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RHEOLOGICAL PROPERTIES OF PRIMARY PHARMACEUTICAL EMULSIONS OBTAINED BY HOMOGENIZATION

WŁAŚCIWOŚCI REOLOGICZNE EMULSJI PIERWOTNYCH O POTENCJALNYM ZNACZENIU FARMACEUTYCZNYM WYTWORZONYCH TECHNIKĄ EMULGOWANIA PRZY UŻYCIU HOMOGENIZATORA

Abstract

The paper presents the results of rheological examinations of primary emulsions with the potential for pharmaceutical applications, created through emulsification using a homogeniser. The water phase of the examined emulsions was made up of water solutions of hydrocolloids, the fatty phase was the pharmaceutical oil Miglyol 812N and canola oil, sunflower seed oil, olive oil. For the determination of relations between the structural parameters of the emulsions and their viscous properties flow curves and viscosity curves were obtained for the examined systems. The obtained results were processed through regression of experimental points by rheological equations, using the own software of the rheometer.

Keywords: *emulsion*, *rheology*, *flow and viscosity curve*

Streszczenie

W artykule przedstawiono wyniki badań reologicznych emulsji pierwotnych o potencjalnym znaczeniu farmaceutycznym, wytworzonych techniką emulgowania z użyciem homogenizatora. Fazę wodną badanych emulsji stanowiły wodne roztwory hydrokoloidów, fazę tłuszczową faza farmaceutyczna Miglyol 812N oraz olej rzepakowy, słonecznikowy, olej oliwkowy. Do określenia zależności pomiędzy parametrami strukturalnymi emulsji a ich właściwościami lepkimi wyznaczono krzywe płynięcia i lepkościowe dla badanych układów. Uzyskane wyniki badań opracowano drogą regresji punktów doświadczalnych za pomocą równań reologicznych, z użyciem oprogramowania firmowego reometru.

Słowa kluczowe: *emulsje*, *reologia*, *krzywe płynięcia i lepkościowe*

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Designations

HPMC – hydroxypropylmethylcellulose
$\dot{Z}$ – gelatine solution
n – homogeniser rotational speed [s^{-1}]
t – emulsification time [s]
ϕ_{mas} – percentage of mass of dispersed phase in emulsions
τ – shear stress [Pa]
η – dynamic viscosity coefficient [Pa·s]
$\dot{\gamma}$ – shear rate [s^{-1}]
τ_0 – yield stress [Pa]
η_p – elastic viscosity [Pa·s]
n – characteristic flow coefficient [–]
K, η_∞, η_b – correlation equation factors

1. Introduction

Tablets quickly dissolving in the mouth are a modern form of medicine, which is a solution to the common problem of swallowing of a traditional form of medicine – a tablet [1–3]. Such systems are manufactured using techniques such as: lyophilisation, spray drying, granulation, sublimation, direct compression. In lyophilisation and spray drying, the substance subjected to drying is the so-called primary emulsion, which turns into a dry emulsion [4–15]. In this case, the properties of a tablets quickly dissolving in the mouth such as disintegration time, reconstruction ability and bioavailability, are closely related to the physical and chemical properties of primary emulsions.

According to the Polish Pharmacopoeia 7th Edition, tablets quickly dissolving in the mouth are systems for which the disintegration time is lower than three minutes [16]. Literature data shows that the lower the viscosity of primary emulsions, the shorter the disintegration time, because excessively high viscosity of primary emulsions may, according to authors, [4, 6, 7, 17] lower the ability of a porous structure, which determines the disintegration times, to be formed.

The rheological research described in literature concerning rheological properties of primary emulsions is not complete. It do not allow the description of general properties which would enable a quantitative, and not only qualitative, description of these systems. It thus seems purposeful to conduct complete examinations of prime emulsions, which should encompass an analysis of the flow and viscosity curves, and a verification of the obtained results through theoretical models.

2. Materials and research methods

The subject of the research were oil-in-water primary emulsions obtained through emulsification using a homogeniser. The emulsions were manufactured using the Miccra D-9 homogeniser, with a rotational speed range of n = 183.3–650 s^{-1}. The emulsification time was t = 60–300 s.

