

VISCOELASTIC PROPERTIES AND RHEOLOGICAL CHARACTERIZATION OF CARBOMERS

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Abstract: This research was conducted to determine the effect of viscoelastic properties and Rheological characterization of carbomers. Carbomers are the generic name for a class of high molecular weight cross linked polymer of acrylic acid. Carbomers play an important role in many commercial products such as gels, creams and lotions, providing viscosity, stabilization and suspension properties. Understanding how the preparation of the carbomers can affect the final. One such factor that can affect the behavior of the carbomers is the method of dispersing the carbomers into an aqueous medium, the carbomers considered in this research were from USP grade of materials, from this investigation conducted, it was found a number of carbomers were affected by shear as a result of the method of dispersion used. Use of the shear sensitive carbomers in commercial production could require the use of low shear mixing which would result in a longer dispersion time and increased production cost.

Keywords: DV-II +Pro Viscometer, Rheometer, Shear rate, Shear stress, Viscoelasticity, Carbomers, Emulsion, Amplitude sweep, Flow curve, Oscillation.

Introduction:

Many researchers and investigators have reported the effectiveness of delivering various drugs through the skin via using emulsion preparations with nano-metric droplets size (usually in the range of 20-200 nm). They have proven that such dosage forms possess influential solubilization capability, thermodynamic stability, controllable droplet size, enhanced permeability, *etc* (1, 2, 3,&4). The research was conducted 0.5% dispersion of carbomer neutralized with 18 % Sodium hydroxide at pH-7.3 substances were prepared and subjected for viscosity and Rheological characterization carbomer, the five different grade carbomers are subjected for freezer and Accelerated study at different stages for investigation of rich sensory, high clarity to use, and it is better application of cosmetic facial lotions and gels, body lotions, creams and sunscreen products, by using Viscometer and Rheometer.

Usually, micro-emulsions and sometimes nano-scaled emulsions show poor rheological properties with a very low viscosity making them behave as Newtonian fluids or semisolids of high fluidity. These properties render them pharmaceutically inapplicable and commercially unacceptable as topical products (5). In such circumstances, the addition of thickening agents or gel-network forming substances becomes highly recommended to overcome these minor drawbacks (6).

Materials, like: Carbomers (poly-acrylic acid polymer), gums (polysaccharides), semi-synthetic cellulosic derivatives, *etc*, are widely used pharmaceutically and cosmetically to achieve various purposes, such as: emulsification, stabilization and rheological control (7).

Recently, Carbomer resins have been considered extensively by many researchers and scientists, since they provide a wide range of applications as thickening agents, emulsifying agents, suspending agents and tablets compressed matrix forming agents, which is particularly used in controlling drug release (8).

In general, Carbomer polymers are polymers of acrylic acid, cross-linked with polyalkenyl ethers or divinyl glycol. They are hydrophilic, tightly coiled, mildly acidic ($pka\ 6.0 \pm 0.5$) fluffy, white and dry flocculated powders with particles having a size of about 0.2 μm in diameter (9). Their neutralized aqueous dispersions demonstrate a high viscosity, which makes them fairly popular for controlling the flow properties of topically applied dosage forms as they are inexpensive, transparent and harmless and easy to prepare and clean (10).

Carbomer polymers are commonly synthesized by crosslinking process with the specific substrate. The degree of cross-linking and the manufacturing conditions usually produce various grades of Carbomers. Each grade demonstrates different criteria that fit it into a specific application (11). Structurally, each discrete unit of this polymer appears as a network of polymer chain interrelated by cross-links. Removing these cross-linkages would render the primary particles to appear as an intertwined but not chemically bonded collection of linear

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polymer chains. Such linear polymers are soluble in water and polar solvents, like Carbomer907. On the other hand, all other types of Carbomers are cross-linked. Because of their hydrophilicity and high water sorption ability, they can distend in water up to 1000 times their original volume and 10 times their original diameter forming a gel upon exposure to a pH environment above a range of 4 to 6. Once these Carbomer molecules are dispersed in water, they start hydrating and uncoiling to a certain extent. Neutralization of the polymer carboxylate groups using an alkaline substance makes them highly ionized to form rigid gels (12, 13, 14 & 15). This neutralization step is considered as the most common way to can be accomplished by adding a common base, like sodium hydroxide or organic amines, such as triethanolamine, which cause the carboxylate groups of these polymers to be converted into a ionization of these carboxylate groups on the polymer backbone, electrostatic repulsion amongst the negatively charged particles is observed which finally adds to the swelling and thickening capabilities of these polymers (15). In addition, determine the pH range that renders Carbomer polymers to be powerful thickening and gelling agents. It was found that a pH range of 5 to 9 usually leads to the formation of highly viscous systems. However, pH values less than 5 and above 9 can be also used, but higher levels of Carbomer must be employed to produce higher viscosity levels (15).

Specifically, Carbomer 934, 940 and Ultrez 10 were reported by many to be of great applications Pharmaceutically and cosmetically (6, 7, 13, 14 & 16). They demonstrate different rheological properties and viscosity values, which are mainly reflected by the polymer particle size, molecular weight between cross-links, allocation of molecular crosslinks and the fraction of the overall units that arises as terminal units, i.e. free chain ends (12). Recently, Carbomer Ultrez 10 was introduced as a hybrid between Carbomer 940 and 934. It shows superior dispersion properties and potentially wider range of applications. These properties make the process of producing homogenous colloidal dispersion of Carbomer Ultrez 10 easier, shorter and cheaper. In other words, less effort and energy are required to produce a lump-free dispersion (14 & 17).

Therefore, the current work is aimed to modify the poor flow properties of this formula and assess the gel-network forming properties of two different types of Carbomer resins. Carbomer 980 and Carbomer 940 at 0.5 % dispersion solution were utilized to achieve the viscosity and flow modification task. Finally, the best carbomers was examined intensively using viscometer and Rheometer compared viscosity and rheological properties.

Materials and Methods:

The research was performed using Brook field DV II +Pro Viscometer, equipped with LV-5 spindle, 10 rpm, and Anton Paar Rheometer, equipped with CP 50 spindle.

Materials:

Carbomer 980 and Carbomer 940 (Pharmacopeia grade)

Apparatus:

Analytical balance capable of ± 0.005 gram accuracy.

Fisher or other mixer capable of 300 RPM, with 3.25-inch "S"-blade stirrer.

Constant temperature water bath.

Brookfield Viscometer, DV II +Pro.

Anton Paar Rheometer (MCR-302).

pH meter.

Sample preparation:

Spread sample evenly in an open aluminum or glass dish. Dry at 80°C in a vacuum oven (minimum of 25 inches of mercury) for 1 hour. NOTE: Drying the sample is not necessary if the sample has recently arrived from production and the sample container has not been previously opened.

Measure 500 mL distilled or demineralized water in a graduated cylinder and transfer to an 800 mL beaker.

After drying the Carbomer polymer, remove to a desiccator and allow to cool to room temperature.

After the Carbomer polymer reaches room temperature, weigh out polymer from the dried sample to ± 0.005 gram onto an aluminum dish. The appropriate amount of polymer for the mucilage concentrations is 2.50 grams for 0.5% solution.

Place the Carbomer polymer dispersion in a $25 \pm 2^\circ\text{C}$ water bath for 30 minutes.

Remove the dispersion from the bath and neutralize with 18% NaOH. Carbomer 980 and Carbomer 940 polymers are neutralized to a pH at 7.3.

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Use the mixer with the "S"-paddle at low speed (300 to 500 rpm) to stir the mucilage. With the mixer off, set the paddle just below the surface so that air will not be drawn into the mucilage. Turn the mixer on and stir for 2 minutes, moving the beaker up and down, being aware that minimal air should be introduced.

Check the pH of the mucilage with a calibrated pH meter. If the pH is below the target range, add additional 18% NaOH and remix. The desired pH is 7.3 for Carbomer 980 and Carbomer940. If the pH is above the desired pH range, discard and remake the mucilage.

Return the neutralized mucilage to the 25°C water bath for one hour. NOTE: The viscosity determination should be made after 60 to 75 minutes to avoid slight viscosity changes occurring with time.

Test procedure for viscometer:

Take a clean and dry 100 ml Borosil glass beaker. Transfer the Sample into the beaker without air gaps, cover the beaker with aluminum foil and keep it in a calibrated water bath (25°C ± 1°C) for 1 to 2 hours to attain the temperature. Measure the viscosity by using spindle LV-5, set the speed 10 rpm, and take the reading.

