

Rheological Characterization of Different Gelling Polymers for Dental Gel Formulation

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Abstract:

Objective: This study is aimed to select the best gelling agents as candidates to be developed into dental gels, based on their rheological profiles.

Significance: This study opens up more options for dental gel formulator to choose regarding the range of good gelling polymers, as the vehicle for their pharmaceutical active ingredients.

Methods: 11 types of gelling agents, which consist of 1%, 3%, and 5% w/w concentration for each gel, were prepared. The rheological profiles were measured using rheometers, and the data was analyzed to calculate their apparent viscosities, rheological modelling, and the linear viscoelastic range profiles.

Results: It was found that 3%, 5% carbopol 940, 5% guar gum, 5% ι-carrageenan 3% kelcogel F, 1%, 3%, and 5% w/w konjac gum are the best candidates to be developed into dental gels based on their rheological properties. They exhibit good viscoelastic properties, acceptable viscosity profiles at three different shear rates of 10 s⁻¹, 50 s⁻¹, and 100 s⁻¹ Pas, having high consistency factor (*K*), best flow behaviour (*n*) value, high *G'* value, *G'*=*G''* value, and the crossing point of *G'* and *G''* happens at further shear stress range compared to other gels.

Conclusion: All the rheological profiles for each of the gels at 3 different concentrations were successfully characterized, analyzed and documented.

Keywords: gels, rheology, viscosity, shear stress, linear viscoelasticity range, gelling polymers

INTRODUCTION

Rheology plays an important part in determining the flow behaviour of the dosage forms. There is specific range of rheology for specific applications. For instance, an oral jelly for geriatrics needs an extent of viscosity, and specific range of flowability in order for the dosage form to be accepted well by patients. In contrast, a topical cream had to be more viscous in order for the drug to maintain at the skin surface for longer time. This is important for the permeation of the active compound from the dosage forms into the skin layers. Otherwise it will be a waste should the topical application only last for a few minutes and easily wiped away by physical movement. Topical application is well known for its poor permeability and slow penetration into the skin [1]. Therefore the rheology profile of the topical dosage form is important to maximize the contact period between the medication and the skin. This can be accomplished by modifying the nature of the vehicle [2].

Topical semi-solid dosage forms include creams, gels, ointments and pastes. Local dental formulations are currently designed with the drugs incorporated in the vehicle and available in various forms such as chips, ointments, fibers, and gels. An effective topical dosage form should enable the drug to remain at the targeted site of action for an adequate time at an effective concentration [3]. Advantages of local drug delivery in the context of

dental treatment includes that drugs can reach the specific sites in adequate amount, improve patient compliance, and improve pharmacokinetics [4]. An ideal dental dosage form should be sufficiently mobile to ease the delivery of the dosage form to the tooth socket. At the same time, it should be adequately viscous in order to remain at the application site [5].

Current topical or dental gels are developed based on the most common gelling agents that are expected to be suitable as polymers for gels. However, there is lack of comparison for candidate gelling polymers especially in term of rheological properties. A few studies characterized individual gelling agents and successfully described their rheological profiles such as gelling agent of keratin hydrogel [6], bleached shellac [7] and gelatins [8]. The objective of this study is to screen the rheological properties of various gelling agents in order to identify their possibility to be developed into vehicles for dental gel formulation.

MATERIALS AND METHODS

Materials

The following gelling polymers were used in this study: carbopol 940 from Acros Organics (Geel, Belgium). fish gelatin 250 bloom, guar gum, ι-carrageenan, κ-carrageenan, low acyl gellan gum (kelcogel F), konjac gum, E grade hydroxypropyl methylcellulose with medium

viscosity of 4000 cP (methocel E4M), F grade hydroxypropyl methylcellulose with low viscosity of 50 cP (methocel F50), A grade supergelling methylcellulose with medium viscosity of 700 cP (methocel SGASGA7C) and high viscosity methylcellulose (methylcellulose HV), all from Modernist Pantry (Massachusetts, United States). Propylene glycol, methyl paraben, propyl paraben and triethanolamine were from Sigma Aldrich (Missouri, United States).

Gel preparation

Hydrogels at concentrations of 1%, 3% and 5% w/w were prepared for each gelling agent. For 100 g gel, 3% w/w (3 g) of the gelling agent, 0.1% w/w (0.1 g) of methyl paraben, 0.03% w/w (0.03 g) of propyl paraben (as preservatives) and 5% w/w (5g) of propylene glycol as a solubilizer [9] were added then sufficient quantity of water to 100 g. For carbopol gel, triethanolamine was added to neutralize the carbopol 940 to pH 6.8 [10]. The gel polymer powder was slowly dispersed into 6 mL deionized water and vigorously stirred using mechanical overhead stirrer (Ika Labor Technik, RW20n, Germany) with 1000 rpm for 60 min until the hydrogel become homogenous. The solubilizer and preservatives were then added. For the carbopol gel, the mechanical stirrer was stopped at 30 min and 9.6 g of triethanolamine was added drop wisely into the gel mixture to neutralize the pH and the mechanical stirrer was continued until 60 min. All gels appeared homogenous after 60 min preparation period. All the gels were left for 24 h at room temperature before further rheological tests were conducted [11].

Measurement of gel rheology

Rheology measurement was made using Haake MARS Rheometer (Thermo Scientific, Massachusetts, United States). Data analysis was made using Haake Rheo-Win 3.61.0000 software. The spindle specification was parallel plate (PP35 Ti) with diameter of 35 mm. The temperature of the gel was set constant at $25 \pm 0.05^\circ \text{C}$ [12]. The flow behavior was measured using the up and down rotational controlled (CR) ramp test. The shear rate is ranging from 0.01 to 100 s^{-1} with the frequency of 1 Hz [13]. Flow curves were measured as up and down loop where initially the spindle was rotated at rate of 0.01 s^{-1} to 100 s^{-1} in 120 seconds at 25°C , followed by constant shear rate at 100 s^{-1} for 30 seconds at 25°C . Lastly, the spindle rotation was slowed down within the rate of 100 s^{-1} to 0.01 s^{-1} in 120 seconds at the same temperature. The graphs were then presented as shear stress (τ) and apparent viscosity (η) to the function of shear rate ($\dot{\gamma}$) [14].