The water phase of the emulsions was made up of liquid solutions of hydrocolloids, i.e. a 2% by mass water solution of HPMC, a 1.5% by mass water solution of $\dot{Z}$, and their mixture. The mass ratio of $\dot{Z}$/HPMC was 44:1.

Miglyol 812N pharmaceutical oil, olive oil, canola oil and sunflower seed oil were used as the oil phase of the primary emulsions. The content of the fatty phase was ϕ_{mas} = 0.1–0.3.

The produced primary emulsions were subject to rheological examinations, which entailed the determination of flow and viscosity curves of the primary emulsions.

The flow and viscosity curves were obtained using the RS 75 rotational rheometer from Haake. The rheometer was controlled through a PC connected to the rheometer, using the RheoWin 3.61 specialist rheometer control application.

The examinations were carried out using a cone-plate set-up, angle 0,5°C; diameter 20 mm. Measurement temperature was 293 K, working mode CS, volume of examined sample – 1 cm^3.

Using the proprietary software of the rheometer a regression of the examination points was conducted. The flow curve equations presented in table 1 were used for this purpose.

Table 1

Mathematical equations describing the rheological behaviour of fluids

Item	Authors	Flow curve equation	Viscosity curve equation
1.	Bingham	$\tau = \tau_y + \eta_p \dot{\gamma}$	$\eta = \frac{\tau_y}{\dot{\gamma}} + \eta_p$
2.	Ostwald de Waele	$\tau = K\dot{\gamma}^n$	$\eta = K\dot{\gamma}^{n-1}$
3.	Herschel Bulkley	$\tau = \tau_y + K\dot{\gamma}^n$	$\eta = \frac{\tau_y}{\dot{\gamma}} + K\dot{\gamma}^{n-1}$
4.	Casson	$\tau = \sqrt[n]{\tau_y^n + (\eta_\infty \dot{\gamma})^n}$	$\eta = \sqrt[n]{\left(\frac{\tau_y}{\dot{\gamma}}\right)^n + (\eta_\infty)^n}$
5.	Windhab	$\tau = \tau_y + \eta_\infty \dot{\gamma} + (\tau_1 - \tau_y)(1 - e^{-\dot{\gamma}/\gamma *})$	$\eta = \frac{\tau_y}{\dot{\gamma}} + \eta_\infty + (\tau_1 - \tau_y)(1 - e^{-\dot{\gamma}/\dot{\gamma}*})$
6.	Tscheuschner	$\tau = \dot{\gamma}(\eta_\infty + \tau_y / \dot{\gamma} + \eta_b / (\dot{\gamma} / \dot{\gamma}_b)^n)$	$\eta = (\eta_\infty + \tau_y / \dot{\gamma} + \eta_b / (\dot{\gamma} / \dot{\gamma}_b)^n)$

3. Examination results, discussion

Own research had shown that the primary emulsions belonged to a group of non-Newtonian liquids – shear thinning, showing a yield stress (Fig. 1). The type of water phase used did not alter the characteristics of the flow curve, however it influenced the value of the yield stress. Low yield stress values showed that the examined primary emulsions have weak flow abilities.

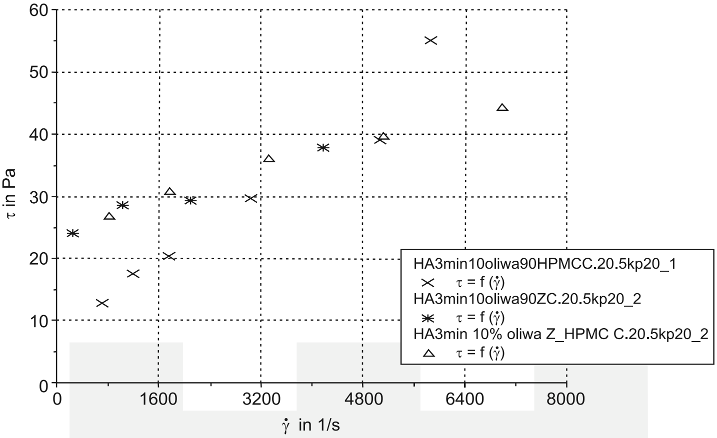

Fig. 1. Flow curves for primary blank emulsions, oil phase olive oil $\phi_{mas} = 0.1$, water phase water solutions of thickening agents 90% by mass: *x* – 2% HPMC by mass, ∗ – 1.5% *Ż* by mass., Δ – 1.5% *Ż* by mass, 2% HPMC by mass (mass ratio *Ż*/HPMC 44:1), $n = 183.3\ s^{-1}$, $t = 180$ s