Assured temperature of sample should be 25°C ± 1°C. Monitor the temperature by sensor which is attached to viscometer. Dip the spindle at center position of beaker up to the mark on the spindle. After 1 minute take constant reading on spindle.

The Real time viscosity values of Carbomer 980 and Carbomer940at different intervals (Table-1).

Table-1: Real time viscosity at 25°C, LV-5 spindle, 10 rpm.

Sl.No	Material name	Initial	10 days	20 days	30 days
1	Carbomer 980	74,000	68,100	66,400	65,000
2	Carbomer 940	76,000	75,000	74,500	73,000

The Accerlated viscosity values of Carbomer 980 andCarbomer940at different intervals (Table-2)

Table-2: Accerlated viscosity at 45°C, LV-5 spindle, 10 rpm.

Sl.No	Material name	10 days	20 days	30 days
1	Carbomer 980	69,000	66,000	64,800
2	Carbomer 940	70,000	61,000	58,500

Test Procedure for Flow curve:

Rheological measurements were performed immediately after pressure treatment using a controlled stress and strain Rheometer (Anton Paar MCR 302, Germany). A parallel plate geometry (50 mm diameter) was used and the gap between the two plates was 0.1 mm. Before each test, the sample was placed between the Rheometer plates for 5 min to allow stress relaxation and temperature equilibration (temperature was kept constant at 25°C). Physical Rheometer Data Analysis software (Rheo compass, version V1.11:173, Germany) was used to obtain experimental data. A rheogram of the samples was plotted using shear rate and shear stress at various revolution rates of the spindle (PP-50).

The Real time viscosity values ofCarbomer980 and Carbomer940 at different intervals (Table-3).

Table-3: Real time viscosity at Initial and 10°C, PP-50 spindle.

Sl.No	Material name	Initial	10 days	20 days	30 days
1	Carbomer 980	64,584	56,358	21,697	48,784
2	Carbomer 940	43,811	64,640	33,870	54,135

The Accerlated viscosity values of Carbomer 980 andCarbomer940 at different intervals (Table-4)

Table-4: Accerlated viscosity at 45°C, PP-50 spindle.

Sl.No	Material name	10 days	20 days	30 days
1	Carbomer 980	50,028	26,438	20,672
2	Carbomer 940	37,566	34,565	25,765

Amplitude sweep:

An amplitude sweep test, as an oscillatory test is characterized by a variable amplitude and constant frequency. The term ‘sweep’ stands for a function with a variable parameter. Either the shear stress (CSS) or the shear deformation (CSD) are controlled. Amplitude sweep tests are conducted to achieve informations about the flow behavior of a substrate and especially its elastic part (stored elasticity), the LVE deformation range, marked as area between the points of the parallel running curves of G' and G'' and their transition. The inflexion (transient) point equals the yield point.

In contrast to amplitude sweep tests a frequency sweep test is built up on a variable frequency and a constant amplitude, usually conducted with controlled shear deformation (CSD). As pre-condition the yield stress has to be determined first to assure that measurements are carried out within the LVE range. Curves of the storage modulus G' , the loss modulus G'' and the complex viscosity $|\eta^*|$ are displayed as a function of the angular frequency ω . alternatively, the complex viscosity $|\eta^*|$ can be replaced by $\tan \delta$. Both give informations about the viscous behavior, respectively the portion of viscosity in relation to elasticity. Frequency sweep tests appropriate to investigation regarding to short-term as well as to long-term behavior. Thus, cyclic adaptations of frequencies might be applied, e.g. frequency changes of farm implements (18).

The so called LVE range (linear viscoelastic) analysis is used for determining yield stress’ deriving from amplitude sweep tests, which have either deformation γ (controlled shear deformation, CSD) or shear stress τ (controlled shear stress, CSS) as default. In the case of frequency sweep tests, calculations are based upon a Carreau equation (Carreau-Yasuda) and are generated automatically during tests (19).

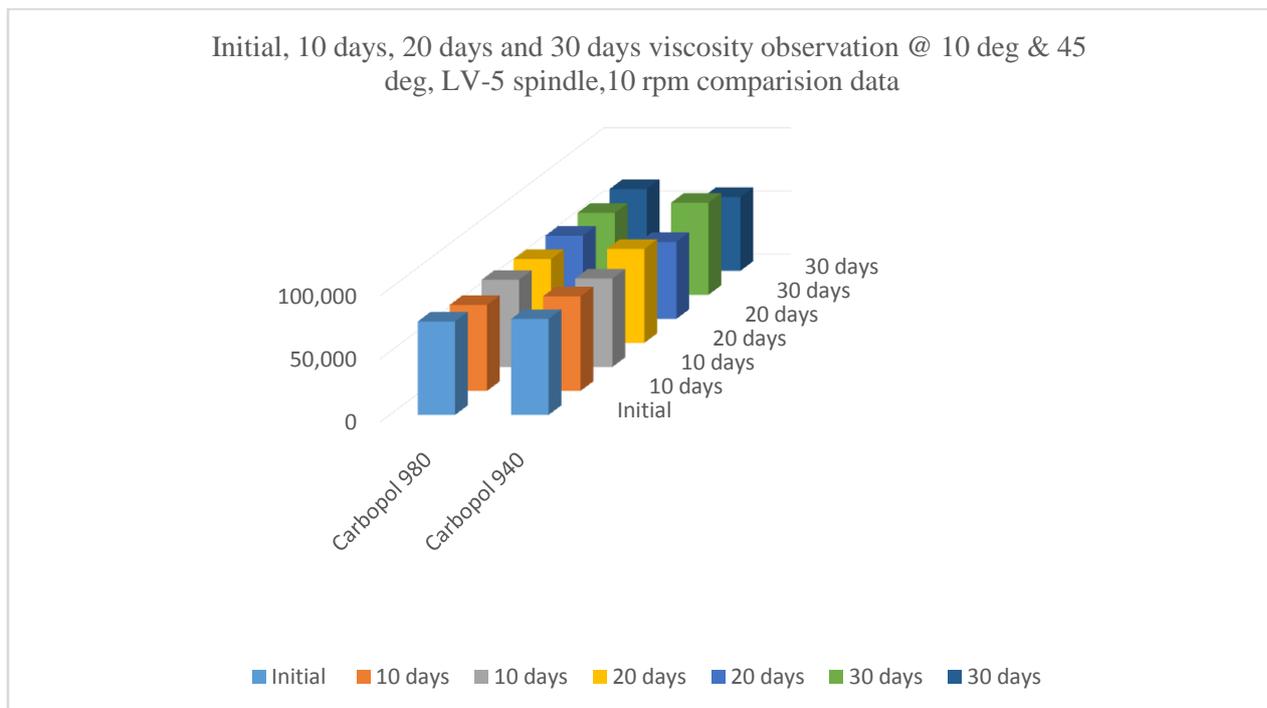
Oscillatory shear responses (G' or elastic modulus, and G'' or loss/viscous modulus) were determined at low strains over the frequency range 0.001–100 rad/s. The linearity of viscoelastic properties was verified for all the material at different conditions and different stages.

Results and discussions:

Viscosity properties:

The different Carbomer 0.5 % dispersion and pH-7.3 material viscosity property studied at Real time, 10 degree and 45 degree at different intervals like 10 days, 20 days and 30 days by using Brook field DV-II +Pro viscometer,

Fig-I: Initial, 10 days, 20 days and 30 days Viscosity profiles at 10 degree and 45 degree, LV-5 spindle, 10 rpm.



The initial, 10 days, 20 days and 30 days Viscosity at 10 degree and 45 degree viscosity profiles of Carbomer 980 and Carbomer 940, materials are plotted in Fig-I, the viscosity profiles at 45 degree there is difference initial viscosity, 10 days, 20 days and 30 days viscosity profile of Carbomer 940 material and these two materials

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viscosity decreasing at 20 days and 30 days study, the viscosity profile of Carbomer 980 material viscosity slightly decreasing the viscosity at 10 degree and 45 degree from initial 10, 20 and 30 days there no much difference in viscosity, so it shows Carbomer980, at 0.5 % dispersionand pH-7.3 the material isbest for freezer and accelerated cosmetic formulations,

Flow curve:

A flow curve, viscosity versus shear rate, across a wide range of shear rates Newtonian flow is the simplest type, displaying as shear-independent viscosity while the material is sheared. Water and some low-molecular-weight mineral oils are typical examples of Newtonian fluids. Pseudo-plastic or shear thinning fluids display viscosity reduction while the shear rate increases. Typical examples of these are colloidal systems. The colloidal structure breaks down while shear rate increases, displaying reduced viscosity. Dilatant or shear thickening flow, in which viscosity increases with shear rate, is seldom encountered in the pharmaceutical and cosmetics fields.

