

Rheological Properties Study of Oral Hydrogels Containing Phenobarbital for a Potential Pediatric Use

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Abstract: This present study is a continuation of our work entitled “pH-thermosensitive oral chitosan-based hydrogels containing phenobarbital for a potential pediatric use”. The results of that previous study have shown their potential use in newborns in particular premature newborns while the oral form containing phenobarbital is a tablet and is unsuitable for newborns. Thus, in order to have a suitable device for the administration of hydrogels oral formulations to newborns, we have done rheology studies to complement our work. For this we have studied the variation of the viscosity of hydrogels containing phenobarbital as a function of shear rate and time. Phenobarbital is an active drug used in neonatal treatment of epilepsy. The viscosity measurements of hydrogels are carried out using a Fungilab V'PAD Rotational Viscometer (100–240V/50–60Hz) Type 'R' series then ANOVA test was used to analysis the results. The results showed that the hydrogels had a non-Newtonian behavior with shear-thinning and thixotropic type which depends on the chitosan concentration, the storage temperature hydrogels, the presence of Eudragit E100 and the final solution's pH. Rheological properties study have shown that a syringe-type device would be suitable for oral administration of hydrogels formulations to neonates.

Keywords: Rheological Properties Study, Oral Hydrogels, Phenobarbital, Pediatric

1. Introduction

Epilepsy is the first pediatrics neurological disease [1-4] and is a real public health problem. Phenobarbital is widely used for his care in the world [1, 5]. In sub-Saharan Africa, the oral form containing phenobarbital is a tablet and is unsuitable for newborns [6]. However, the work of Djiboune A. R et al. [7], on a pH-thermosensitive oral chitosan-based hydrogels containing phenobarbital have shown their potential use in newborns, especially in premature newborns. In a goal to continue these work, we were interested in rheology in order to find a suitable device for their oral administration. The objective of rheology is

the study of the deformation of a material, including its flow, under the influence of the stresses applied to it [8, 9, and 10]. It is comparable to human mechanical digestion in a different pH values specific to the gastrointestinal tract (in the case of chewing food) [11] and to the deformation of semi-solid food (case of hydrogels) when they are administered by a suitable device. These processes allowed to modify the structure of the semi-solid food when a mechanical force is applied to it and facilitate their administration and transport from mouth to stomach without incurring risk because it became fluid [10, 11]. This latter form is generally suitable for premature newborns because sucking-swallowing coordination is not optimal and mechanical digestion

is also weak for this population. Indeed, the oral administration of semi-solid or solid food to the premature newborn can cause a transit of the food bolus in the trachea which can cause a blockage of the airways and which can lead to his death [12, 13]. To this end, the administration of a semi-solid food to these newborns requires the use of a device which makes it fluid. In this context, we decided to study the variation of the viscosity of these oral hydrogels (semi-solid food) as a function of the deformation (shear rate) and time. This study provides us more details about their storage, administration, transport, and the phenobarbital release from the hydrogels. The conclusion of this study would allow us to take a good orientations for a suitable device for a potential pediatric formulation.

2. Materials and Methods

2.1. Materials

Phenobarbital base, chitosan with low molecular weight and more than 75% deacetylation degree (DAD), sodium bicarbonate and 99.8% acetic acid, purchased from Sigma Aldrich laboratories and Eudragit E100, purchased from Evonik Röhm GmbH Pharma

Polymers (Darmstadt, Germany) were used. All these excipients were used in powder form except acetic acid which was used in liquid form. We had also used distilled water as solvent produced by a millipore system from Fisher Scientific Limited, Nepean ON, Canada. A water bath and a pH meter 781pH/ion meter (Metrohm) fitted with a temperature probe were used for the hydrogels preparation. For the rheological characterization, a cone-plate rheometer called Fungilab V'PAD Rotational Viscometer (100–240V/50–60Hz) Type 'R' series was used.

2.2. Methods

2.2.1. Preparations of Hydrogels

We prepared two batches of hydrogels: batch 1 and batch 2. The first batch had included the formulations F₁, F₂, F₃, and F₄ while the second included the formulations F'₁, F'₂, F'₃ and F'₄. The preparation protocol is detailed in the previous works of Djiboune A. R., and *al.*, (2020). Therefore, here we focus on the rheological method and before, all these formulations are kept cool (2–8°C) and between 20–23°C for 3 hours for rheological properties characterization. Their composition and final solution's pH are indicated in table 1.