Rys. 1. Przebieg krzywych płynięcia dla emulsji pierwotnych blank, faza tłuszczowa olej oliwkowy $\phi_{mas} = 0{,}1$, faza wodna wodne roztwory zagęstników 90% mas.: *x* – 2% mas. HPMC, ∗ – 1,5% mas. *Ż*, Δ – 1,5% mas. *Ż*, 2% mas. HPMC (stos. mas. *Ż*/HPMC 44:1), $n = 183{,}3\ s^{-1}$, $t = 180$ s

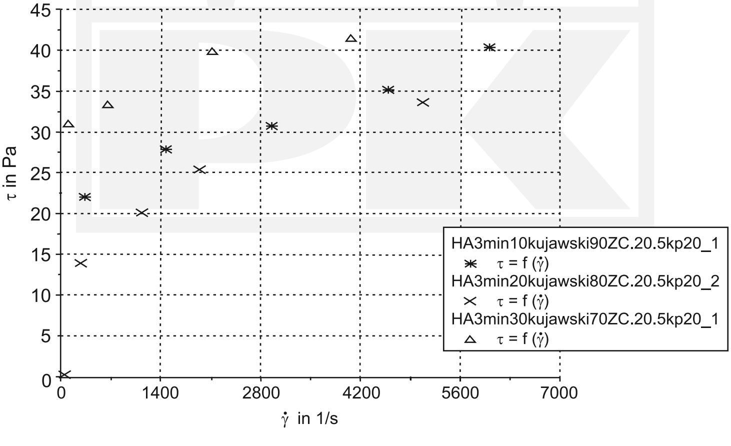

Fig. 2. Flow curves for primary blank emulsions, oil phase ‘Kujawski’ cooking oil, ∗ – $\phi_{mas} = 0.1$; *x* – $\phi_{mas} = 0.2$; Δ – $\phi_{mas} = 0{,}3$; water phase 1.5% by mass *Ż* water solution, $t = 180$ s, $n = 183.3\ s^{-1}$

Rys. 2. Przebieg krzywych płynięcia emulsji pierwotnych blank, faza tłuszczowa olej Kujawski, ∗ – $\phi_{mas} = 0{,}1$; *x* – $\phi_{mas} = 0{,}2$; Δ – $\phi_{mas} = 0{,}3$; faza wodna 1,5% mas. wodny roztwór *Ż*, $t = 180$ s, $n = 183{,}3\ s^{-1}$

Own research had shown that with an increase in the share of the fatty phase in the blank primary emulsion preparation, the value of the flow limit tended to increase (Fig. 2).

In the analysed range of emulsification times the flow curves of the primary emulsions blank overlapped (Fig. 3).

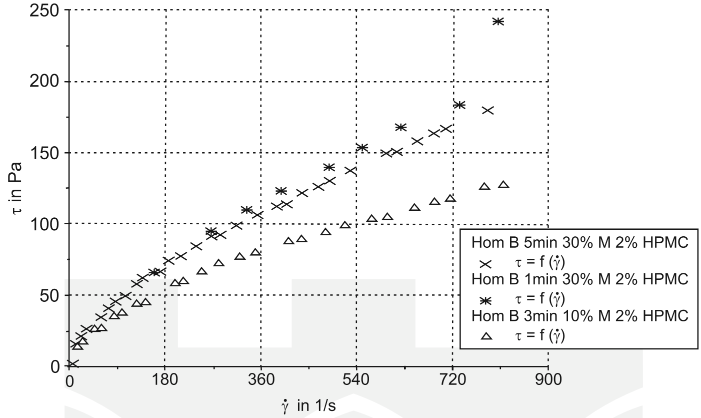

Fig. 3. Flow curves for primary blank emulsions, water phase 70% by mass 2% HPMC by mass, oil phase Miglyol 812N $\phi_{mas} = 0.3$; $n = 266.6\ s^{-1}$, emulsification time: $* - t = 60$ s, $x - t = 180$ s, $\Delta - t = 300$ s