Data of upward curve was used for rheological modelling which is either Ostwald-de-Waele or Herschel Bulkley. Ostwald-de-Waele was chosen in the case where the gel had no yield stress τ_0 . Should there is yield stress, Herschel Bulkley was used since the equation of both models had the difference at the point of yield stress τ_0 . Herschel Bulkley (eqn. 1) is a generalized model of non-Newtonian fluid, which comprises the relationship of 3 parameters: consistency factor K , flow index n , and the yield stress τ_0 . Whereas, the Ostwald-de-Waele (eqn. 2), which is also

known as power-law fluid, is a generalized Newtonian fluid. The gels were also characterized for the stress sweep test to find the linear viscosity range (LVR) of the gels. In this case, all gels were measured at shear stress of 0.01τ until 100τ . The equation is described as below:

$$\tau = \tau_0 + K(\dot{\gamma})^n \quad (\text{eqn. 1})$$

where τ is shear stress Pa, τ_0 is yield stress (mpa), K is consistency factor, $\dot{\gamma}$ is shear rate s^{-1} , and n is flowability index [15].

$$\tau = K(\dot{\gamma})^n \quad (\text{eqn. 2})$$

where τ is shear stress, K is consistency factor (Pas^n), $\dot{\gamma}$ is shear rate, and n is flow behavior index [14].

Statistical Analysis

The data were obtained in triplicate and analyzed with the application of one-way analysis of variance followed by Tukey's test of multiple comparisons. The significance of the differences between mean values was determined based on p value, where p value ≤ 0.05 is considered statistically significant.

RESULTS AND DISCUSSIONS

Intended behavior of gels for dental applications is pseudoplastic (non-Newtonian), in which the apparent viscosity decreases with increased shear rate. This is needed for easy application from the tube or syringe to the intended site. At the same time, the gel should be viscous enough in order to stay at the applied location (such as extracted tooth socket). The shear rate in the dental gel filled in a tube can be understood as the variation between the velocity and the diameter of the tube [16]. In this study, different types of gelling polymers were tested. The selection included synthetic polymers such as carbopol 940, plant base carrageenan such as iota carrageenan, and animal base such as fish gelatin 250 bloom. Commercial gelatin's strength typically classified according to bloom value, and gelatin of bloom value 250-260 are the best choice [17]. The viscosity was measured at different shear rate points so that the viscosity changes can be investigated with different shear rate applied. It was found that all the gels experienced decrease in viscosity with increasing shear rate (Table 1). The initial viscosity (considered as viscosity at shear rate of 10 s^{-1}) increased with increase of concentration of each gelling agent. However, the differences of the viscosity of each gel varied ($p < 0.05$) at concentrations of 1%, 3%, and 5%. For example, at shear rate of 10 s^{-1} , kelcogel F had viscosity of $0.942 \pm 0.124 \text{ Pas}$ at 1%, $20.109 \pm 1.022 \text{ Pa}$ at 3%, and 42.503 ± 0.871 at 5% ($p < 0.05$). The changes of the viscosity is obvious between them compared to methocel SGA 7c, methocel F50, and fish gelatin 250 bloom which the viscosity difference is not as big as kelcogel F. Gels with high viscosity at all three points of shear rates are good candidates to be selected as dental gel's gelling agents. Examples of good candidates include carbopol 940, guar gum, ι-carrageenan, κ-carrageenan, kelcogel F, and konjac gum.

All the 11 gelling agents can be modelled with either Ostwald de-Waele or Herschel Bulkley (Table 1). Gels with yield stress τ_0 were modelled with Herschel Bulkley model, while those with no yield stress were modelled

according to Ostwald-de-Waele equation. It was found that 3% and 5% carbopol 940, 1% fish gelatin, 1% guar gum, 1% and 5% ι-carrageenan, 1% and 5% κ-carrageenan, 1% and 5% kelcogel F, 1% konjac gum, and 3% methocel E4M had no yield stress (denoted by the negative value of τ_0) and exhibited Ostwald de-Waele behavior. Whereas the rest of the gels had yield stress (denoted by the positive τ_0 values) thus exhibited the behavior of Herschel Bulkley model. In a previous study, 0.5% guar gum emulsions had viscosity of 2.46 Pas at shear rate of 10 s^{-1} [18]. In this study, the nearest concentration that can be taken as comparison is 1% guar gum, which had the viscosity value of $2.230 \pm 0.104 \text{ Pas}$ at shear rate of 10 s^{-1} with yield stress of $7.82 \pm 0.07 \text{ Pa}$. However, the modelling that fits this gel in the previous study was Ostwald De-Waele instead of Herschel Bulkley (having yield stress). The difference in this characterization was believed to be caused by different concentration of the preparation, and the one that was investigated by in the previous study was an emulsions incorporated with guar gum.