Table 1. Formulations composition and final solution's pH.

Formulations Code	Chitosan (%)	Eudragit E100 (%)	Phenobarbital (mg/ml)	Sodium Bicarbonate (M)	Distilled water (g)	Final solution's pH
F ₁	2.45	-	0.0293	1.12	45	6.85
F' ₁	2.45	0.0245	0.0293	1.12	45	6.85
F ₂	2.55	-	0.0293	1.12	45	6.85
F' ₂	2.55	0.0255	0.0293	1.12	45	6.85
F ₃	2.45	-	0.0293	1.12	45	6.8
F' ₃	2.45	0.0245	0.0293	1.12	45	6.8
F ₄	2.55	-	0.0293	1.12	45	6.8
F' ₄	2.55	0.0255	0.0293	1.12	45	6.8

2.2.2. Rheological Properties Characterization of the Formulations

In this study, the rheological properties characterization was based on the viscosity measurements as function of shear rate and time. It was carried out using a Fungilab V'PAD Rotational Viscometer (100–240V/50–60Hz) Type 'R'. It consisted in immersing a steel rod of conical shape in rotation into the gel contained in a cylindrical steel cell with a flat base and measure the resistance (viscosity) of it during shearing. The rod is coupled to a mainspring which rotates at a prescribed speed. The angle of deflection, which is measured electronically, gives the measure of the torsional force. The calculations carried out in the viscometer from the measurements of the torsional force, the speed of the axis and the characteristics of the gels, allowed a direct reading of the viscosity (cP or mPa.s), of the shear rate (1 / s) and the corresponding time (s) on a touch screen android tablet separate from the rest of the device. For every sample of hydrogel, all measurements were performed in triplicate and the average apparent viscosity and shear rate were determined, with a standard deviation which were mentioned in tables 2 and 3. All the measurements were carried out at a temperature between 21 and 23°C and during four minutes. The gels which have been the subject of this measurement were previously kept in a cool place (2–8°C) and between 20 and 23°C for 3 hours.

2.2.3. Statistical Analysis

One way analysis of variance (ANOVA) with excel software had been used as a statistical analysis test to study the influence of variation of the chitosan concentration, the storage temperature hydrogels, the presence of Eudragit E100 and the final solution's pH on the viscosity of hydrogels.

3. Results

3.1. Preparation of Hydrogels

The aspect of the hydrogels formulated is presented in the following figure:

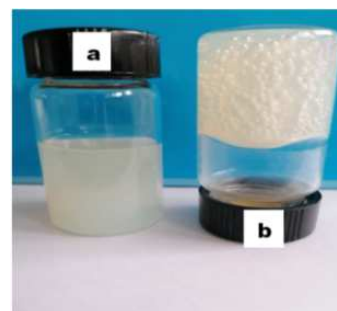


Figure 1. Sol (a)-gel (b) transition images.

3.2. Rheological Properties Characterization of the Formulations

The data of viscosity measurements of hydrogels are mentioned in tables 2 and 3.

Table 2. Viscosity and shear rate data of the formulations keeping between 2 and 8°C.