Steady state viscosities of two samples were measured for a temperature range covering 10 to 45°C at 10 days increments. For clarity, the flow curves at only two different temperatures for samples viscosity flow curve are shown in Fig. II to VIII, It is apparent from Fig. II to VIII that carbomer gels exhibit remarkable temperature stability. For a particular shear rate, viscosity of these materials change appreciably with change in temperature. Weak temperature dependency of carbomers gels is also supported by experimental literature (20 & 21). The temperature stability or insensitivity can be explained in terms of the elastic or cross-link structure of the micro gels thermal fluctuation or increased thermal mobility of the polymer chain strands are suppressed by the cross-link junctions. Therefore viscosity does not change appreciably with temperature.

The flow curves for different temperatures were fitted with Ostwald's model (22) $\tau = K \dot{\gamma}^n$. The fluidity or power law index n in this equation represents departure from Newtonian behavior ($n = 1$ for Newtonian fluids) and is a measure of pseudo plastic or shear thinning extent of the fluid. It can be interpreted as the rate of change of structure with shear rate ($\dot{\gamma}$) (23). The gel network structure can be changed due to deformation induced changes in shapes of the microgel particles, alignment of polymer chain segments, and decrease in the number of entanglements between polymer chain segments and side chains. In accordance with this argument, the values of n will be lower in case of stronger gels due to increased noncovalent forces of attraction between neighboring particles, which increase lifetime of the temporary entanglement junctions.

The Initial, 10 days, 20 days and 30 days Viscosity v/s shear rate at 10 degree flow curve profiles of Carbomer980 and Carbomer 940materials are plotted in Fig-II, III, IV and V, the flow curve profiles at 10 degree there is no much differences in initialto 30 days viscosityand shear rateof flow curve profile of twomaterials but slightly decreasing the viscosity but there is differ in shear rate so it shows at 10 degree the flow cure profiles of Carbomer 980 and Carbomer 940 at 0.5 % dispersionand pH-7.3 are not effectedto Freezer cosmetic formulations

Figure-II: Flow curve, Initial (0.5 % dispersion, pH – 7.3)

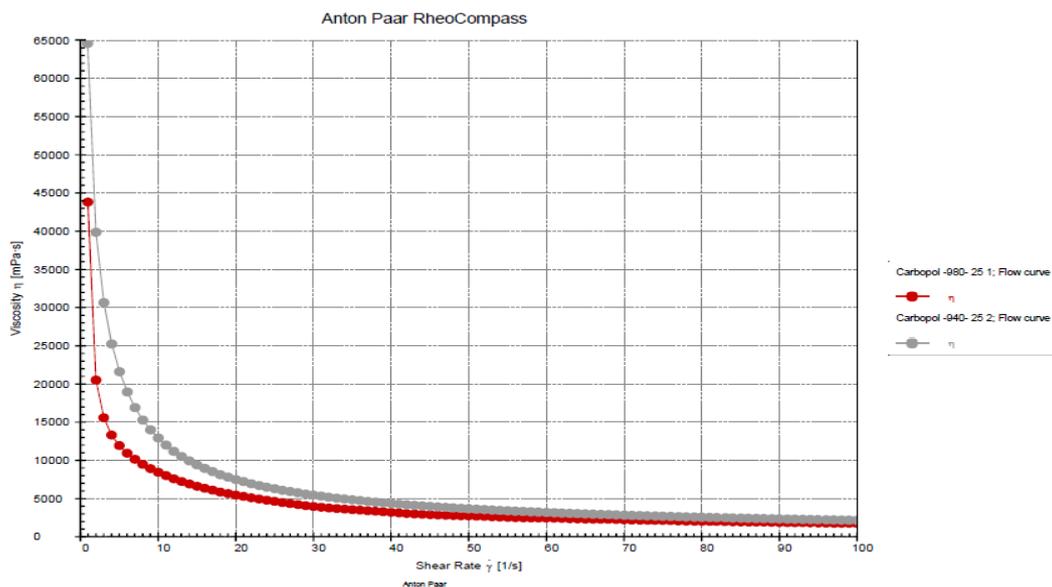


Figure-III: Flow curve, 10 degree- 10 days (0.5 % dispersion, pH – 7.3)

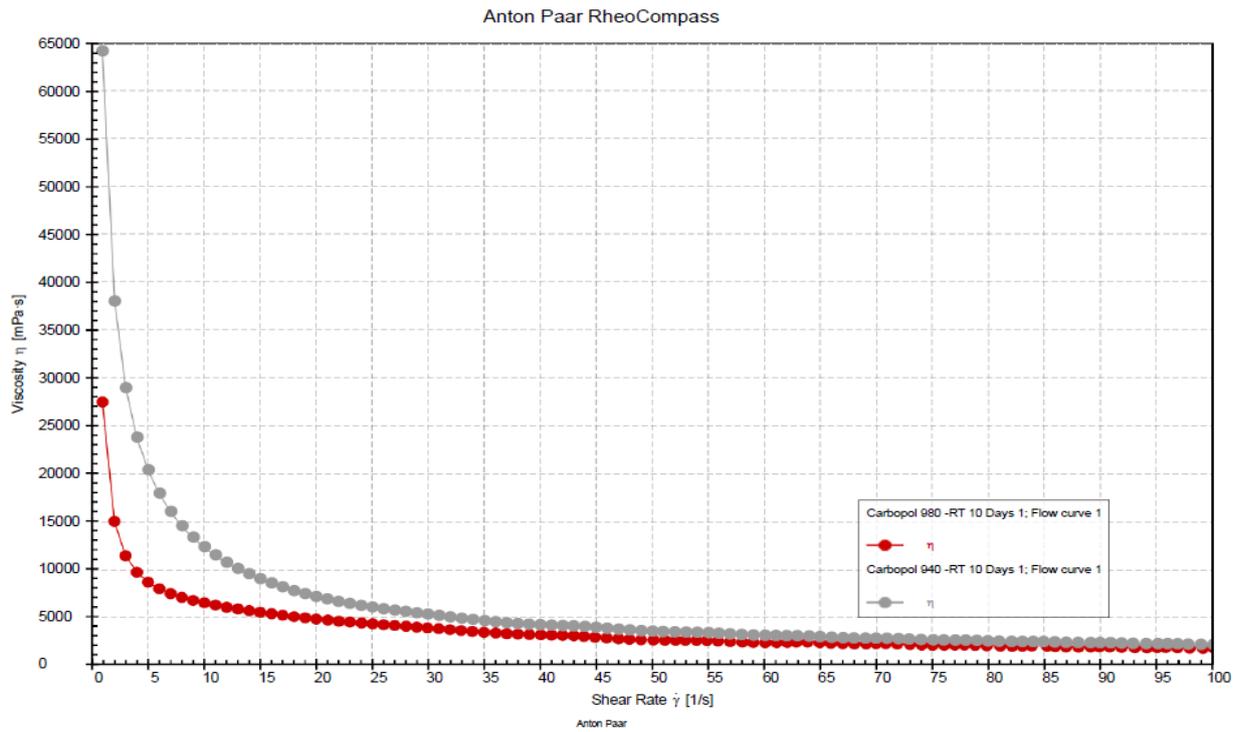


Figure-IV: Flow curve, 10 degree- 20 days (0.5 % dispersion, pH – 7.3)

