PHYSICAL-CHEMICAL CHARACTERIZATION OF SUSPENSION WITH PROLONGED RELEASE

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INTRODUCTION

Pharmaceutical products with extended release are designed for weekly, monthly, or multi-month use, formulated to allow controlled release of the active substance. They provide patients with a constant therapeutic concentration of the drug, and thus more effective treatment. In Figure 1 is presented four classes of pharmaceutical products with extended release. One of the most common formulations in the development of extended-release pharmaceutical systems is aqueous suspension, which this study will focus on in terms of its physicochemical properties. During the development of such systems, one key property to consider is the long-term stability of the formulation, influenced by unfavorable thermodynamics of suspensions. Core components that determine the safety and efficacy of suspensions are formulation, particle size distribution, and physical stability. The main challenges in physical stability include processes such as agglomeration, sedimentation, Ostwald ripening, and secondary nucleation. [1,2] Smaller particles compensate sedimentation through Brownian motion, so reducing particle size is often used to prevent significant particle settling. Agglomeration is influenced by surface tension, the structure of surfactants, and zeta potential, while drug diffusion from particle surfaces is affected by the viscosity of the suspension medium. Therefore, the most stable suspensions have relatively low water solubility and are suspended in a medium containing viscosity-enhancing additives. [1,2] This study presents the physicochemical characterization of an aqueous suspension formulated as extended release product using rheological measurements and sedimentation rate analysis.

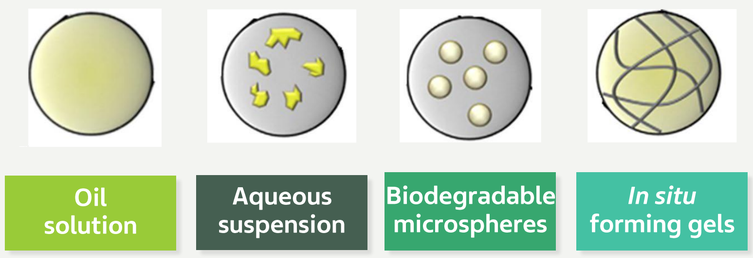

Figure 1. Four classes of pharmaceutical products with extended release.

PHYSICAL-CHEMICAL CHARACTERIZATION RESULTS

Rheological measurements

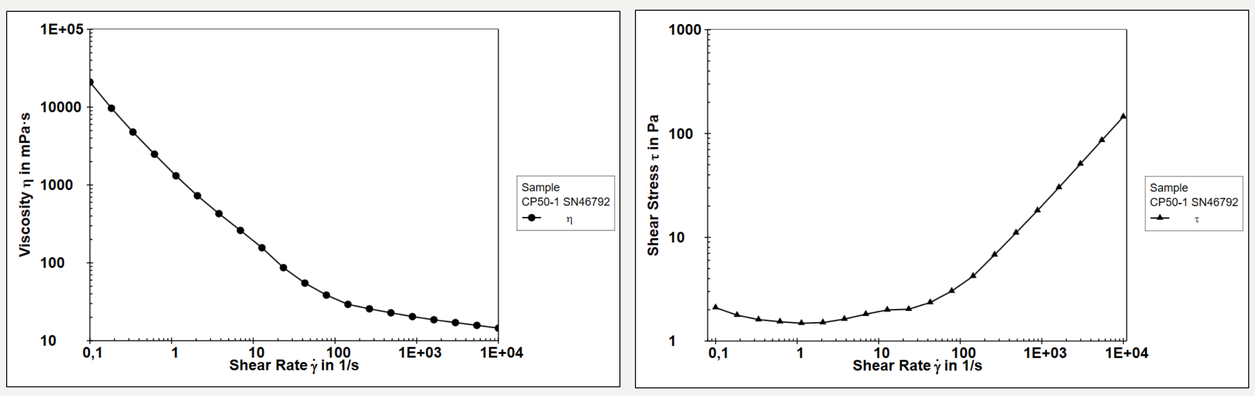

Figure 2. Flow curve of the sample examined at 25°C.