Formulations code									
F ₁	Viscosity (mPa.s)	601.3	486.633	414.883	383.033	373.833	368.167	350.7	321.067
	SD (mPa.s)	73.044	85.294	53.625	33.497	43.302	22.481	20.281	26.9
	Shear rate (1/s)	18.3	32.253	45.81	59.273	73.947	85.993	99.52	112.4
	SD (1/s)	0.000	0.006	0.017	0.236	0.181	0.021	0.03	0.000
F ₁	Viscosity (mPa.s)	2497.657	1818.57	1489.681	1184.38	1067.573	916.761	889.897	817.102
	SD (mPa.s)	12.78	20.467	19.341	15.92	11.872	13.897	8.567	14.5
	Shear rate (1/s)	11.73	22.874	34.037	45.167	55.187	65.476	75.835	87.287
	SD (1/s)	0.138	0.014	0.027	0.012	0.007	0.035	0.025	0.006
F ₂	Viscosity (mPa.s)	5274.633	3810.467	3029.367	2435.033	2084.133	1941.5	1717.333	1554.533
	SD (mPa.s)	47.987	97.978	24.457	37.9	34.97	16.981	35.765	21.756
	Shear rate (1/s)	9.12	18.127	26.887	35.757	44.59	53.33	62.16	70.477
	SD (1/s)	0.162	0.124	0.169	0.107	0.000	0.033	0.047	0.004
F ₂	Viscosity (mPa.s)	6655.833	4486.583	3696.7	3132.233	2698.867	2348.467	2143.333	2067.867
	SD (mPa.s)	1485.387	702.631	646.873	571.089	366.287	283.613	214.947	156.658
	Shear rate (1/s)	5.68	10.113	14.443	18.863	23.15	27.447	31.8	35.9
	SD (1/s)	0.000	0.081	0.118	0.092	0.000	0.006	0.01	0.000
F ₃	Viscosity (mPa.s)	1528.467	1106.733	949.0667	894.567	866.667	837.233	826.5	784.767
	SD (mPa.s)	282.623	211.840	177.439	155.734	177.684	152.235	165.717	115.439
	Shear rate (1/s)	11.843	22.327	32.647	42.747	53.32	63.82	74.243	84.1
	SD (1/s)	0.442	0.4	0.431	0.395	0.428	0.419	0.419	0.369
F ₃	Viscosity (mPa.s)	3372.767	2557.967	2165.8	1962.3	1870.733	1703.567	1587.533	1544.833
	SD (mPa.s)	219.055	33.217	110.075	658.069	52.036	29.023	56.214	58.953
	Shear rate (1/s)	7.13	13.237	19.26	25.313	31.233	37.303	43.023	49.04
	SD (1/s)	0.122	0.574	0.905	0.103	0.132	0.155	0.209	0.194
F ₄	Viscosity (mPa.s)	6582.367	5096.283	4634.733	3794.633	3391.033	3257.067	3192.167	3074.867
	SD (mPa.s)	1310.570	850.179	154.65	210.856	125.607	76.842	76.87	38.368
	Shear rate (1/s)	6.58	11.29	16.07	20.8	25.59	30.283	34.697	39.48
	SD (1/s)	0.121	0.069	0.087	0.07	0.060	0.006	0.368	0.000
F ₄	Viscosity (mPa.s)	11383.333	7530	5691.7	4620.4	4093.5	3606.567	3215.333	3083.2
	SD (mPa.s)	1204.47	733.28	644.795	612.777	369.328	239.887	304.982	25.159
	Shear rate (1/s)	5.19	9.94	14.68	19.337	24.086	28.86	33.61	38.06
	SD (1/s)	0.000	0.00	0.000	0.006	0.006	0.01	0.01	0.000

Table 3. Viscosity and shear rate data of the formulations keeping between 20 and 23°C.

Formulations code									
F ₁	Viscosity (mPa.s)	801.85	553.867	447.833	387.4	341.8	311.133	289.6	270.433
	SD (mPa.s)	24.747	17.029	3.024	8.022	7.938	7.407	7.594	8.568
	Shear rate (1/s)	23.463	40.504	56.963	73.983	90.923	107.5	124.433	140.5
	SD (1/s)	0.444	0.503	0.326	0.015	0.228	0.346	0.462	0
F ₁	Viscosity (mPa.s)	2137.675	1757.897	1471.947	1168.579	1078.645	897.876	861.978	797.937
	SD (mPa.s)	14.78	23.467	19.897	12.972	17.378	15.633	10.999	14.5
	Shear rate (1/s)	11.782	23.074	34.187	45.456	55.457	65.987	76.057	87.789
	SD (1/s)	0.138	0.014	0.006	0.032	0.007	0.061	0.006	0.000
F ₂	Viscosity (mPa.s)	3274.467	2345.033	1970.6	1770.6	1652.767	1571.2	1463.3	1386.1
	SD (mPa.s)	57.444	84.222	32.456	37.067	11.844	15.87	23.133	14.067
	Shear rate (1/s)	8.696	15.703	22.093	28.637	35.222	41.867	48.347	54.77
	SD (1/s)	0.115	0.444	0.004	0.009	0.015	0.004	0.102	0.000
F ₂	Viscosity (mPa.s)	4733.4	3392.3	2664.367	2269.233	2015.867	1990.7	1779.833	1675.566
	SD (mPa.s)	125.266	316.743	184.635	158.726	190.789	160.827	91.914	101.144
	Shear rate (1/s)	10.13	18.933	27.567	36.28	44.997	53.683	62.303	70.393
	SD (1/s)	0.173	0.006	0.174	0.147	0.111	0.138	0.206	0.006
F ₃	Viscosity (mPa.s)	2052.3	1620.633	1263.5	1084.8	938.5	877.567	827.867	769.4
	SD (mPa.s)	150.429	134.86	105.935	75.211	24.094	12.482	19.519	9.027
	Shear rate (1/s)	11.31	20.737	30.147	40.28	50.493	59.937	69.79	80.413
	SD (1/s)	0.188	0.25	0.398	0.449	0.388	0.506	0.599	0.562
F ₃	Viscosity (mPa.s)	2775.8	1876.533	1545.567	1270.7	1116.967	973.5	908.7	855.933
	SD (mPa.s)	339.929	157.875	100.014	60.659	25.540	19.6879	16.337	29.67
	Shear rate (1/s)	11.58	22.393	33.05	43.743	54.324	64.857	75.373	85.577
	SD (1/s)	0.034	0.0058	0.01	0.037	0.012	0.179	0.136	0.012

