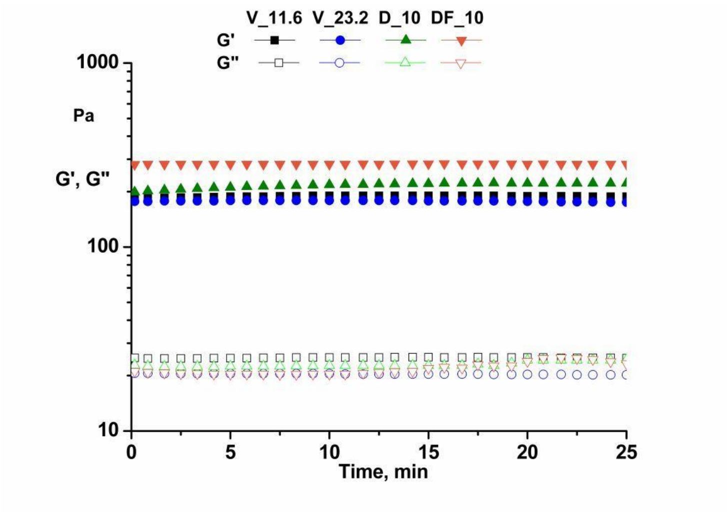


Fig. 5 – Time test at 25ºC for analyzed gels.

3. Conclusions

A significant quality indicator of gels is their rheological profile. Additionally, to evaluating the quality of preparation, these properties significantly influence critical manufacturing processes parameters, the products shelf-life, and the establishment of storage conditions.

This study explores the potential of rheological measurements in the characterization of gels. The rheological properties of gels were further characterized by calculating yield stress (τ_0), infinite shear viscosity (η_∞), and elastic modulus (G'), respectively. The rheological tests employed were both simple and predictive, with the viscoelastic properties correlating with the end-use performance properties (applicability, processing and storage stability).

It can be concluded that the samples exhibit gel-specific properties, including spreadability, viscosity, and consistency. The optimization of diclofenac gels is a significant step in enhancing clinical care techniques. The results obtained (structural stability, time stability, gel structure) indicate the utility of diclofenac gels for this purpose.

REFERENCES

Altman R., Bosch B., Brune K., Patrignani P., Young C., *Advances in NSAID development: evolution of diclofenac products using pharmaceutical technology*, Drugs, **75(8)**, 859-877 (2015).

Baibhav J., Gurpreet S. *et al.*, *Emulgel: a comprehensive review on the recent advances in topical drug delivery*, Int Res J Pharm, **2**, 66-70 (2011).

Chenite A., Buschmann M., Wang D., Chaput C., Kandani N., *Rheological Characterization of Thermogelling Chitosan/Glycerol-Phosphate Solutions*, Carbohydr. Polym., **46**, 39-47 (2001).

Danu M., Rotaru I., Ibănescu C., Hurduc N., Ibănescu S. A., Simionescu B. C., *Gluten content influence on rheological behavior of starch-gluten networks*, EEMJ, **11(11)**, 1883-1888 (2012).

El-Setouhy D.A., El-Ashmony S.M.A., *Ketorolac trometamol topical formulations: release behaviour, physical characterization, skin permeation, efficacy and gastric safety*, J Pharm Pharmacol, **62**, 25-34 (2010).

Fini A., Cavallari C., Bassini G., Ospitali F., Morigi R., *Diclofenac salts, part 7: Are the pharmaceutical salts with aliphatic amines stable?*, J Pharm Sci, **101(9)**, 3157-3168 (2012).

Goh C.F., Lane M.E., *Formulation of diclofenac for dermal delivery*, Int J Pharm, **473(1-2)**, 607-616 (2014).

Hamed R., Basil M., AlBaraghthi T., Sunoqrot S, Tarawneh O., *Nanoemulsion-based gel formulation of diclofenac diethylamine: design, optimization, rheological behavior and in vitro diffusion studies*, Pharm Dev Technol, Early Online: 1-10 (2015).

Hamed R., Mahmoud N.N., Alnadi S.H., Alkilani A.Z., Hussein G., *Diclofenac diethylamine nanosystems-loaded bigels for topical delivery: development, rheological characterization, and release studies*, Drug Dev Ind Pharm, **46(10)**, 1-35 (2020).

Ibănescu C, Danu M., Nanu A., Lungu M., Simionescu B.C., *Stability of disperse systems estimated using rheological oscillatory shear tests*, Rev Roum Chim, **55(11-12)**, 933-940 (2010).

Krishnaiah Y.S.R. *et al.*, *Development of performance matrix for generic product equivalence of acyclovir topical creams*, Int J Pharm, **475**, 110-122 (2014).

Lucero M.J., Ferris C., Sánchez-Gutiérrez C.A., Jiménez-Castellanos M.R., de-Paz M.-V., *Novel aqueous chitosan-based dispersions as efficient drug delivery systems* *for topical use. Rheological, textural and release studies*, Carbohydr Polym, **151**, 692-699 (2016).

Pleguezuelos-Villa M. *et al.*, *Relationship between rheological properties, in vitro release and in vivo equivalency of topical formulations of diclofenac*, Int J Pharm, **572**, 118755 (2019).

Shiva Prasada N., Mutta S.K., *A review on emulgel*, Asian J Pharm Life Dev, **9(4)**, 147-150 (2021).

Simionescu B., Ibănescu S.A., Danu M., Rotaru I., Ibănescu C., *Rheology of gelatin – starch systems. I. Influence of systems composition*, Rev. Chim., **64(8)**, 909-913 (2013).

Trivedi N., Mishra S., Prakash J., *Emulgel: A review*, Int J Pharm Res Appl, **7(4)**, 859-870 (2022).

Walicka A., Falicki J., Iwanowska-Chomiak B., *Rheology of Drugs for Topical and Transdermal Delivery*, Int J Appl Mech Eng, **24**, 179-198 (2019).

Washington N., Washington C., Wilson C., *Transdermal drug delivery. Physiological pharmaceutics: barriers to drug absorption*, New York: CRC Press; 181-195 (2000).

COMPORTAMENTUL REOLOGIC AL UNOR GELURI PE BAZĂ DE DICLOFENAC

(Rezumat)

Administrarea produselor farmaceutice la nivelul pielii se poate realiza prin două metode: topic și transdermic. În contextul administrării topice, medicamentul este destinat să acționeze la nivelul pielii și este frecvent utilizat în tratamentul bolilor de piele. Administrarea transdermică realizează o eliberarea sistemică, în care pielea este o barieră, nu o țintă. Obiectivul acestui studiu este de a caracteriza comportamentul reologic al unor geluri utilizate în administrarea topică. În acest scop, s-au testat reologic câteva geluri comerciale care conțin diclofenac.

Studiul demonstrează aplicarea măsurătorilor reologice în caracterizarea produselor farmaceutice. Proprietățile viscoelastice pot fi corelate cu proprietățile de performanță la utilizarea finală, cum ar fi: aplicabilitatea, comportamentul la procesare, depozitarea și stabilitatea termică.