Flow behavior index (n) illustrates the type of fluid, in which if $n < 1$ the fluid exhibits pseudoplastic behavior. If $n = 1$, the fluid is Newtonian and if $n > 1$, the fluid is dilatant [13, 17, 19]. It was found that all the gels exhibited pseudoplastic non-Newtonian behavior due to the value of $n < 1$ (Table 1), but the extent of n value was the one that differentiated their degree of pseudoplasticity. Comparing all the gels in term of consistency factor (K), it was found that the higher the K value, the better the gel consistency with lower n value. Gels having high K value includes 1%, 3% and 5% carbopol 940, 3% and, 5% fish gelatin, 1%, 3% and 5% guar gum, 3% and 5% ι-carrageenan, 1%, 3% and 5% κ-Carrageenan, 3% and 5% kelcogel F, 1%, 3% and 5% konjac gum, 3% and 5% methocel E4M, and 3% and 5% methyl cellulose HV (identified as $K > 5 \text{ Pas}^n$). According to study done by Di Giuseppe et al., 2015 regarding the trend of K value for different types of carbopol, it was found that the higher the value of consistency factor (K), the lower the value of flow behaviour index (n) [20], which complies with the results of this study. Di Giuseppe et al., 2015 also found that all types of carbopol gels (ETD 2050, ETD2623, U10, U21, EZ2, EZ3) exhibited yield stress value in all the concentrations tested (0.1% w/w, 0.5% w/w, and 1.0% w/w). This supports the findings of this research which showed that carbopol 940 of concentration 1% exhibited yield stress value. However, the exact value varies between different grades of carbopol in both studies due to different physicochemical properties of the different carbopol grades. On the other hand, this study had found that carbopol changes its modelling properties from Herschel Bulkley to Ostwald De-Waele at the concentration of 3%. This is an additional finding because the study done by Giuseppe *et al*, did not test the gel concentration of more than 1% w/w.

The value of consistency factor (K) and flow behavior index (n) varied in each individual gel depending on the gelling agent concentration. For example, carbopol 3% had higher K value compared to 5% strength. However, the

flow behavior index (the pseudoplastic properties) of carbopol 5% was higher than 3%. This means the 5% carbopol had more shear thinning properties compared to 3% carbopol. This was proven with the apparent viscosity at shear rate of 100 s^{-1} of 5% carbopol value of 4.289 Pas, compared to 6.518 Pas for 3% concentration. Regarding the flow behavior, carbopol gel differs in term of their fit towards the two different models. Carbopol 1% fitted to Herschel Bulkley model, whereas the 3% and 5% fitted to Ostwald de-Waele model. The high value of R illustrates that the curve fits well to the equation for each of them. According to a study by Phaeacamud et al., 2016, consistency factor and flow behavior index were measured for bleached shellac gelling agents incorporated with 3 different types of active ingredients (doxycycline, metronidazole, and benzoyl peroxide), and the lowest concentration of gels compared was 15%. Based on trends, it was found that the lowest consistency index (K) at 25° C belongs to 15% shellac + doxycycline with the value of 17.80 Pas^n and the highest belongs to 25% shellac + metronidazole with values of 224.57 Pas^n . Comparing the results from both studies, it can be understood that the consistency factor of 15% shellac + doxycycline is about the same value with 1% plane guar gum that had the consistency factor value of 19.7 Pa.s^n . However, the plane carbopol investigated in this study and shellac gel incorporated with active ingredients were not comparable since the lowest concentration of carbopol in this study (which is 5%) had higher consistency factor value than the lowest concentration of shellac gel (15% w/w) [7]

One previous study regarding the rheology of 1% w/w guar gum had the same findings as this study where it exhibited Ostwald-de-Waele modelling and the absence of yield stress [21]. However, the values of consistency factor (K) and flow behavior index (n) were not exactly as expected. This might be caused by different composition of excipients used in this study where propylene glycol had been added as solubilizer as well as methyl and propyl paraben as preservatives. Generally the consistency index, K for 1% fish gelatin, 1% ι-Carrageenan, 1% methocel E4M, 1%, 3% and 5% methocel F50, 1%, 3% and 5% methocel SGA 7C and 1% methycellulose HV was very low (denoted by $K < 5 \text{ Pas}^n$) even though their n value was less than 1. Besides, their apparent viscosity was also very low and liquid-like. Therefore, these gelling agent at these concentrations are not suitable candidates for dental gel formulation but maybe suitable for some other applications. Generally, 1%, 3%, and 5% carbopol 940, 5% guar gum, 5% ι-carrageenan, 3% and 5% kelcogel F, and 1%, 3% and 5% konjac gum were among the best candidates to be developed into dental gel. This can be attributed to their high apparent viscosity ($> 3 \text{ Pas}$) at highest tested shear rate (100 s^{-1}) as well as high consistency factor K ($> 100 \text{ Pas}^n$) and good flow behavior index n . Figures 1 and 2 are examples of the good candidate gels in term of apparent viscosity and consistency index.

Gels were also studied in term of linear viscoelasticity range (LVR). Storage modulus (G') illustrates the elastic

modulus where it shows how elastic or how much energy can be stored in order to pull back gels that had been applied with shear stress onto it. G'' is known as loss modulus where it illustrates the dissipation of energy when shear stress is applied to the gel [16]. LVR was tested using stress sweep test, which revealed the range of shear stress that the polymer network would remain intact and interconnected. Beyond the LVR range, the network is expected to entangle and break down; causing the gel elasticity to be reduced and the gel will not be in stable network as it should [22, 23]. As shown in Table 2, most of the gelling agents exhibited values of G' higher than G'' . This includes 1%, 3%, and 5% carbopol 940, 3% and 5% fish gelatin 250 bloom, 1%, 3% and 5% guar gum, 3% and 5% ι -carrageenan, 1%, 3% and 5% κ -carrageenan, 1%, 3% and 5% kelcogel F, 1%, 3% and 5% konjac gum, and 3% and 5% methyl cellulose HV ($p < 0.05$). This means the elasticity (storage modulus) of these gels is higher than their viscous behavior (loss modulus), producing a well viscoelastic and stable gel [22, 24]. However, 1% fish gelatin 250 bloom, 1% ι -carrageenan, 1%, 3% and 5% methocel E4M, 1%, 3% and 5% methocel F50, 1%, 3% and 5% methocel SGA 7C, and 1% methylcellulose HV had values of G'' more than G' . This means that their loss modulus overrides their elastic properties, producing low viscous gels with lack of ability to return to their normal network arrangement once the shear is removed. Among all the gel polymers, 5% konjac gum had the highest G' values, which is 12222 ± 669.50 Pa, followed by 5% kelcogel F with the value of 8433.48 ± 213.71 Pa and 3% konjac gum with the value of 2848.50 ± 192.50 Pa ($p < 0.05$).