Formulations code									
F ₄	Viscosity (mPa.s)	3840.9	2962.1	2357.883	2161.767	1945.5	1681.267	1587.4	1485.333
	SD (mPa.s)	252.948	44.947	107.487	48.851	29.065	15.142	89.485	94.437
	Shear rate (1/s)	12.293	20.563	29.07	37.437	45.777	54.13	62.573	70.433
	SD (1/s)	0.219	0.274	0.191	0.219	0.006	0.01	0.011	0.006
F ₇	Viscosity (mPa.s)	8666.667	6225	5158.167	4406.4	3818.233	3425.733	3098.7	2917.3
	SD (mPa.s)	350.148	176.547	330.072	250.299	80.572	97.707	37.596	135.84
	Shear rate (1/s)	5.66	11.117	16.273	21.6	26.86	31.653	37.37	42.257
	SD (1/s)	0.156	0.075	0.101	0.078	0.01	0.808	0.03	0.025

Moreover, the viscosity as function of shear rate and time is presented in figures 2 to 17.

These figures show the influence of the chitosan concentration, the storage temperature hydrogels, the presence of Eudragit E100 and the final solution's pH on the viscosity's of hydrogels.

3.2.1. Influence of the Chitosan Concentration

For all the formulations, we noticed that the viscosity increased with the chitosan concentration. It varied from 601.3 to 3372.767 mPa.s for 2.45% of chitosan and to 11383.333mPa.s for 2.55% of chitosan. These results are shown in the figures 2 to 5.

3.2.2. Influence of the Storage Temperature Hydrogels

In this part, we noticed that the viscosity increased when the hydrogel storage temperature decrease except the formulation F₁. It varied from 601.3 to 11383.333mPa.s for the hydrogels stored between 2 and 8°C and from 801.85 to 8666.667mPa.s for those stored between 20 and 23°C. These results are shown in the figures 6 to 9.

3.2.3. Influence of the Presence of Eudragit E100

For all the formulations, we noticed that the viscosity increased when they are the presence of Eudragit E100 in the hydrogels. It was from 601.3 to 6582.367mPa.s for the hydrogels without Eudragit E100 and from 2137.675 to 11383.333mPa.s for those with Eudragit E100. These results are shown in the figures 10 to 13.

3.2.4. Influence of the Final Solution's pH

In this part, also for all formulations, we noticed that the viscosity increased when the final solution's pH decrease. It varied from 601.3 to 6655.833mPa.s for the final solution's pH equal to pH6.85 and from 1528.467 to 11383.333mPa.s for the final solution's pH equal to pH6.8. These results are shown in the figures 14 to 17. On the other hand, the viscosity decreased when the shear rate and time increased. These results are presented in the figures 2 to 17.

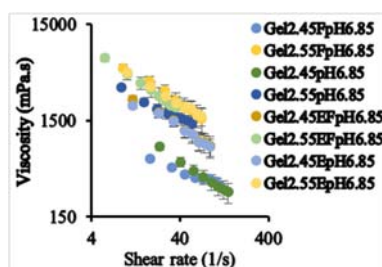


Figure 2. Viscosity as a function of shear rate for all formulations: influence chitosan concentration at pH6.85.