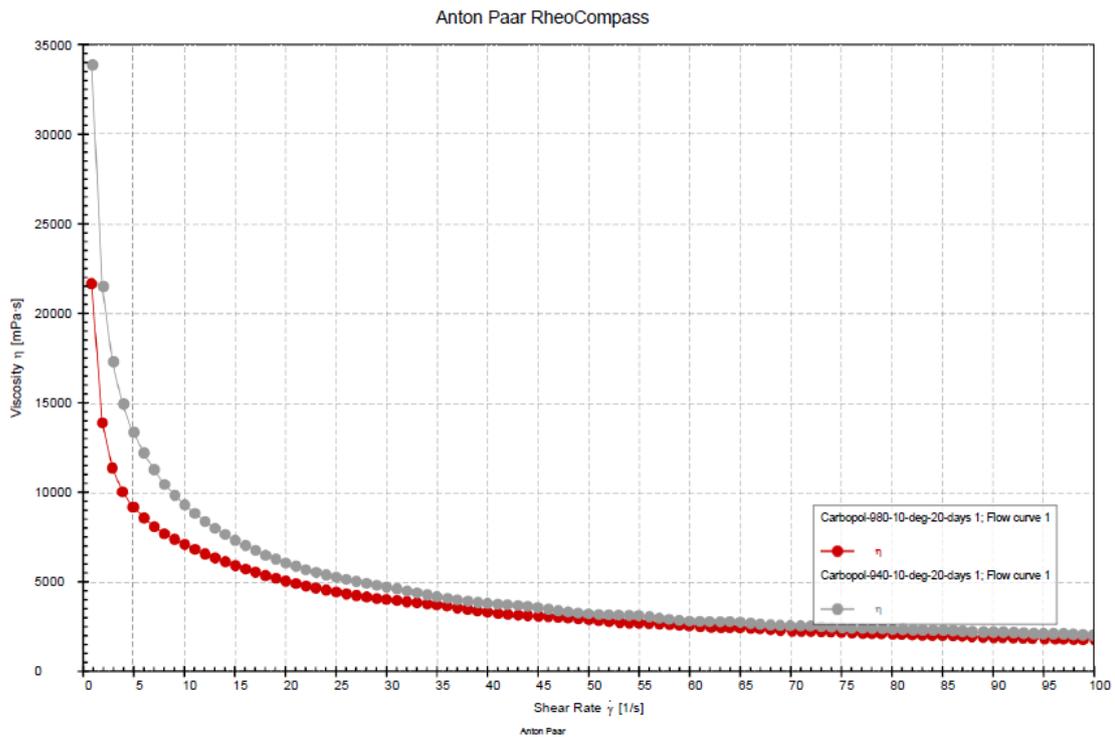
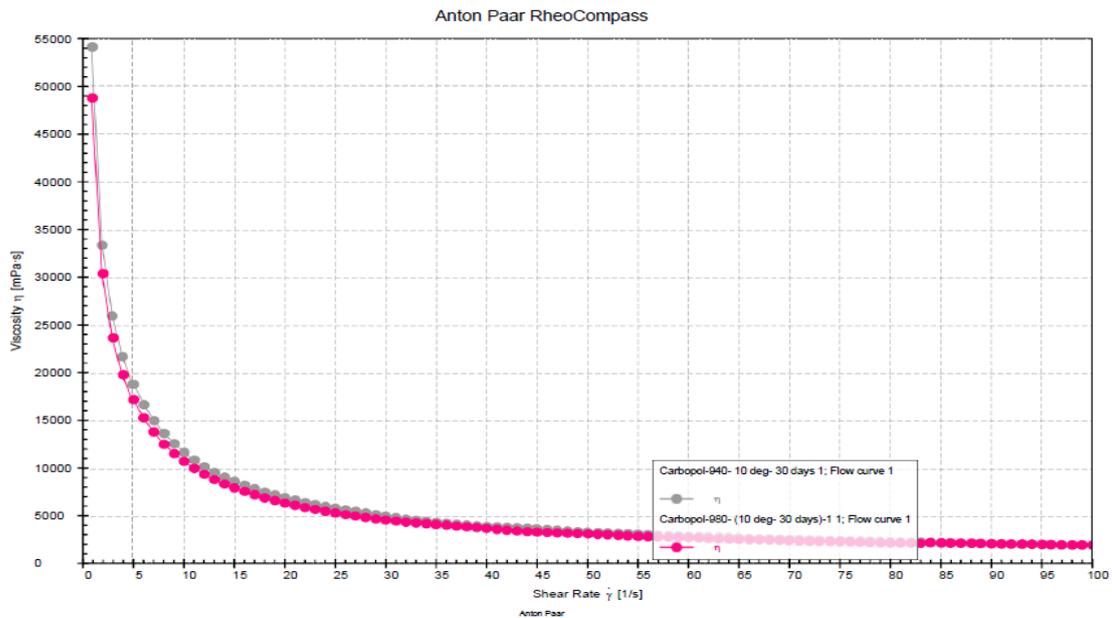


Figure-V: Flow curve, 10 degree- 30 days (0.5 % dispersion, pH – 7.3)



The 10 days, 20 days and 30 days Viscosity vs shear rate at 45 degree flow curve profiles of Carbomer 980 and Carbomer 940 materials are plotted in Fig-VI, VII and VIII the flow curve profiles at 45 degree there is much difference in shear rate, 10 days, 20 days and 30 days flow curve profile of Carbomer 980 materials slightly decreasing the viscosity, there is no difference in shear rate flow curve profiles, so it shows Carbomer 980 is stable at 0.5 % concentration and pH-7.3 and it is suitable for cosmetic formulations.

Figure-VI: Flow curve, 45 degree- 10 days (0.5 % dispersion, pH – 7.3)

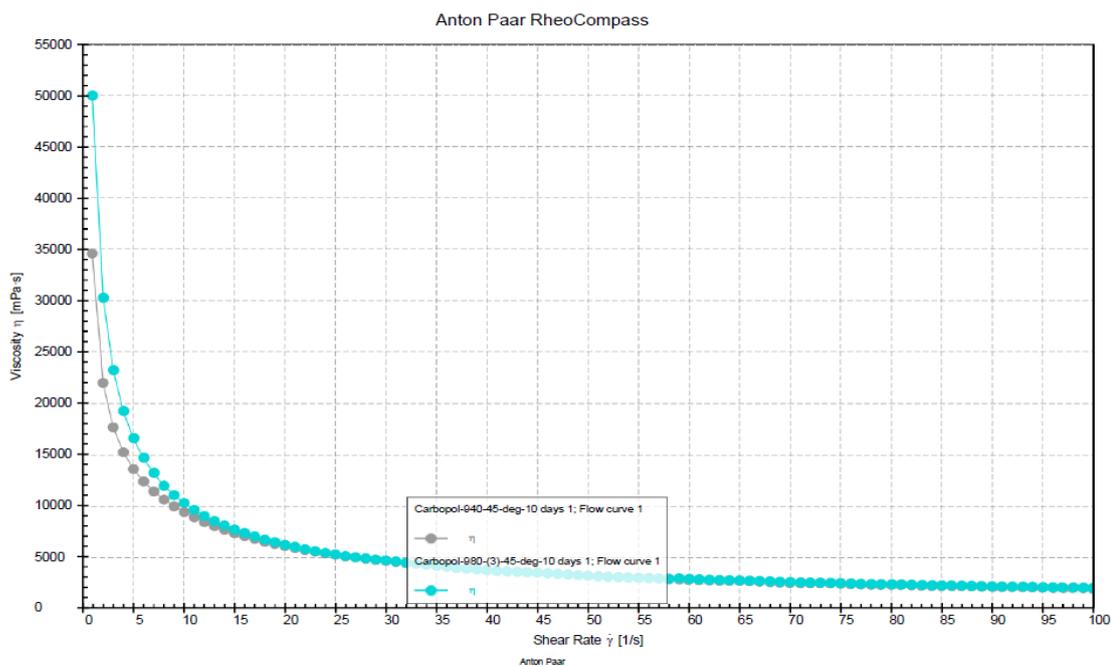


Figure-VII: Flow curve, 45 degree- 20 days (0.5 % dispersion, pH – 7.3)