Values of G' and G'' changed at different concentrations of the gels. For example, the increase of gel concentration of κ -carrageenan from 1% to 5% lead to increase in G' and G'' value ($p < 0.05$). The same findings had been found by Derkach et al., where the increase of κ -carrageenan concentration of 0.1% to 1.0% w/w added to native gelatin gels had increased the gels' G' and G'' [25]. The value of $\tan \delta$ of κ -carrageenan had shown decreasing value pattern from 1% to 5% gel concentration, indicating that the gels became more viscous. The high value of $G' = G''$ and the crossing point of G' and G'' indicated that the elasticity modulus is getting more robust against the loss modulus causing the crossing point to happen at higher values of shear stress. This means the LVR is wider and the G' was dominated against G'' at higher gel concentration.

Regarding linear viscoelasticity range (LVR), it was found that all gels with G' value higher than G'' had wide LVR. On the other hand, gels with values of G'' more than G' exhibited narrow or no LVR. This can be explained by the unstable network of the gel polymers that contributes to the lack of storage modulus (G'). Gels such as 5% fish gelatin, 3% κ -carrageenan and 3% methylcellulose HV are some examples of good gels that have G' higher than G'' ($p < 0.05$). They might be a good candidate due to their good Herschel Bulkley/Ostwald de-Waele model and their high apparent viscosity. However the crossover point between

the G' and G'' in these three gels happened at the lower shear stress value compared to others. This means their linear viscoelasticity range is not wide enough, which is not a good indicator for the dental gel. Oral environment is exposed to variable shear stress due to movement of the tongue, teeth and mouth during talking and chewing. Thus, dental gels need to be stable among wide range of shear stress so that the gel network does not break down easily. The crossing point of G' and G'' is the point where a stable and intact gel network starts to break down, entangled and the gels are about to dissolve into saliva. Therefore, gels with higher value of G' and G'' crossing point are more suitable to be developed into dental gels such as 3% and 5% carbopol 940, 3% and 5% guar gum, 5% ι -carrageenan, 3% kelcogel F, 1%, 3%, and 5% konjac gum, and 5% methyl cellulose HV (crossing point value > 300 Pa). Figure 2 illustrates example of some gels with clear LVR line. From the figure, $\tan \delta$ value starts to increase when the G' and G'' approaching of cross over point, indicating the breaking down of the gel networks and the gels starts to become liquid like with further increase of shear stress (denoted by $\tan \delta$ approaching the value of 1).

$\tan \delta$ explains the liquid or viscous behavior of a gel. If $\tan \delta$ value is >1 , the gel is liquid-like. $\tan \delta$ of values < 1 shows that the gel is viscous [26]. The lesser the value of $\tan \delta$, the more viscous the gel is. In this study, it was found that most of the gels exhibited values of $\tan \delta < 1$, except for 1% fish gelatin, 1% guar gum, 1% ι -carrageenan, 1%, 3% and 5% methocel E4M, 1%, 3% and 5% methocel F50, 1%, 3% and 5% methocel SGA7C, and 1% methyl cellulose HV. Among the viscous gels, 3% carbopol 940 exhibited the lowest value of $\tan \delta$ (0.0779 ± 0.019). This shows that 3% carbopol 940 produced the most viscous gel compared to other gelling agents. This is followed by 5% carbopol 940 which had $\tan \delta$ values of 0.086 ± 0.004 . However, they are statistically not significant different ($p > 0.05$). The highest value of $\tan \delta$ that falls within the value of less than 1 was seen in 1% guar gum with the value of 0.964 ± 0.021 . As a candidate for dental application, a gel with small value of $\tan \delta$ is needed.

In considering which gelling agent is a good candidate for dental gel development, all rheology aspects should be considered. The gel might be a good viscous gel but it is not necessarily viscoelastic enough to retain its viscosity after application. A gel might not have a good apparent viscosity at the three shear stress points but its G' , G'' , $\tan \delta$ and crossing points of G' and G'' might prove that it is good viscoelastic gel. For example, 3% methyl cellulose HV exhibited an acceptable consistency index and apparent viscosity at 100 s^{-1} . However, the difference in value of G' and G'' were very small, and the crossing point of G' and G'' is as early as at 49.23 Pas shear stress. Thus it is not a good candidate as compared to others such as 3% konjac gum that had better LVR properties as well as the crossing point of G' and G'' happens at higher shear stress.

Table 1: Rheological profiles for gelling agents.