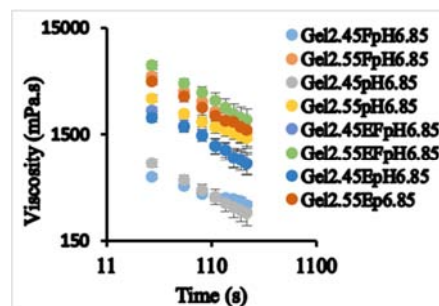


Figure 3. Viscosity as a function of time for all formulations: influence chitosan concentration at pH6.85.

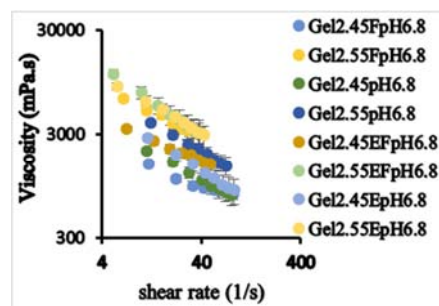


Figure 4. Viscosity as a function of shear rate for all formulations: influence chitosan concentration at pH6.8.

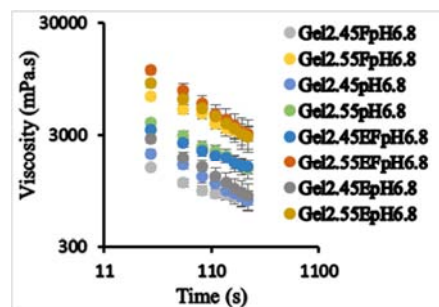


Figure 5. Viscosity as a function of time for all formulations: influence chitosan concentration at pH6.8.

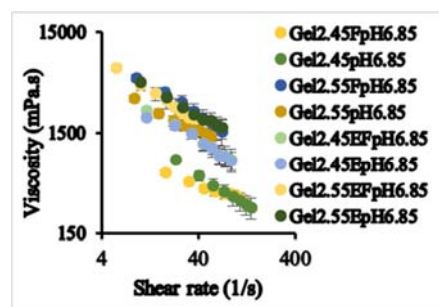


Figure 6. Viscosity as a function of shear rate for all formulations: influence the hydrogels' storage temperature at pH6.85.

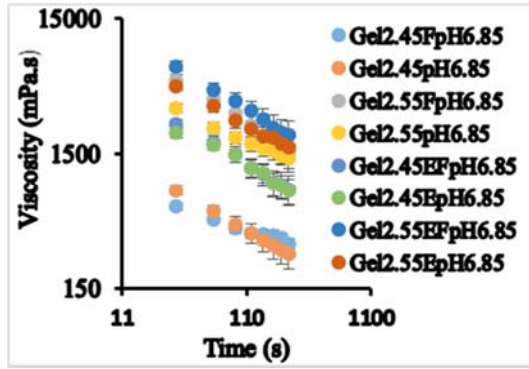


Figure 7. Viscosity as a function of time for all formulations: influence the hydrogels storage temperature at pH6.85.

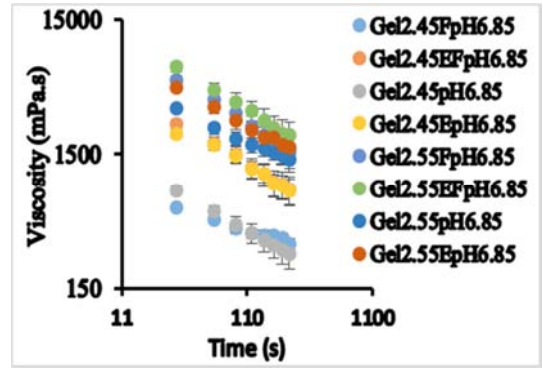


Figure 11. Viscosity as a function of time for all formulations: influence the presence of EudragitE100 at pH6.85.

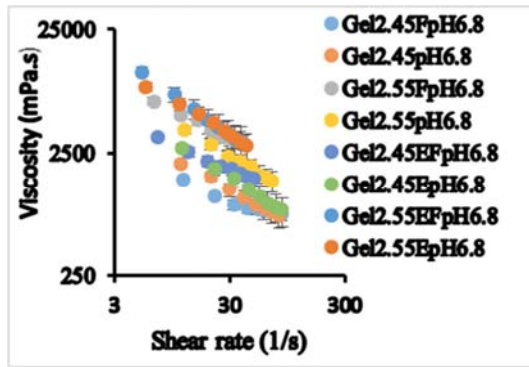


Figure 8. Viscosity as function of shear for all formulations: influence the hydrogels' storage temperature at pH6.8.