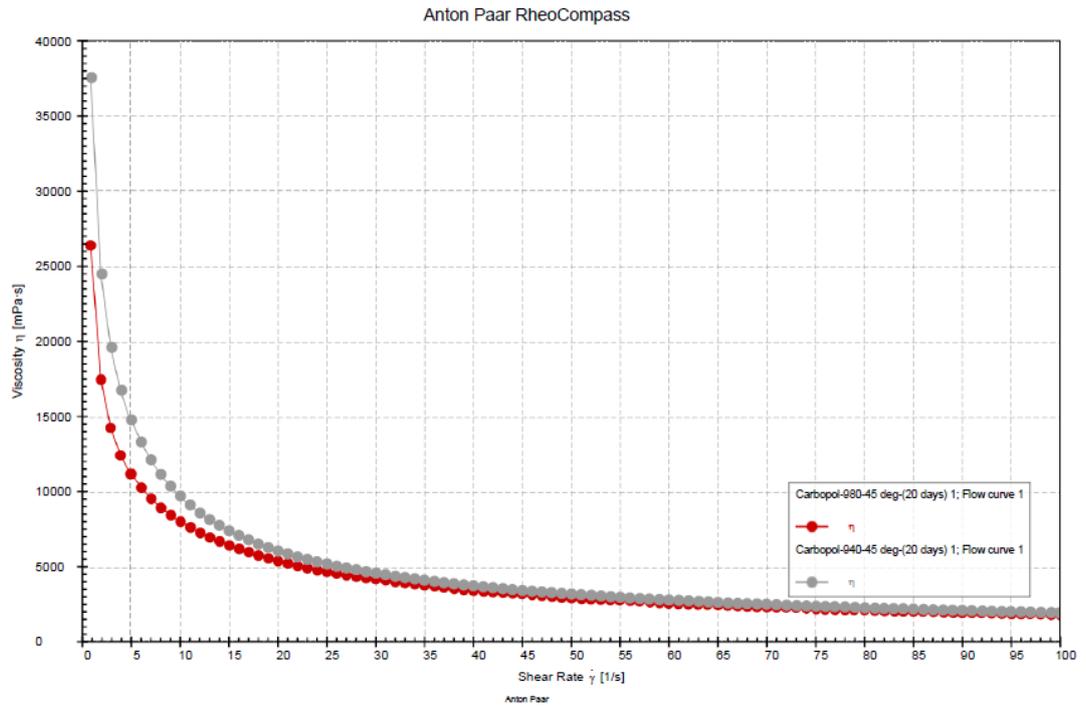
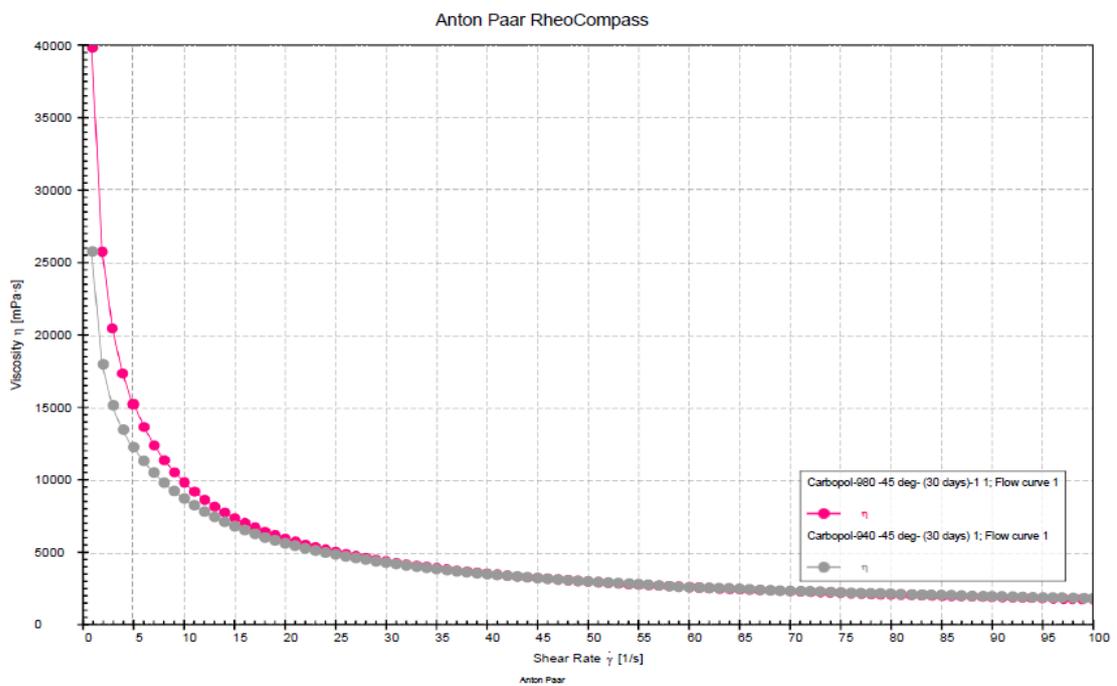


Figure-VIII: Flow curve, 45 degree- 30 days (0.5 % dispersion, pH – 7.3)



Amplitude sweep Test:

Strain sweep experiments were typically performed at constant oscillating frequencies with increased strain from 0.001 to 10. Little differences in the G'' and $\tan(\delta)$ [$\tan(\delta) = G''/G'$] profiles of these materials were observed at different constant frequencies (0.01 Hz, 1 Hz, 100 Hz) (Fig. I to IV). The observations further substantiates that the gels' responses are elastic in the frequency range 0.01 to 100 Hz.

As evident from Fig. I to IV, the complex modulus is dominated by the elastic contribution at low strains. For sample Carbomer 980 up to a strain of about 10%, the loss modulus (G'') is less than 20% of the elastic modulus indicating full elasticity of the system. In this regime, the gel network can be considered as closely packed hard sphere dispersion. At higher strains, the elastic structure breaks down and consequently the elastic modulus decreases steeply with increasing strain (Fig. I to IV). A crossover strain (γ_c) can be identified above which the gels behave predominantly as liquid because G'' becomes greater than G' [$\tan(\delta) > 1$]. Because Carbomer concentration is same in all five samples, the breakdown strain is similar ($\gamma_c = 0.8 \pm 0.2$). The collapse of the gel structure at such low strains is indicative of a closer packing of the microgel particles (24), smaller spheres lead to a lower breakdown strain.

The 10 degree Initial, 10 days, 20 days and 30 days strain sweep experiment were typically performed at constant oscillating frequencies with increased strain from 0.001 to 10. Little differences in the G' and $\tan(\delta)$ [$\tan(\delta) = G''/G'$] profiles of these materials were observed at different constant frequencies (0.01 Hz, 1 Hz, 100 Hz) (Fig. I to IV). The observations further substantiates that the gels' responses are elastic in the frequency range 0.01 to 100 Hz, at 10 degree strain sweep experiment of Carbomer 980 and Carbomer 940 samples are plotted in Fig-I, II, III and IV, the elastic structure breaks down and consequently the elastic modulus decreases steeply with increasing strain. A crossover strain (γ_c) can be identified above which the gels behave predominantly as liquid because G'' becomes lesser than G' [$\tan(\delta) < 1$]. Because Carbomer concentration is same in all five samples, the breakdown strain is similar. The collapse of the gel structure at such low strains is indicative of a closer packing of the microgel particles(24), smaller spheres lead to a lower breakdown strain.

At 10 degree strain sweep experiment of Carbomer 980 and Carbomer 940 materials are plotted in Fig-I, II, III and IV, the elastic structure not breaks down and consequently the elastic modulus stable with increasing strain. A crossover strain (γ_c) can be identified above which the gels behave predominantly as liquid because G'' becomes greater than G' [$\tan(\delta) > 1$]. Yield stress can be defined as the minimum stress that must be applied before the starts to flow (25). This is an important parameter for carbomers. Yield stress of Carbomer 980 material the cross linked microgel structure where individual particles are closely packed with their neighbors is responsible for yield stress. The magnitude of the yield stress is a measure of the strength of the closed pack structure that must be exceeded for the material to flow appreciably. Because Carbomer 980 yield stress value is more compare to Carbomer 940.

Figure-I: Amplitude sweep initial (0.5 % dispersion, pH – 7.3)