Rys. 3. Krzywe płynięcia emulsji pierwotnych blank, fazę wodna 70% mas. 2% mas. HPMC, faza tłuszczowa Miglyol 812N $\phi_{mas} = 0,3$; $n = 266,6\ s^{-1}$, czas emulgowania: $* - t = 60$ s, $x - t = 180$ s, $\Delta - t = 300$ s

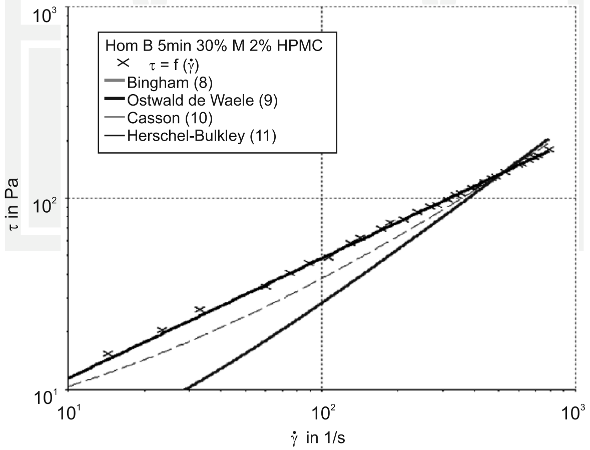

Fig. 4. Flow curves with adapted rheological models, primary blank emulsion, fatty phase Miglyol 812N $\phi_{mas} = 0,3$, water phase 70% by mass HPMC water solution 2% by mass, $n = 266,6\ s^{-1}$, $t = 300$ s

Rys. 4. Krzywe płynięcia wraz z dopasowanymi modelami reologicznymi, emulsja pierwotna blank, faza tłuszczowa Miglyol 812N $\phi_{mas} = 0,3$, faza wodna 70% mas. 2% mas. wodny roztwór HPMC, $n = 266,6\ s^{-1}$, $t = 300$ s

Good correlation of experimental with calculation data from models available in literature was shown by the models of Widhab, Ostwald de Waele, Herschel-Bulkley, Casson, lowest correlation was obtained for the model of Bingham. Despite high correlation factors for some models, negative values for certain parameter models were obtained, which is contrary to physical possibility. Sample results of own research were presented in Fig. 4. Parameters of the individual models were presented in Table 2.

Table 2

Rheological models and their parameters for blank primary emulsion: fatty phase Miglyol 812N ϕ_{mas} = 0.3; water phase 70% by mass 2% by mass HPMC water solution, t = 300 s, n = 266.6 s^{-1}

Rheological model	Model parameters	R^2 correlation factor
Bingham	$\tau_0 = 25,83$ $\eta_p = 0,2128$	0,9826
Ostwald de Waele	$K = 1,697$ $n = 0,7056$	0,9820
Herschel-Bulkley	$\tau_0 = 16,37$ $K = 0,5697$ $n = 0,8580$	0,9836
Casson	$\tau_y = 8,552$ $\eta_p = 0,500$ $n = 0,1500$	0,9840

From the practical point of view, the most important rheological property of primary emulsions is their viscosity.

Obtaining low viscosity values for emulsions with high coagulation speeds stemmed from ordered grid structures. At high coagulation speeds de-aggregation of the grid begins, with ordering of the individual macromolecules aiming at coagulation (Fig. 5). Comparing the viscosity of primary emulsions at the same coagulation speeds it was shown that the lowest viscosity was found in primary emulsions containing a 2% by mass HPMC water solution as the water phase.