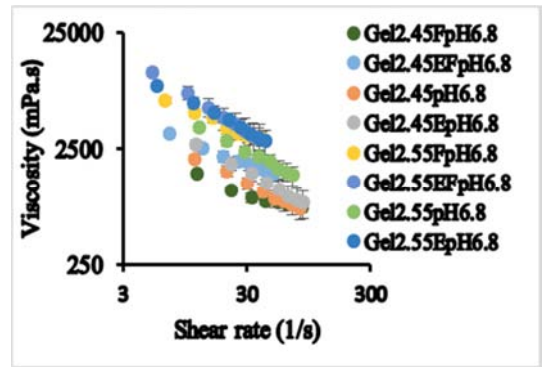


Figure 12. Viscosity as a function of shear rate for all formulations: influence the presence of EudragitE100 at pH6.8.

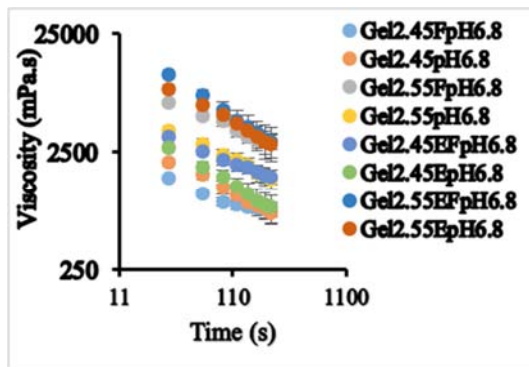


Figure 9. Viscosity as a function of time for all formulations: influence the hydrogels' storage temperature at pH6.8.

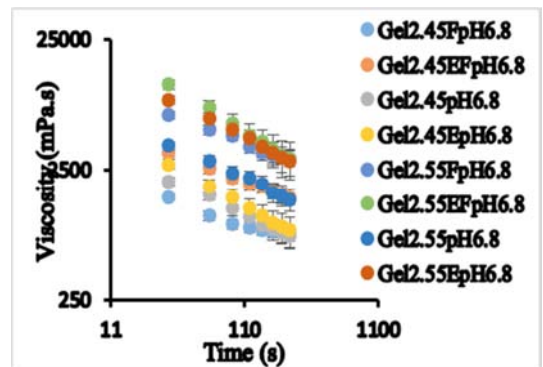


Figure 13. Viscosity as a function of time for all formulations: influence the presence of EudragitE100 at pH6.8.

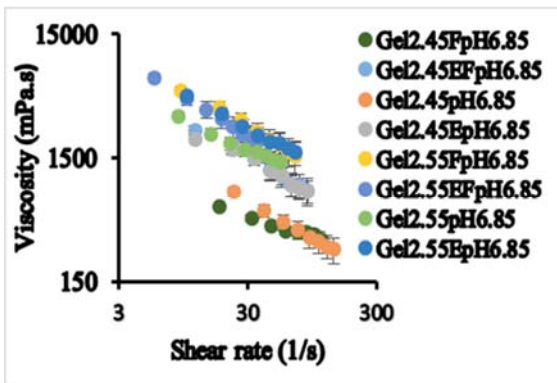


Figure 10. Viscosity as a function of shear rate for all formulations: influence the presence of EudragitE100 at pH6.85.

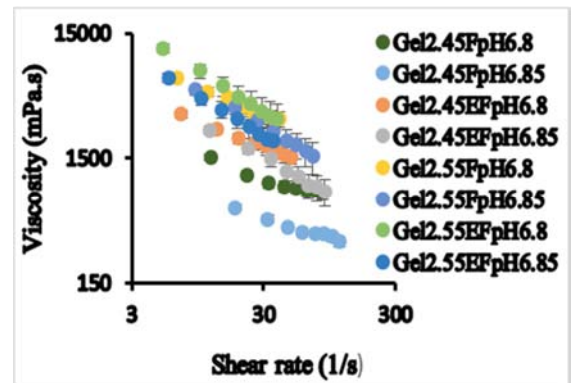


Figure 14. Viscosity as a function of shear rate for all formulations: influence the pH for hydrogels keeping between 2 and 8°C.