Gel Polymer		Mean Apparent Viscosity ± SD (Pas)			Herschel Bulkley Model				Ostwald de-Waele Model		
		shear rate 10 s ^{-1*}	shear rate 50 s ^{-1*}	shear rate 100 s ^{-1*}	r	τ0 (Pas)	k(Pas ⁿ)	n	r	k(Pas ⁿ)	n
Carbopol 940	1%	31.313±0.032 ^h	8.750 ±0.009 ^{ef}	5.461±0.007 ^e	0.9978	14.2	161.1	0.26	-	-	-
	3%	36.481±0.029 ^g	10.502±0.022 ^d	6.518±0.011 ^d	-	-	-	-	0.9528	100	0.41
	5%	44.229±0.027 ^e	13.044±0.020 ^c	8.084 ±0.007 ^c	-	-	-	-	0.9936	147	0.23
Fish gelatin 250 bloom	1%	0.021±0.010 ^l	0.004±0.008 ⁿ	0.002±0.013 ^p	-	-	-	-	0.9005	0.12	0.20
	3%	1.082±0.008 ^{kl}	0.364±0.006 ^{mn}	0.175±0.006 ^{nop}	0.9745	3.67	8.14	0.17	-	-	-
	5%	2.112±0.028 ^{kl}	0.566±0.006 ^{lmn}	0.327±0.011 ^{no}	0.9966	4.12	9.28	0.25	-	-	-
Guar gum	1%	2.230 ±0.104 ^{kl}	0.730±0.007 ^{lmn}	0.454±0.006 ^{mn}	-	-	-	-	0.8933	19.7	0.30
	3%	32.014±0.219 ^h	6.815±0.224 ^g	0.733±0.058 ^{lm}	0.9747	4.17	42.3	0.47	-	-	-
	5%	99.693±3.281 ^c	21.310±1.201 ^b	10.768±0.153 ^a	0.9999	29.6	209	0.35	-	-	-
ι-carrageenan	1%	0.477±0.012 ^l	0.218±0.011 ^{mn}	0.128±0.010 ^{op}	-	-	-	-	0.9998	1.91	0.41
	3%	20.752±0.051 ⁱ	4.358±0.011 ⁱ	2.263±0.012 ^j	0.9745	4.65	35.3	0.40	-	-	-
	5%	46.328±0.027 ^e	10.543±0.031 ^d	5.571±0.021 ^e	-	-	-	-	0.8293	290	0.16
κ-carrageenan	1%	4.829±0.009 ^k	0.878±0.002 ^{lm}	0.474±0.001 ^{mn}	-	-	-	-	0.7541	34.1	0.08
	3%	9.010±0.273 ^j	1.838±0.00 ^{jk}	0.949±0.008 ^l	0.9747	13.4	36.3	0.21	-	-	-
	5%	21.412±0.131 ⁱ	5.179±0.021 ^h	2.773±0.032 ⁱ	-	-	-	-	0.9642	153	0.14
Kelcogel F	1%	0.942±0.124 ^{kl}	0.289±0.042 ^{mn}	0.192±0.018 ^{nop}	-	-	-	-	0.9960	4.27	0.32
	3%	20.109±1.022 ⁱ	5.396±0.092 ^h	2.819±0.022 ⁱ	0.9747	60.7	148	0.14	-	-	-
	5%	42.503±0.871 ^{ef}	9.438±0.057 ^e	4.777±0.089 ^f	-	-	-	-	0.9467	304	0.12
Konjac gum	1%	23.551±0.894 ⁱ	5.798±0.361 ^h	3.215±0.277 ^h	-	-	-	-	0.9753	150	0.17
	3%	123.213±0.497 ^b	20.931±0.038 ^b	10.078±0.038 ^b	0.9747	25.4	168	0.39	-	-	-
	5%	235.024±6.266 ^a	24.012±0.221 ^a	11.073±0.431 ^a	0.9753	154	474	0.195	-	-	-
Methocel E4M	1%	0.293±0.002 ^l	0.232±0.003 ^{mn}	0.205±0.006 ^{nop}	0.9996	0.17	0.43	0.839	-	-	-
	3%	9.960±0.024 ^j	5.206±0.031 ^h	3.560±0.047 ^g	-	-	-	-	0.9989	33.1	0.52
	5%	72.559±0.087 ^d	12.746±0.077 ^c	2.759±0.029 ⁱ	0.9996	1.60	21.1	0.55	-	-	-
Methocel F50	1%	0.018±0.001 ^l	0.013±0.004 ⁿ	0.012±0.001 ^p	0.9984	0.04	0.01	0.95	-	-	-
	3%	0.204±0.002 ^l	0.193±0.001 ^{mn}	0.190±0.001 ^{nop}	1.0000	0.03	0.21	0.98	-	-	-
	5%	1.396±0.005 ^{kl}	1.129±0.001 ^{kl}	1.023±0.002 ^l	0.9996	0.08	2.82	0.78	-	-	-
Methocel SGA 7C	1%	0.012±0.000 ^l	0.003±0.000 ⁿ	0.002±0.000 ^p	0.6019	0.02	0.06	0.24	-	-	-
	3%	0.026±0.001 ^l	0.018±0.000 ⁿ	0.015±0.001 ^{op}	0.9985	0.07	0.02	0.93	-	-	-
	5%	0.444±0.003 ^l	0.246±0.002 ^{mn}	0.197±0.000 ^{nop}	0.9999	0.09	0.86	0.68	-	-	-
Methyl Cellulose HV	1%	0.167±0.002 ^l	0.097±0.002 ⁿ	0.074±0.001 ^{op}	0.9999	0.22	1.27	0.38	-	-	-
	3%	10.062±0.036 ^j	2.406±0.009 ^j	1.552±0.006 ^k	-	-	-	-	0.9696	60.2	0.20
	5%	38.663±0.081 ^{fg}	8.153±0.038 ^f	4.701±0.050 ^f	0.9999	2.80	38.7	0.55	-	-	-

*Values are Mean + SD. Statistical analysis were expressed using alphabetical superscript where different alphabet in each group means the data were statistically significant different (p < 0.05), while the same alphabetical superscript means they are statistically not significant different (p > 0.05)

Table 2: Stress sweep test and linear viscoelasticity range for gelling agents.