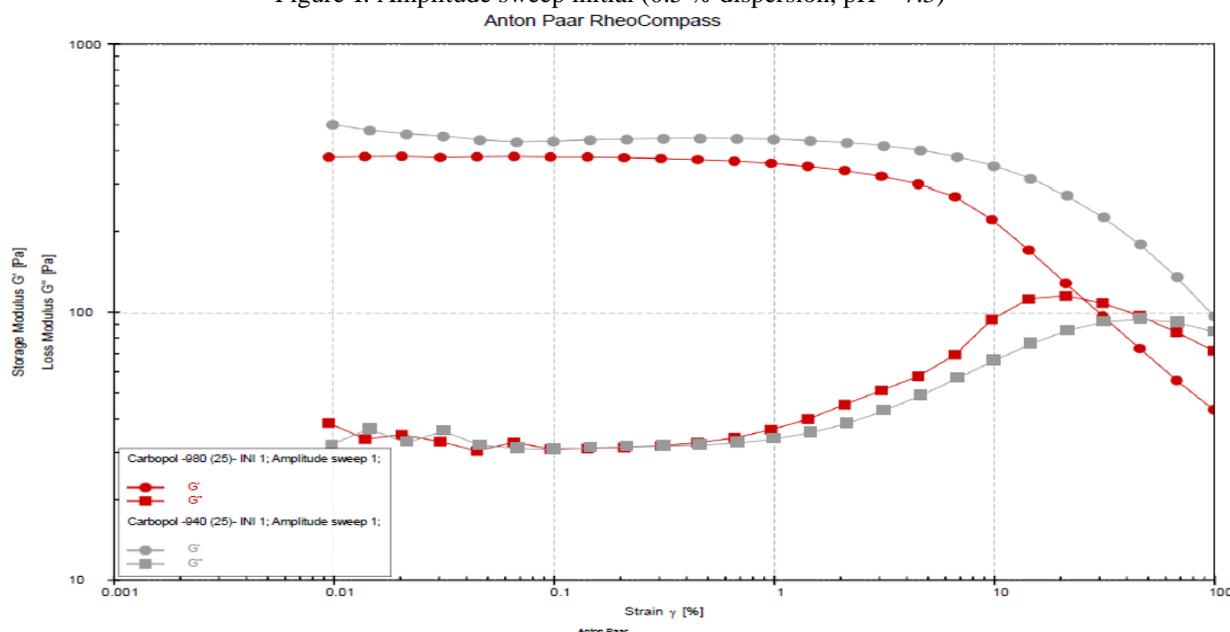


Figure-II: Amplitude sweep, 10 degree-10 days (0.5 % dispersion, pH – 7.3)

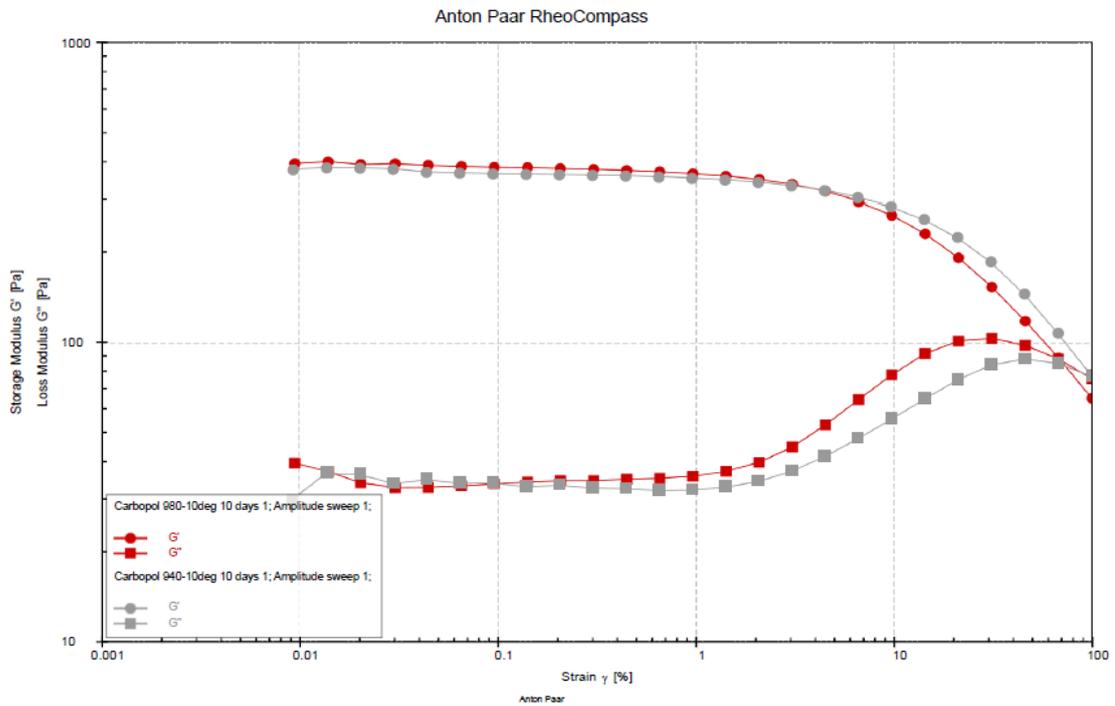


Figure-III: Amplitude sweep, 10 degree-20 days (0.5 % dispersion, pH – 7.3)

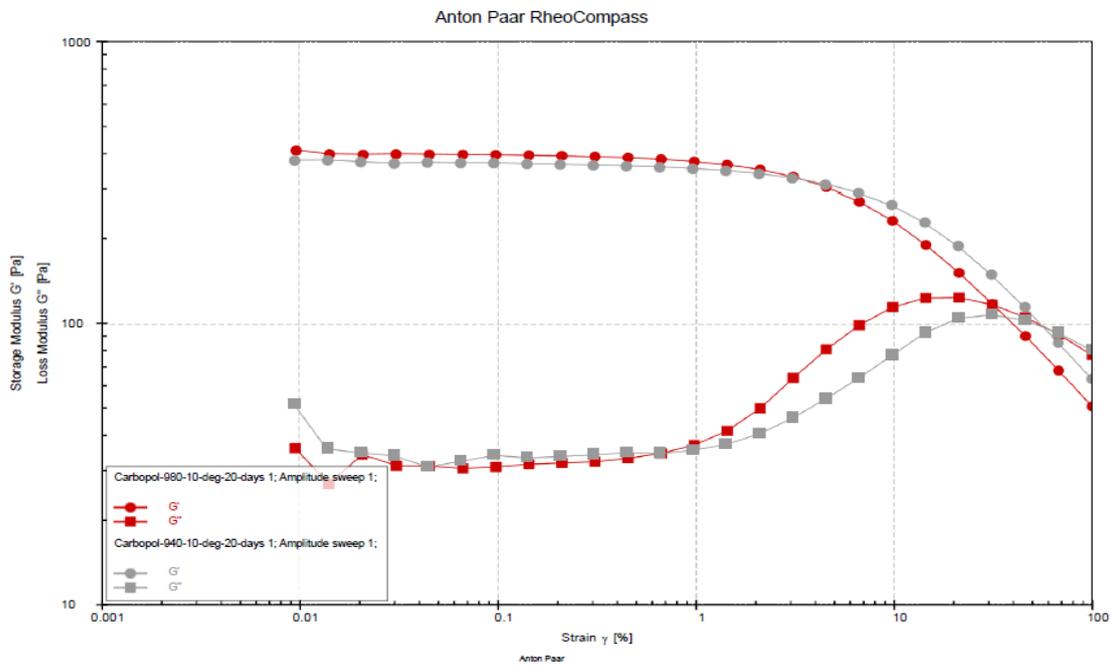
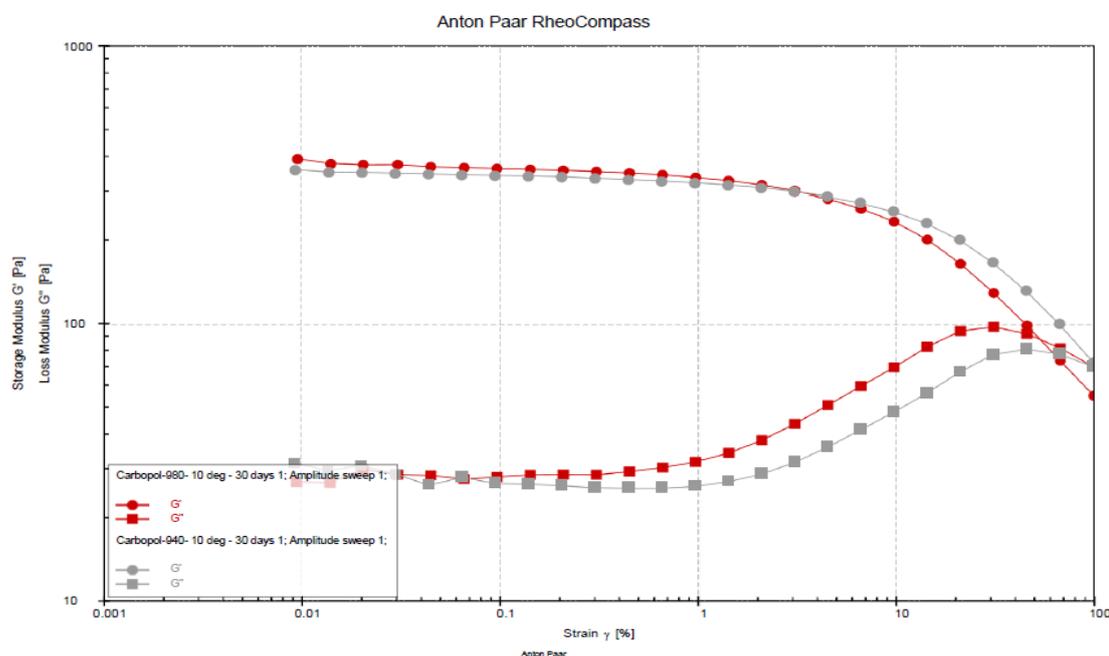