SHEAR THINNING BEHAVIOUR

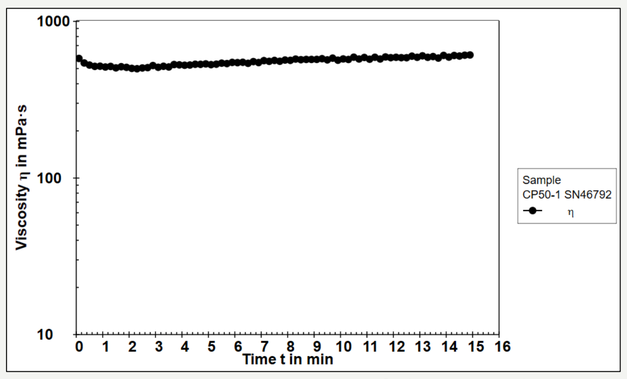

Figure 3. Shear viscosity of the sample at a constant shear rate γ =1 s^{-1} examined at 25°C

Table 1. Viscosity of the sample at different shear rates at 25°C.

$\dot{\gamma}/s^{-1}$	η/mPa×s
0.1	20993
1	556.8
10000	14.5

SHEAR THINNING

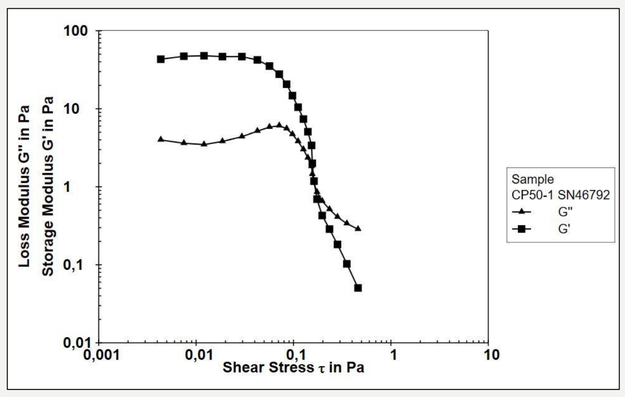

Figure 4. Amplitude sweep test of the sample examined at 25°C.

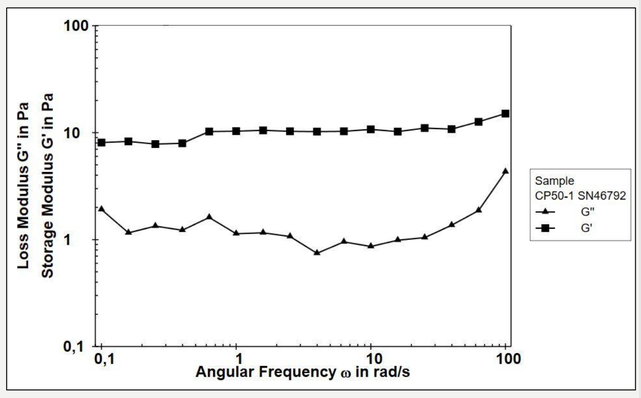

Figure 5. Frequency sweep test (*G´* and *G´´* values) of the sample performed at 0.05% strain at 25°C.

Solid like sample (*G' > G''*)

Table 2. Results of amplitude sweep test of the sample examined at 25°C.

LVR			Yield point/Pa		Flow point/Pa	
G'/Pa	*G''*/Pa	tan δ	τ/Pa	γ/%	τ/Pa	γ/%
47.8	3.5	0.07	0.04	0.1	0.2	11.2