Gelling agent		G' (Pa)*	G'' (Pa)*	Tan δ*	G' = G'' (Pa)	Crossing point of G' and G'' (Pa)
Carbopol 940	1%	429.24±42.12 ^{efg}	52.16±9.77 ^{hi}	0.097±0.016 ^f	97.6	256.3
	3%	503.29±35.89 ^{ef}	42.14±10.52 ⁱ	0.079±0.019 ^f	115.3	306.1
	5%	752.25±33.82 ^{fg}	68.99±7.57 ^{hi}	0.086±0.004 ^f	184.5	499.3
Fish gelatin 250 bloom	1%	2.66±0.20 ^g	2.93±0.35 ⁱ	2.932±0.350 ^{ef}	-	-
	3%	15.52 ± 4.77 ^{fg}	3.84 ± 2.71 ⁱ	0.361 ± 0.217 ^f	6.6	6.846
	5%	360.43±16.31 ^{efg}	69.51±10.67 ^{hi}	0.188±0.039 ^f	115.8	87.36
Guar gum	1%	17.22±0.72 ^g	16.69±0.33 ⁱ	0.964±0.021 ^f	16.4	4.63
	3%	282.65 ± 20.75 ^{efg}	138.45 ± 7.25 ^{gh}	0.501 ± 0.085 ^f	156.1	351.1
	5%	2598.52±67.49 ^{cd}	777.95±27.39 ^d	0.299±0.01 ^f	1239.3	966.1
ι-carrageenan	1%	2.03±0.64 ^g	2.76±0.28 ⁱ	1.082±0.059 ^f	-	-
	3%	245.15 ± 33.75 ^{fg}	43.49 ± 16.19 ⁱ	0.203 ± 0.079 ^f	82.5	269.7
	5%	689.67±15.46 ^c	67.63±5.65 ^{hi}	0.095±0.005 ^f	218.8	504.2
κ-carrageenan	1%	6.06±0.83 ^g	2.27±0.20 ⁱ	0.420±0.156 ^f	6.4	1.38
	3%	226.20 ± 33.90 ^{fg}	62.38 ± 15.3 ^{hi}	0.316 ± 0.088 ^f	51.8	73.30
	5%	680.08±40.10 ^c	182.15±5.31 ^g	0.260±0.033 ^f	161.3	138.4
Kelcogel F	1%	58.90±6.04 ^g	29.50±0.64 ⁱ	0.718±0.418 ^f	27.03	18.89
	3%	2391.00 ± 91.00 ^d	364.65 ± 14.85 ^f	0.166 ± 0.017 ^f	1923.8	347.8
	5%	8433.48±213.71 ^b	1227.5±28.10 ^b	0.144±0.014 ^f	3455.0	226.70
Konjac gum	1%	710.41±4.74 ^c	290.58±9.53 ^f	0.425±0.026 ^f	298.1	549.5
	3%	2848.50 ± 192.50 ^c	999.4 ± 134.6 ^c	0.341 ± 0.032 ^f	1323.2	1472.2
	5%	12 222±669.50 ^a	2812.22±48.10 ^a	0.221±0.027 ^f	5367.1	2636.1
Methocel E4M	1%	0.84±0.02 ^g	2.08±0.04 ⁱ	3.55±0.27 ^{ef}	-	-
	3%	16.44± 0.54 ^g	37.82 ± 19.76 ⁱ	2.358 ± 0.612 ^{ef}	-	-
	5%	426.67±3.07 ^{efg}	572.93 ±4.80 ^g	1.346±0.016 ^f	-	-
Methocel F50	1%	0.01±0.00 ^g	0.08±0.01 ⁱ	15.278±2.25 ^b	-	-
	3%	0.40 ± 0.40 ^g	1.18 ± 0.44 ⁱ	689.912 ± 688 ^a	-	-
	5%	1.23±0.04 ^g	8.33±0.12 ⁱ	6.951±0.362 ^{cde}	-	-
Methocel SGA 7C	1%	0.012±0.01 ^g	0.59±0.43 ⁱ	9.370±1.374 ^c	-	-
	3%	1.58 ± 1.25 ^g	3.52 ± 2.17 ⁱ	3.406 ± 3.406 ^{ef}	-	-
	5%	1.29±0.30 ^g	3.71±0.22 ⁱ	4.091±0.603 ^{def}	-	-
Methyl cellulose HV	1%	0.12±0.01 ^g	0.89±0.02 ⁱ	8.421±1.262 ^{cd}	-	-
	3%	45.99 ± 11.66 ^g	39.31 ± 7.88 ⁱ	0.795 ± 0.121 ^f	41.6	49.23
	5%	294.47±10.16 ^{efg}	174.26±7.17 ^g	0.603±0.021 ^f	143.4	380.6

*Values are Mean + SD. Statistical analysis were expressed using alphabetical superscript where different alphabet in each group means the data were statistically significant different (p < 0.05), while the same alphabetical superscript means they are statistically not significant different (p > 0.05)