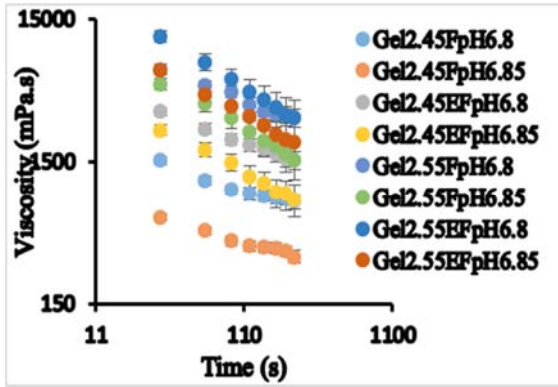


Figure 15. Viscosity as a function of time for all formulations: influence the pH for hydrogels keeping between 2 and 8°C.

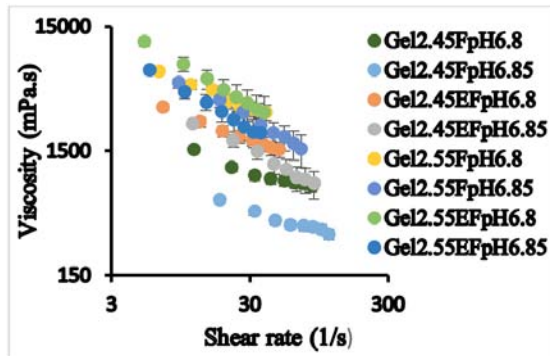


Figure 16. Viscosity as a function of shear rate for all formulations: influence the pH for hydrogels keeping between 20 and 23°C.

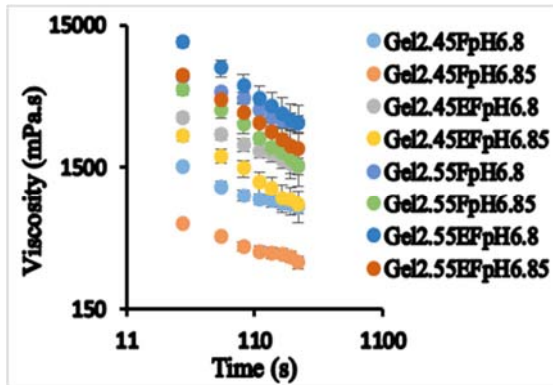


Figure 17. Viscosity as a function of time for all formulations: influence the pH for hydrogels keeping between 20 and 23°C.

4. Discussion

4.1. Preparation of Hydrogels

The passage from solution to hydrogel is linked to the formation of new reticulations networks following the activation of the interactions of coulombs, hydrophobes, Van der Waals and the hydrogen bonds in mixtures with a dominant hydrophobic interactions effect [7].

4.2. Rheological Properties Characterization of the Formulations

For rheological properties characterization, the choice of

viscosity measurements is guided by the fact that this is the physical quantity most used to describe the behavior of a fluid but also it measures the intrinsic property of the material [9] and therefore it alone is sufficient to this characterization [14]. The viscosity measurements was carried out using a cone-plane rheometer because compared to the others geometries of rheometers, this one gives the true values of viscosity [15]. The main of the study was to analyse the variation of the viscosity of oral hydrogels as function of the shear rate and time. In fact, we analysed the influence of the following parameters on this variation.

4.2.1. Influence of the Chitosan Concentration

The influence of chitosan concentration was significant (P -value<0.05) for the viscosity's of hydrogels. The latter increased with the chitosan concentration. It was from 601.3 to 3372.8767mPa.s for 2.45% of chitosan and to 11383,333mPa.s for 2.55% of chitosan. This result can be attributed to the surplus of interactions bonds in the hydrogels containing 2.55% of chitosan. In addition, this result was similar to that of Lee and Rha (1979) which reported that the effect of concentration on the increase in viscosity is due to the coming together of molecules which promote interactions between them [16, 17] This results confirms also the increase of conductivities values of hydrogels containing 2.55% of chitosan compared to those containing 2.45% of chitosan (Djiboune A. R and *al.*, 2020) [7]. Moreover, the viscosity of chitosan-based hydrogels increase with to the chitosan concentration because the crosslinking density increases with the amount of polymer [18, 19].