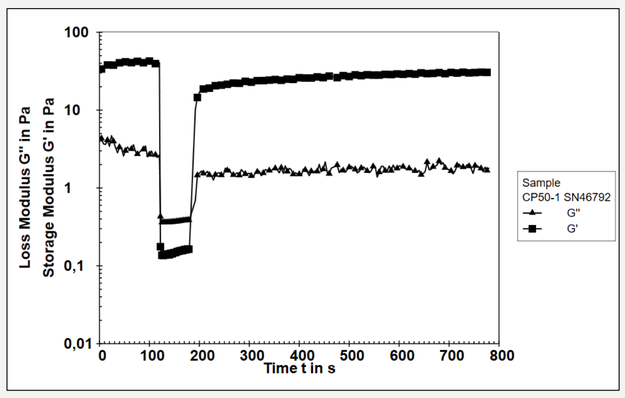

Figure 6. 3-interval thixotropy test (3ITT) (G´ and G´´ values) of the sample at 25°C. Linear viscoelastic region (LVR): strain=0.05%, frequency=10 rad/s; destructive region (DR): strain=100%, frequency=10 rad/s; recovery region: linear viscoelastic region (LVR): strain=0.05%, frequency=10 rad/s.

Table 3. Self-healing properties of the sample determined in 3-interval thixotropy test at 25°C.

Recovery (t=60s)/%	Recovery (t=300s)/%	Recovery (t=500s)/%
49.2	64.5	70.3

Sedimentation rate analysis

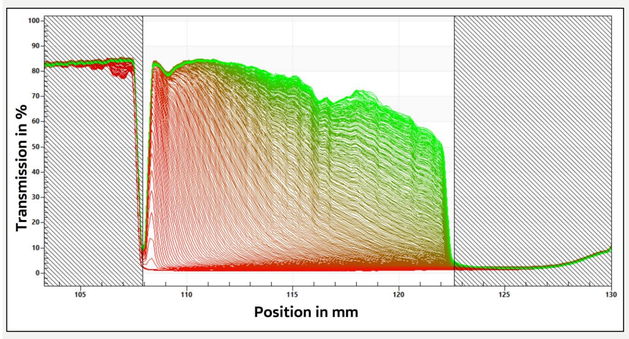

Figure 7. Evolution of transmission profiles of the sample measured at 1500 RPM for 500 s than at 4000 RMP for 7680 s.

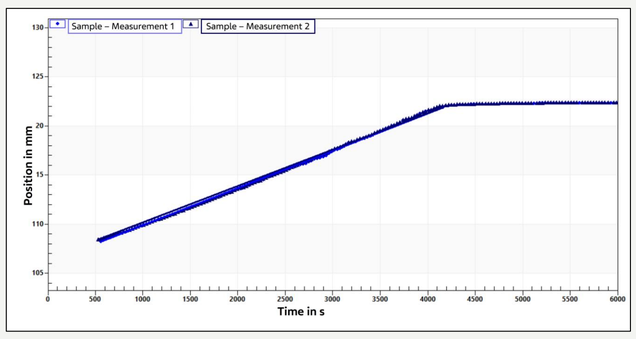

Figure 8. Sedimentation kinetics of the sample during centrifugation at 25°C.

POLYDISPERSE SEDIMENTATION BEHAVIOUR

Gradual decrease in spacing between transmission profiles

Table 4. Results of sedimentation velocities of the sample examined at 25°C.

Velocity/ µm/s	Mean RCA/ g
3.793	2053

CONCLUSION

Results of this study reveal that an investigated sample exhibited a non-Newtonian shear-thinning behavior, characterized by a decrease in viscosity with increasing shear rate. Specifically, as the shear rate increased, the viscosity decreased from 20993 to 14.5 mPas. The oscillatory measurements confirmed that the sample displays solid characteristics and can be described as a viscoelastic solid with storage modulus (*G´*) values higher than loss modulus (*G´´*) values. The measured recovery after shear was slow and incomplete, reaching 70% of the initial structure after 500 seconds. The transmission profiles reflect polydisperse sedimentation, meaning that particles move independently with different velocities based on their size. Larger particles sediment at considerably higher velocities. Additionally, the sample exhibited compression of the flocculated network, resulting in a gradual decrease in spacing between transmission profiles. The determined sedimentation velocity value was 3.8 µm/s.

LITERATURE

[1] R.Holm, R.W. Lee, J. Glassco et. al, AAPS J. 25, 49 (2023)
[2] J. E. Kipp, Int. J. Pharm 284 (2004) 109-112

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