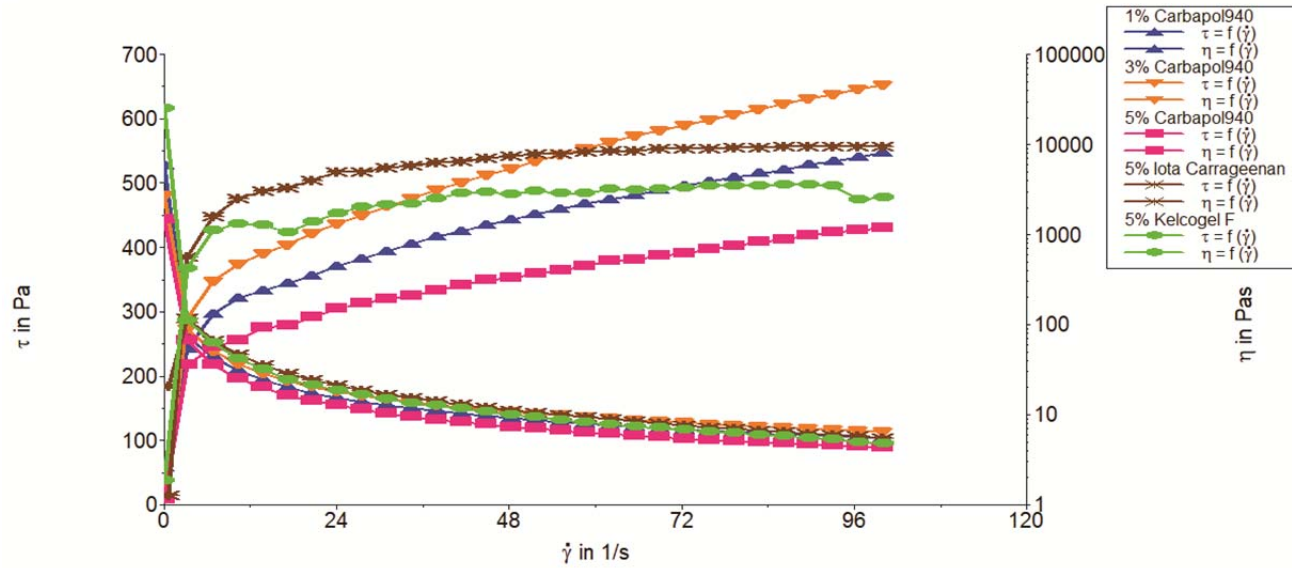


Fig. 1: Shear stress and viscosity vs. shear rate of some good gelling agents.

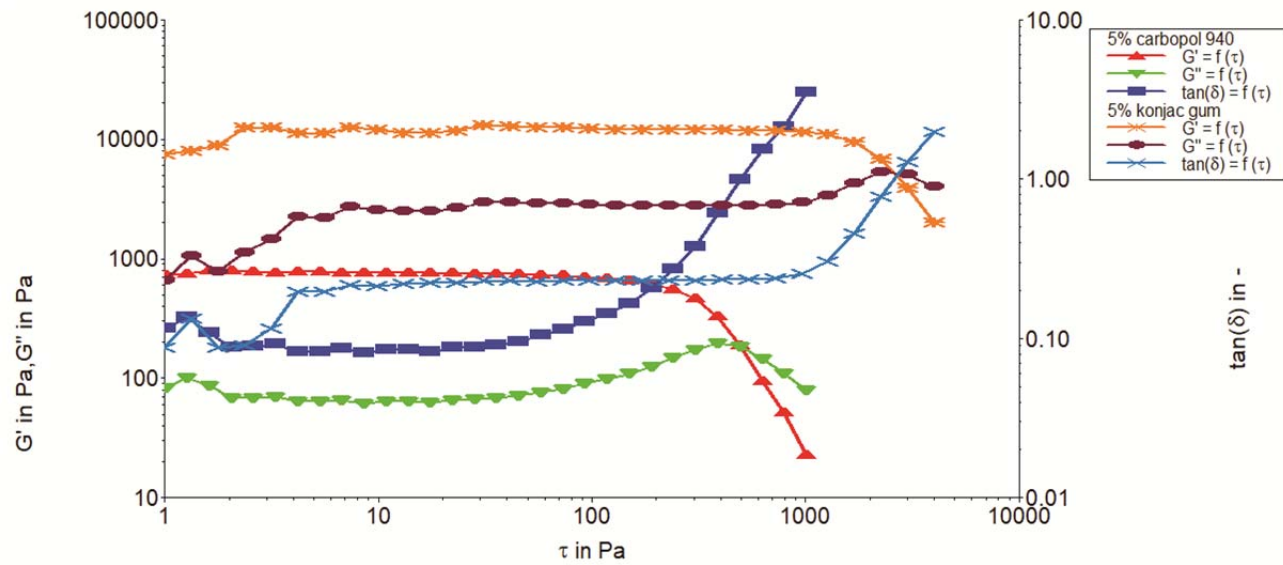


Fig. 2: Stress sweep test of some good candidate gels (carbopol 940[®] and kelcogel F).

CONCLUSION

The gels rheological profiles including the apparent viscosities at 3 shear rates, rheological modeling, consistency factor (K), flow behavior index (n), values of G' , G'' , and the crossing points of G' and G'' for all 11 gelling agents at 3 different concentrations were demonstrated and discussed for their suitability as dental gels. Various gelling agents exhibited potential rheological profiles for dental applications. These includes 3% and 5% carbopol 940, 5% guar gum, 5% ι -carrageenan, 3% kelcogel F, and 1%, 3% and 5% konjac gum. These gels were found to be viscoelastic, yet consistent in behaving as pseudoplastic gel with acceptable viscosity profiles at high shear rates (100 s^{-1}), having high consistency factor (K), good flow behavior (n), high value of G' , and the crossing points of G' and G'' happened at high shear stress. Other gels such as 1% carbopol 940, 3% and 5% of guar gum and ι -carrageenan, 1% and 5% of kelcogel F, 1%, 3% and 5% concentrations of fish gelatin, κ -carrageenan, methocel E4M, methocel F50, and methocel SGA 7C and methyl cellulose HV might not be good candidates due to their low viscosity or their viscous behavior overtook their elasticity behavior. This study suggests variable gelling agents as vehicles for dental gels. Hence, it gives the formulator more options other than the limited available gels used frequently as dental gels.

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DECLARATION OF INTEREST STATEMENT

There is no conflict of interest regarding this research and written content.