The conducted research shows that the viscosity of the primary emulsions is influenced by the content of the fatty phase (Fig. 6). The higher the content of the fatty phase, the higher its viscosity, whereby the value of the viscosity depended on the utilised fatty phase and thickening agent. This is caused by an increase of the number of drops of the fatty phase per volume unit of the primary emulsion. An increase of the drop count of the dispersed phase is accompanied by a decrease of the distances between the drops. As the force of interactions between the drops increases, collision processes become more frequent, which may consequently lead to the creation of agglomerates or floccules.

Similarly as for the flow curves, the obtained results of analyses of viscosity curves were processed via regression of analytical points using the equations shown in Table 1, using the proprietary software of the rheometer. Based on the obtained correlation factor values it was determined that in the examined range of concentrations and emulsification process parameters, the viscosity models describing blank primary emulsions containing as the water phase water hydrocolloid solutions and as the fatty phase Miglyol 812N or sunflower seed oil, castor or olive oil well, were: the Bingham model, the Ostwald de Waele model and the Herschel-Bulkley model.

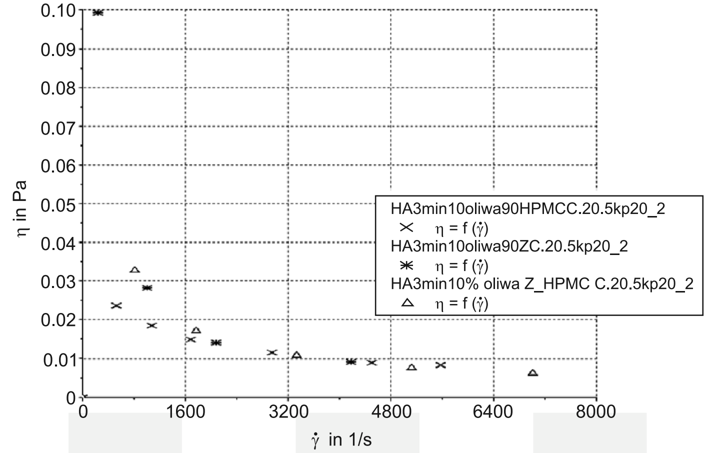

Fig. 5. Viscosity curves of primary blank emulsions, oil phase – olive oil $\phi_{mas} = 0.1$; water phase 90% by mass: Δ – 1.5% by mass Ż water solution Ż, 2% by mass HPMC water solution (mass ratio Ż/HPMC 4:1), *x* – 2% by mass HPMC water solution, ∗ – 1,5% by mass Ż water solution, *t* =180 s, *n* = 183.3 s^{-1}

Rys. 5. Przebieg krzywych lepkościowych emulsji pierwotnych blank, faza tłuszczowa olej oliwkowy $\phi_{mas} = 0,1$; faza wodna 90% mas.: Δ – 1,5% mas. wodny roztwór Ż, 2% mas. wodny roztwór HPMC (stosunek mas. Ż/HPMC 4:1), *x* – 2% mas. wodny roztwór HPMC, ∗ – 1,5% mas. wodny roztwór Ż, *t* =180 s, *n* = 183,3 s^{-1}

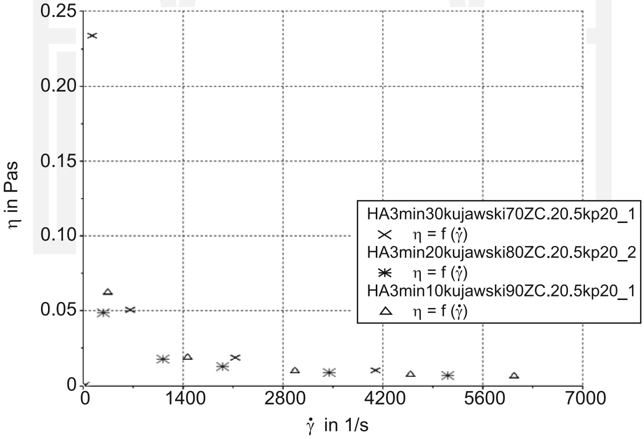

Fig. 6. Viscosity curves for primary blank emulsions, oil phase 'Kujawski' cooking oil: Δ – $\phi_{mas} = 0.1$; ∗ – $\phi_{mas} = 0.2$; *x*– $\phi_{mas} = 0.3$; water phase 1.5% by mass Ż water solution, *t* = 180 s, *n* = 183.3 s^{-1}