Figure-IV: Amplitude sweep, 10 degree-30 days (0.5 % dispersion, pH – 7.3)



The 45 degree, 10 days, 20 days and 30 days strain sweep experiment were typically performed at constant oscillating frequencies with increased strain from 0.001 to 10. Little differences in the G' and $\tan(\delta)$ [$\tan(\delta) = G''/G'$] profiles of these materials were observed at different constant frequencies (0.01 Hz, 1 Hz, 100 Hz) (Fig. V to VII). The observations further substantiates that the gels' responses are elastic in the frequency range 0.01 to 100 Hz, at 45 degree strain sweep experiment of Carbomer 980 and Carbomer 940 materials are plotted in Fig-V, VI and VII, the Carbomer 940 elastic structure breaks down and consequently the elastic modulus decreases steeply with increasing strain. A crossover strain (γ_c) can be identified above which the gels behave predominantly as liquid because G'' becomes lesser than G' [$\tan(\delta) < 1$]. Because Carbomer concentration is same in two materials, the breakdown strain is similar. The collapse of the gel structure at such low strains is indicative of a closer packing of the microgel particles(24), smaller spheres lead to a lower breakdown strain. At 45 degree strain sweep experiment of Carbomer 980 and Carbomer 940 materials are plotted in Fig-I, II, III and IV, the elastic structure not breaks down and consequently the elastic modulus stable with increasing strain. A crossover strain (γ_c) can be identified above which the gels behave predominantly as liquid because G'' becomes greater than G' [$\tan(\delta) > 1$]. Yield stress can be defined as the minimum stress that must be applied before the starts to flow (25). This is an important parameter for carbomers. Yield stress of Carbomer 980 sample the cross linked microgel structure where individual particles are closely packed with their neighbors is responsible for yield stress. The magnitude of the yield stress is a measure of the strength of the closed pack structure that must be exceeded for the material to flow appreciably. Because Carbomer 980 yield stress value is more compare to Carbomer 940.

Figure-5: Amplitude sweep, 45 degree-10 days (0.5 % dispersion, pH – 7.3)

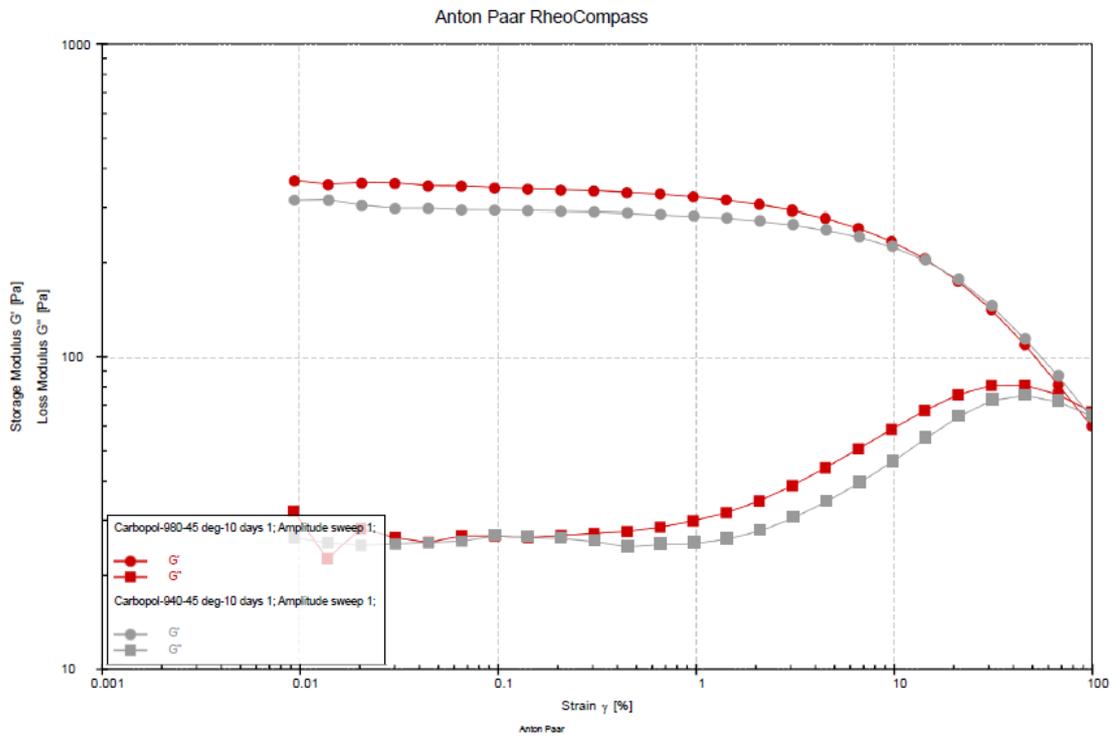


Figure-6: Amplitude sweep, 45 degree-20 days (0.5 % dispersion, pH – 7.3)

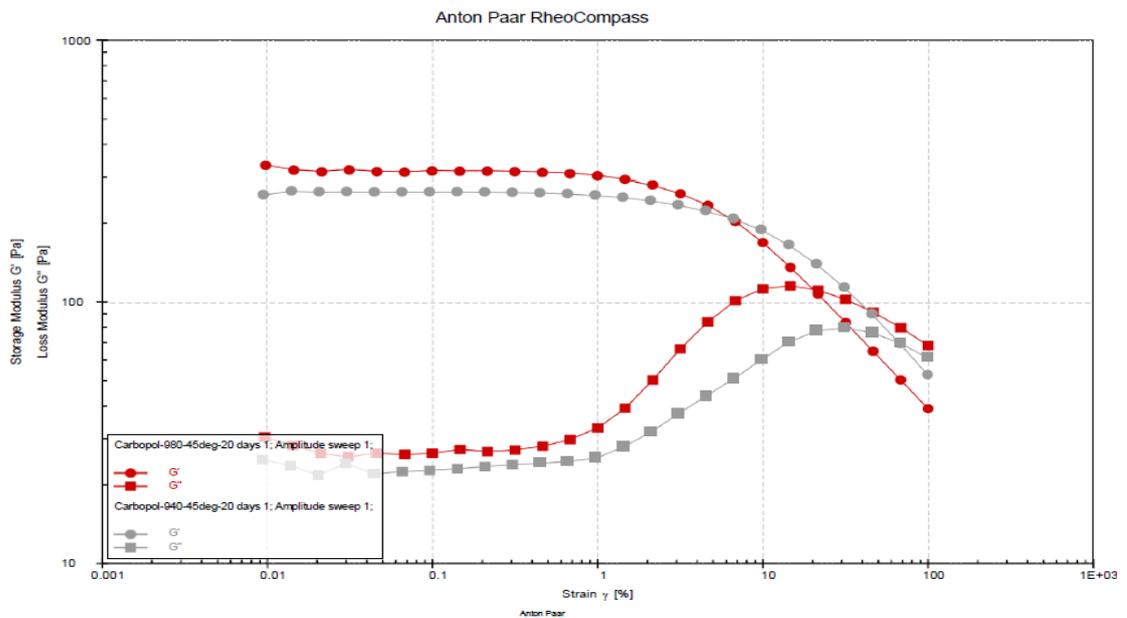
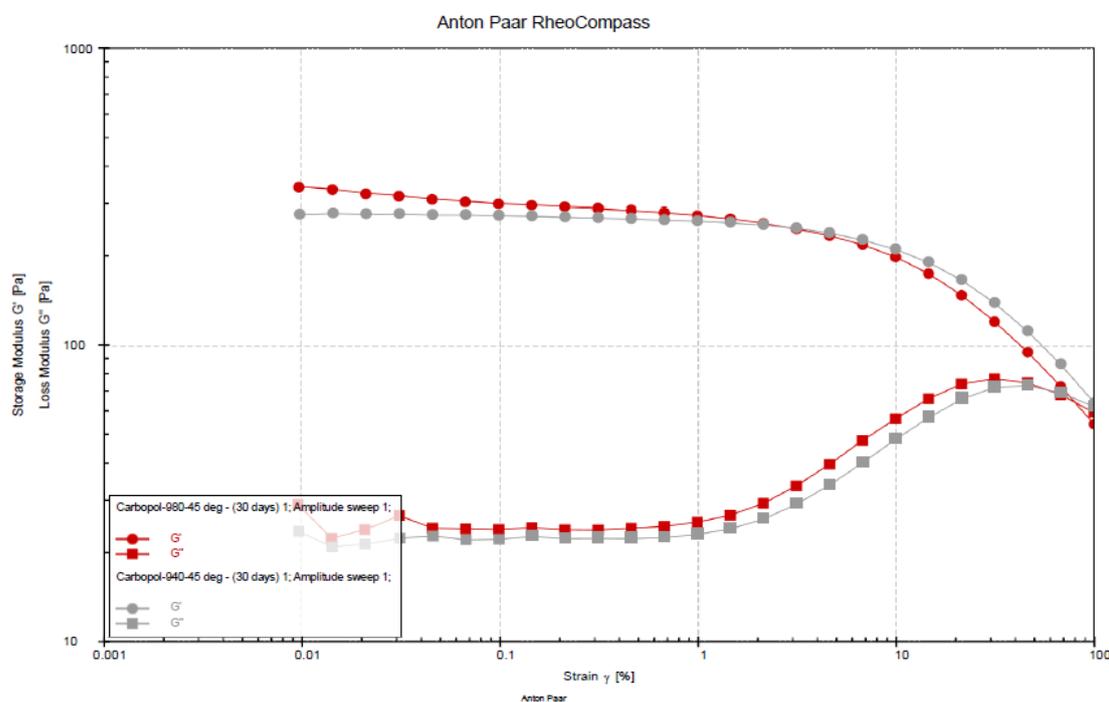