REFERENCES

- Das B, Nayak AK, Nanda U. Topical gels of lidocaine HCl using cashew gum and Carbopol 940: preparation and in vitro skin permeation. *Int J Biol Macromol.* 2013;62:514-7. doi: 10.1016/j.ijbiomac.2013.09.049. PubMed PMID: 24099938.
- Abid Hussain GMK, Syed Umer Jan, Shefaat Ullah Shah, Kifayatullah Shah,, Muhammad Akhlaq NR, Asif Nawaz and Abdul Wahab. Effect of olive oil on transdermal penetration of flurbiprofen from topical gel as enhancer. *Pak J Pharm Sci.* 2012;25(2):365-9.
- Malathi K, Jeevrekha M, Rajula MPB, et al. Local Drug Delivery –A Targeted Approach. *International Journal of Medicine and Biosciences.* 2014;3(2):29-34.
- Raghavendra Rao NG, Rao K, Muthalik S, et al. Clinical studies and antimicrobial activity of ciprofloxacin hydrochloride medicated dental gels for periodontal infection. *Asian Journal of Pharmaceutics.* 2009;3(2):125-34. doi: 10.4103/0973-8398.55050.
- Jones DS, Woolfson AD, Brown AF, et al. Design, characterisation and preliminary clinical evaluation of a novel mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease. *Journal Of Controlled Release.* 2000;67:357-68.
- Sharma LA, Love RM, Ali MA, et al. Healing Response of Rat Pulp treated with Injectable Keratin Hydrogel. *J Appl Biomater Funct Mater* 2017;15(3):244-50.
- Phacchamud T, Mahadlek J, Chuenbarn T. In situ forming gel comprising bleached shellac loaded with antimicrobial drugs for periodontitis treatment. *Materials and Design.* 2016;89:294-303.
- Ersch C, Meinders MJB, Bouwman WG, et al. Microstructure and rheology of globular protein gels in the presence of gelatin. *Food Hydrocolloids.* 2015 30 September 2015
- Rowe RC, Sheskey PJ, Quinn ME. *Handbook of Pharmaceutical Excipients.* 6 ed.: Pharmaceutical Press; 2009.
- Agnihotri S, Wakode S, Agnihotri A. Formulation and Evaluation of Herbal Antiacne Gel of Myrica Esculenta. *Asian Journal of Pharmaceutical and Clinical Research.* 2016;9(4):358-61.
- Kaleemullah M, K. J. M. GT, et al. The Effect of various vehicles on in-vivo performance of indomethacin from different topical formulations. *World Journal of Pharmaceutical Research.* 2015;4(4):157-72.
- Kassab JK, Thomas LM, Jabir SA. Development and Physical Characterisation of a Periodontal Bioadhesive Gel of Gatifloxacin. *International Journal of Applied Pharmaceutics.* 2017;9(3):31-6.
- Ibrahim NH, Che Man Y, Tan CP, et al. Mixture-Design-Experiment-on-Flow-Behaviour-of-OW-Emulsions-as-Affected-by-Polysaccharide-Interactions. *International Journal of Biological, Biomolecular, Agricultural, Food and Biotechnological Engineering.* 2010;4(7):464-70.
- de Cássia da Fonseca V, Haminiuk CWI, Izydor DR, et al. Stability and rheological behaviour of salad dressing obtained with whey and different combinations of stabilizers. *International Journal of Food Science & Technology.* 2009;44(4):777-783. doi: 10.1111/j.1365-2621.2008.01897.x.
- Markis F, Baudez J-C, Parthasarathy R, et al. Rheological characterisation of primary and secondary sludge: impact of solids concentration. *Chemical Engineering Journal.* 2014. doi: http://dx.doi.org/10.1016/j.cj.2014.05.085.
- Ricci EJ, Bentley MVLB, Farah M, et al. Rheological characterization of Poloxamer 407 lidocaine hydrochloride gels. *European Journal of Pharmaceutical Sciences.* 2002;17:161-7.
- Binsi PK, Shamasundar BA, Dileep AO, et al. Rheological and functional properties of gelatin from the skin of Bigeye snapper (*Priacanthus hamrur*) fish: Influence of gelatin on the gel-forming ability of fish mince. *Food Hydrocolloids.* 2009;23(1):132-145. doi: 10.1016/j.foodhyd.2007.12.004.
- Ibrahim NH, Ching CW, Rozaini MZH. Flow properties of o/w emulsions as affected by xanthan gum, guar gum and carboxymethyl cellulose interactions studied by a mixture regression modelling. *Food Hydrocolloids.* 2016;53:199-208.
- Lewis MJ. *Physical properties of foods and food processing systems.* Elsevier; 1990.
- Di Giuseppe E, Corbi F, Funicello F, et al. Characterization of Carbopol® hydrogel rheology for experimental tectonics and geodynamics. *Tectonophysics.* 2015;642:29-45. doi: 10.1016/j.tecto.2014.12.005.
- Tipvarakarnkoon T, Senge B. Rheological behaviour of gum solutions and their interactions after mixing. *Annual transactions of the nordic rheology society.* 2008;16.
- Weiss RG. The Past, Present, and Future of Molecular Gels. What Is the Status of the Field, and Where Is It Going? *Journal of The American Chemical Society.* 2014;136(21):7519-30. doi: 10.1021/ja503363v.
- Angelova LV, Terech P, Natali I, et al. Cosolvent gel-like materials from partially hydrolyzed poly (vinyl acetate) s and borax. *Langmuir.* 2011;27(18):11671-82.
- Nagelreiter C, Raffener S, Geyerhofer C, et al. Influence of drug content, type of semi-solid vehicle and rheological properties on the skin penetration of the model drug fludrocortisone acetate. *Int J Pharm.* 2013;448(1):305-12. doi: 10.1016/j.ijpharm.2013.03.042. PubMed PMID: 23541986.
- Derkach SR, Ilyin SO, Maklakova AA, et al. The rheology of gelatin hydrogels modified by κ -carrageenan. *LWT- Food Science and Technology.* 2015;63(1):612-9.
- Qiao L, Li Y, Chi Y, et al. Rheological properties, gelling behavior and texture characteristics of polysaccharide from *Enteromorpha prolifera*. *Carbohydrate Polymers.* 2016;136:1307-14.