Rys. 6. Przebieg krzywych lepkościowych emulsji pierwotnych blank, faza tłuszczowa olej Kujawski: Δ – $\phi_{mas} = 0.1$; ∗ – $\phi_{mas} = 0.2$; *x*– $\phi_{mas} = 0.3$; faza wodna 1,5% mas. wodny roztwór Ż, *t* = 180 s, *n* = 183,3 s^{-1}

Sample examination results for viscosity curves, verified through viscosity models, were presented in Fig. 7 and Table 3.

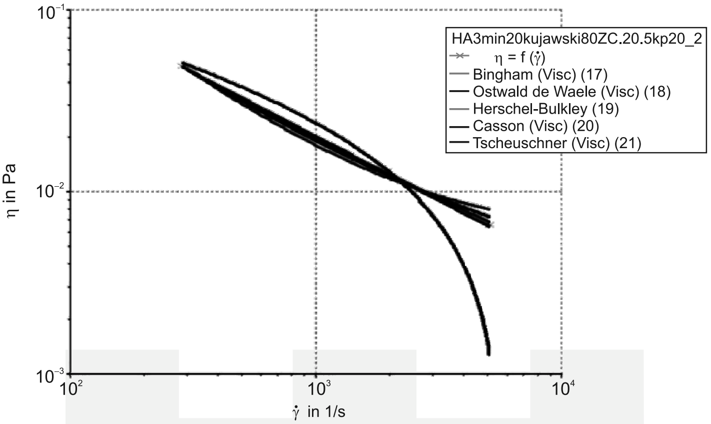

Fig. 7. Viscosity curve for primary blank emulsions with adapted viscosity models, water phase 90% by mass 1.5% *Ż* water solution, oil phase 'Kujawski' cooking oil $\phi_{mas} = 0.2$; $t = 180$ s, $n = 183{,}3$ s^{-1}

Rys. 7. Krzywa lepkościowa emulsji pierwotnej blank wraz z dopasowanymi modelami lepkościowymi. Faza wodna 90% mas. 1,5% wodny roztwór *Ż*, faza tłuszczowa olej Kujawski $\phi_{mas} = 0{,}2$; $t = 180$ s, $n = 183{,}3$ s^{-1}

Table 3

Parameters of viscosity models ($\eta = f(\dot{\gamma})$), blank primary emulsion water phase 90% by mass 1,5% *Ż* water solution, fatty phase 'Kujawski' cooking oil $\phi_{mas} = 0.2$; $t = 180$ s, $n = 183.3$ s^{-1}

Rheological viscosity model	Model parameters	R^2 Correlation factor
Bingham	$\tau_y / \dot{\gamma} = 0{,}005573$ $\eta_p = 12{,}50$	0,9979
Ostwald de Waele	$K = 2{,}619$ $n - 1 = 0{,}2959$	0,9997
Herschel-Bulkley	$\tau_y / \dot{\gamma} = 6{,}961$ $K = 0{,}4735$ $n - 1 = 0{,}4769$	0,9999
Casson	$\tau_y / \dot{\gamma} = 9{,}102$ $\eta_p = 0{,}500$ $n = 0{,}001852$	0,9996
Tscheuschner	$\eta_\infty = -0{,}03220$ $\tau_y / \dot{\gamma} = 0{,}04892$ $\eta_b = 0{,}5000$ $\dot{\gamma} / \dot{\gamma}_b = 1{,}000$ $n = 0{,}3169$	0,9750

4. Conclusions

Primary emulsions with potential pharmaceutical applications containing hydrocolloid water solutions as the water phase in the examined concentration range belonged to the non-Newtonian group of liquids shear thinning, showing a yield stress.

The execution of complete rheological research encompassing the determination of flow and viscosity curves for primary emulsions allows the determination of the most favourable formulations for these systems. Assuming their lowest possible viscosity as a criterion of quality for primary emulsions, the rheological analyses supply guidelines enabling the selection of a water phase, and the determination of the type and content of the oily phase to be used for this purpose.

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