4.2.2. Influence of the Storage Temperature Hydrogels

Regarding to the hydrogels storage temperature, we noted that the viscosity of the hydrogels increased when the temperature decreased. This result can be explained by the fact that there is formation of new hydrogen bonds which are due to the decrease of the order of the water structure, the negative entropy excess and the increase of a large positive free energy after gelation governed by hydrophobic interactions [20, 21]. According the Andrade Equation, the logarithm of the viscosity increases linearly as a function of the inverse of the absolute temperature:

$$\text{Log}\eta = B + \frac{E_e}{R * T}$$

Where η is the viscosity (mPa.s), B is a constant, E_e is apparent flow activation energy (J.mol^{-1}); R is perfect gas constant ($8.3143 \text{ J.mol}^{-1} * \text{K}^{-1}$) and T absolute temperature (K) [16]. This result is also similar to those reported by Ruihong Wang and *al.*, which found that viscosity increased significantly when the egg yolks frozen for the designed amount of time (1, 2, 3, 4, 5 and 6) [22]. However, we noticed that the viscosity decreased when the storage temperature hydrogel decrease for F_1 . This result could be attributed to the fact that the promoting of the attraction interaction was weak and the water contained in the hydrogel

could create a network hydrolysis phenomenon because probably F_1 contained a small number of groups.

4.2.3. Influence of the Presence of Eudragit E100

The presence of Eudragit E100 had influenced the viscosity of hydrogels. Therefore, the viscosity of hydrogels containing Eudragit E100 was higher than that of hydrogels without Eudragit E100. This result could reflect the existence of additional bonds within the hydrogel. And it confirms also the study reported by Djiboune et al., (2020) that stunned gelification phenomenon would take place in seconds during the sol-gel transition [7].

4.2.4. Influence of the Final Solution's pH

For the final solution's pH, we found that the viscosity of the hydrogels increased when the pH decreased. This result is attributed to a surplus interactions when the pH decreases. This result confirms the study reported by Djiboune et al., (2020) that stunned conductivity increased when pH decreased [7]. This result can be also explained by the fact that the major interactions (hydrophobic interactions, hydrogen bonds and ionic interactions) increase when the pH decrease [21].

On the other hand, the major interactions responsables to formation of the physical hydrogels are hydrophobic interactions and hydrogen bonds reflecting their strength, their density and their viscosity [23, 24]. In this study, we noticed that the viscosity of the hydrogels decreased as the shear rate and time increased for all formulations under applied a shear stress. It reflects the characteristics of a non-Newtonian behavior [25] with the shear thinning and thixotropic type [15, 23]. This result is linked to the dissociated reticulation networks formed into the hydrogels due to their chains relaxation depending of time [24] but also to the reorientation of particulate entities in the direction of flow and under the effect of shear and hydrodynamic forces [9, 26]. This result is similar to those reported by Minna H Chen, and al., (2019) which states that the shear thinning hydrogels experience decreases in viscosity upon application of shear stress, which are enabled by reversible cross-linking mechanisms. The flow of hydrogels is due to the displacement or changes of structure units of reversible reticulation networks which make hydrogel to become a fluid (sol) when a critical shear rate is exceeded (pseudo-elastic behavior materials) [27, 28]. The destroy of polymeric network can be partial or complete depending the force of the strain applied to them and the time [18, 29]. In addition, the acid hydrogels had formed by the weak interactions energy (hydrophobic interactions and hydrogen bonds) which make their reticulations networks more sensitive to the shear inherent in viscosity measurement. This fact may also explain the flow of hydrogels when a stress is applied to them [7]. In this fact, the bonds formed hydrogels are easily broken upon with a weak application force [24]. But, when shear is remove, their networks reassemble into hydrogels [15] because it are considered as a pseudo-elastic materials and self assembly is the main route for cross-linking for shear-thinning hydrogels; [11, 15, and 24]. Moreover, the modulus, the shear-thinning/self-healing

kinetics and thixotropic are important parameters that determine the suitability of the system for biomedical applications [15, 24]. In addition, the thixotropic behavior of hydrogels is linked to the fact that structural breakdown of hydrogels become superior than it buildup and it the increases over time when one shear stress is applied [30].

5. Conclusion

According these results of the study, these formulations could be orally administered to the newborns with a syringe-type device and without a blockage of their airways. From then on, it would be one additional pediatric form containing phenobarbital. However, this possibility and the facilitation depend on viscosity hydrogels which depend also on chitosan concentration, the hydrogels storage temperature and the final solution's pH. The limitation of this study was the lack of a precise information about the shear-thinning kinetics. For the next step, we will study the modulus parameters (G' and G''), the shear-thinning kinetics, the stability and the cytotoxicity of hydrogels.

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