Figure-7: Amplitude sweep, 45 degree-30 days (0.5 % dispersion, pH – 7.3)



Conclusions:

From this study, it can be concluded that out of two pharmacopeia grades of Carbomers used neutralized with 18% NaOH by pH 7.3, and 0.5 % dispersion Carbomer 980 was found to be the best in modifying the rheological and viscosity properties of nano-scaled emulsion designed for topical application.

Neutralizing 0.5 % dispersion of Carbomer 980 by 18% NaOH made this polymer stronger as a gelling agent and as a rheology modifier, since the calculated intrinsic viscosity of the sample studied. Yield stress is a critical parameter for characterizing a wide variety of complex fluids, and is a key factor for many real-life processes and applications involving Carbomer 980 material. In order to obtain relevant, robust and reproducible yield stress. The excellent rheology and suspension performance, efficient thickening, able to thicken over a broad pH range, including low pH system, electrolyte tolerance, rich sensory, high clarity to use, and it is better application of cosmetic facial lotions and gels, body lotions, creams and sunscreen products.

References:

- [1]. Baroli B, López-Quintela MA, Delgado-Charro MBA, Fadda AM and Blanco-Méndez J (2000). Microemulsions for topical delivery of 8-methoxsalen. *J. Control. Release.*, **69**: 209-218.
- [2]. Puglia C, Liotta M, Drechsler M, Rizza L and Bonina F (2006). Evaluation of in vitro percutaneous absorption of glycyrrhetic acid from nanoemulsions obtained by the phase inversion temperature (PIT) method. 5th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Switzerland.
- [3]. Yilmaz E and Borchert HH (2006). Effect of lipid containing, positively charged nanoemulsions on skin hydration, elasticity and erythema: An in vivo study. *Int. J. Pharm.*, **307**: 232-238.
- [4]. Baboota S, Shakeel F, Ahuja A, Ali J and Shafiq S (2007). Design, development and evaluation of novel nanoemulsion formulations for transdermal potential of celecoxib. *Acta. Pharm.*, **57**: 315-332.
- [5]. Zhu W, Guo C, Yu A, Gao Y, Cao F and Zhai G (2009). Microemulsion-based hydrogel formulation of penciclovir for topical delivery. *Int. J. Pharm.*, **378**: 152-158.
- [6]. Mou D, Chen H, Du D, Mao C, Wan J, Xu H and Yang X (2008). Hydrogel-thickened nanoemulsion system for topical delivery of lipophilic drugs. *Int. J. Pharm.*, **353**: 270-276.
- [7]. Kim JY, Song JY, Lee EJ and Park SK (2003). Rheological properties and microstructures of Carbopol® gel network system. *Colloid. Polym. Sci.*, **281**: 614-623.

- [8]. Neau SH, Chow MY, Hileman GA, Durrani MJ, Gheyas F and Evans BA (2000). Formulation and Process considerations for beads containing Carbopol® 974P, NF resin made by extrusion-spheronization. *Int. J. Pharm.*, **199**: 129-140.
- [9]. Lubrizol Advanced Materials Inc. Pharmaceutical Bulletin 6 (2008). Thickening Properties. Cleveland, Ohio, The Lubrizol Corporation.
- [10]. Piau JM (2007). Carbopol® gels: Elastoviscoplastic and slippery glasses made of individual swollen sponges: Meso- and macroscopic properties, constitutive equations and scaling laws. *J. Nonnewton. Fluid. Mech.*, **144**: 1-29.
- [11]. Hosmani AH, Thorat YS and Kasture PV (2006). Carbopol® and its Pharmaceutical Significance: A Review. *Pharma. Rev.*, **4**. Available at: <http://www.pharmainfo.net/reviews/carbopol-and-itspharmaceutical-significance-review> Accessed on 10 May 2011.
- [12]. Lubrizol Advanced Materials Inc. TDS-222 (2008). Molecular Weight of Carbopol® and Pemulen™ Polymers Cleveland, Ohio, The Lubrizol Corporation.
- [13]. Lu G and Jun HW (1998). Diffusion studies of methotrexate in Carbopol® and Poloxamer gels. *Int. J. Pharm.*, **160**: 1-9.
- [14]. Fresno MJC, Ramírez AD and Jiménez MM (2002). Systematic study of the flow behaviour and mechanical properties of Carbopol® Ultrez(TM) 10 hydroalcoholic gels. *Eur. J. Pharm. Biopharm.*, **54**: 329-335.
- [15]. Lubrizol Advanced Materials Inc. TDS-237 (2009). Neutralizing Carbopol® and Pemulen™ Polymers in Aqueous and Hydroalcoholic Systems Cleveland, Ohio, The Lubrizol Corporation.
- [16]. Blanco-Fuente H, Anguiano-Igea S, Otero-Espinar FJ and Blanco-Méndez J (1996). In-vitro bioadhesion of carbopol hydrogels. *Int. J. Pharm.*, **142**, 169-174.
- [17]. Welin-Berger K, Neelissen JAM and Bergenståhl B (2001). The effect of rheological behaviour of a Topical anaesthetic formulation on the release and permeation rates of the active compound. *Eur. J. Pharm. Sci.*, **13**: 309-318.
- [18]. Garciano L, Torisu, R, Takeda, J. and Yoshida, J. (2001), "Resonance Identification and Mode Shape Analysis of Tractor Vibrations" *J. JSAM* 63: 45-50.
- [19]. Ghezzehei, T. A., and D. Or, 2001. Rheological Properties of Wet Soils and Clays under Steady and Oscillator Stresses. *Soil Sci. Soc. Am. J.* 65: 624-637.
- [20]. J. Y. Kim, J. Y. Song, E. J. Lee, and S. K. Park. Rheological properties and microstructures of Carbopol gel network system. *Colloid Polym. Sci.* **281**: 614-623 (2003).
- [21]. H. N. Nae and W. W. Reichert. Rheological properties of lightly crosslinked carboxy copolymers in aqueous solutions. *Rheol. Acta* **31**: 351-360 (1992).
- [22]. R. B. Bird, R. C. Armstrong, and O. Hassager. *Dynamics of Polymer Liquids*, 2nd Ed., Wiley, New York, 1987.
- [23]. A. Ramirez, M. J. Fresno, M. M. Jimenez, and E. Selles. Rheological study of Carbopol (R) Ultrez (TM) 10 hydroalcoholic gels, I: Flow and thixotropic behavior as a function of pH and polymer concentration. *Pharmazie* **54**: 444-447 (1999).
- [24]. R. J. Ketz, R. K. Prud'homme, and W. W. Graessley. Rheology of concentrated microgel solutions. *Rheol. Acta.* **27**: 531-539 (1988).
- [25]. H. A. Barnes. A brief history of the yield stress. *Appl. Rheol.* **9**: 262-266 (1999).