Rheometric Characterization of Carbopol974p for application in controlled drug delivery

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भारतीय प्रौद्योगिकी संस्थान हैदराबाद
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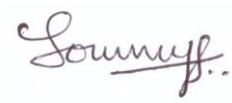

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This thesis entitled "Rheometric Characterization of Carbopol974p for application in controlled drug delivery" by Bandi Sowmya is approved for the degree of Master of Technology from IIT Hyderabad.

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Dedicated to

Family members.

Abstract

Carbopol974p is a poly acrylic acid which contains carboxylic acid groups. Carbopol974p has major application in controlled drug delivery as a drug carrier for treating diseases related to human digestive tract. The rheological properties of Carbopol974p vary in the pHs (1.5 to 8.5) and temperatures (36.5°C to 39.5°C) of the human digestive tract, and have not been documented. Rheological measurements were carried out on Carbopol974p samples using shear rheometer (Anton Paar Physica MCR301) with Cone and Plate geometry (Plate diameter was 75mm, and cone angle was 2°). Carbopol974p has pH 3.38 when made-up with distilled water at a concentration of 1.7% (w/v). Carbopol974p of pHs 4.5, 5.5, 6.5, 7.5 and 8.5 were prepared using buffer solutions of pH 4, pH 9.2, and pH 11. Steady state rheological measurements were conducted to characterize the Carbopol974p samples at different pHs and temperatures. Temperature ramp test was also conducted to record the effect of temperature on viscosity of Carbopol974p.

Results of the flow test (viscosity versus shear rate data) showed that Carbopol974p exhibits non-Newtonian shear thinning behavior at all the temperatures and pHs tested. Constant shear test (viscosity versus time data) showed that Carbopol974p exhibits thixotropic behavior at a (constant) shear rate of $0.1s^{-1}$ and only shear thinning behavior at shear rate of $10s^{-1}$. Hysteresis test (viscosity during ramp up and ramp down of shear rate) showed that there was a non-zero area under the curve at low shear rates (quantitative values were different for various pHs and temperatures) whereas the area was zero at high shear rates. Results from temperature ramp test showed that the viscosity of Carbopol974p decreases as temperature rises, and the effect of temperature on Carbopol974p increases as pH increases. Results of all the rheological measurements showed that the viscosity of Carbopol974p increases as pH increases.

Glossary

Acrylic acid : A pungent organic acid with molecular formula CH_2=CHCOOH, which contains a vinyl group connected with unsaturated carboxylic acid group.

Polyacrylic acid : The polymer of acrylic acid with trade name carbomer or carbopol.

Carbopol974p : A high molecular weight polymer from the family of carbopols, with molecular formula $(C_3H_4O_2)_n$

Micro structure : Structure of a material at micro level.

Shear rate : Ratio of relative velocity of a fluid layer with respect to a layer below it to the distance between two layers. Or the rate of deformation of fluid when it is sheared, units [s^{-1}].

Shear stress : Force applied (shear force) on a material per unit area perpendicular to the flow, symbol Tau (τ),γ° units [Pa].

Viscosity : Ratio of shear stress to shear rate or the resistance to flow of a material, symbol (μ), units [Pa.s]

Rheological properties : The properties of a material (except solids) which describe its flow behavior and characterization.

Rheometry : A technique used to measure rheological properties of the materials.

Rheometer : An equipment or a device used for measuring rheological properties.

Flow curve : The curve relating shear stress and shear rate applied on a material.

Hysteresis : A phenomenon that the physical property of a material after certain cause lags behind the same physical property before the cause.

Drug : A medicine or a chemical compound used for curing or controlling diseases.

Contents

Declaration........ii
Approval Sheet........iii
Acknowledgements........iv
Abstract........vi

Glossary vii

1 Introduction........1

1.1 Carbopols........1
1.2 Rheometry........2
1.2.1 Rheometer........2
4.2.2 Geometries........3
1.3 Thixotropy........3
1.4 Literature Survey........4

2 Materials and Methods........5

2.1 Chemicals and Equipment........5
2.1.1 Samples Preparation........6
2.2 Experimental Procedure........7
2.2.1 Flow test........8
2.2.2 Constant Shear test........9
2.2.3 Hysteresis test........10
2.2.4 Temperature Ramp test........11

3 Results........12

3.1 Viscosity versus Shear rate (Flow test)........13
3.2 Viscosity versus Time (Constant Shear test)........15
3.3 Hysteresis test........17
3.4 Viscosity versus Temperature (Temperature Ramp test)........19
3.5 Microscopic Analysis........20

4 Dicussion........21

4.1 Viscosity versus Shear rate (Flow test)........21
4.2 Viscosity versus Time (Constant Shear test)........22
4.3 Hysteresis test........23

4.4 Viscosity versus Temperature (Temperature Ramp test) 24
4.5 Effect of pH on Carbopol974p..25
4.6 Microscopic Analysis..25
4.7 Conclusions..26

5. References..27

Chapter 1

Introduction

1.1 Carbopols

Carbopols are Poly Acrylic Acid (PAA) hydrogels. They primarily occur in the form of very soft powder. There are many compounds in the family of carbopols like Carbopol-Ex-214, Carbopol934, Carbopol940, Carbopol974p, Carbopol980, NoveonAA-1, etc. All of them are cross-linked polymers of the same monomer but have different number of monomers and different crosslinking agents. The numerical value in the name of a carbopol indicates its molecular weight- Tamburic and Craig (1995). The Carbopol molecular structure contains unbound carboxylic acid groups: hence it is acidic in nature. It has pH in the range of 3-4 when made up with distilled water.

Carbopols have applications in bio adhesive formulations and formation of viscous gels, emulsions, and suspensions. Some carbopols can also be used as drug carriers for controlled drug delivery because of their thixotropic behavior. In the family of carbopols, we have selected Carbopol974p for extensive study. Carbopol974p is said to exhibit thixotropic behavior, and finds use in the formulation of topical hydrogels- Lee et.al (2009). Its molecular structure is given in Fig.1.1.

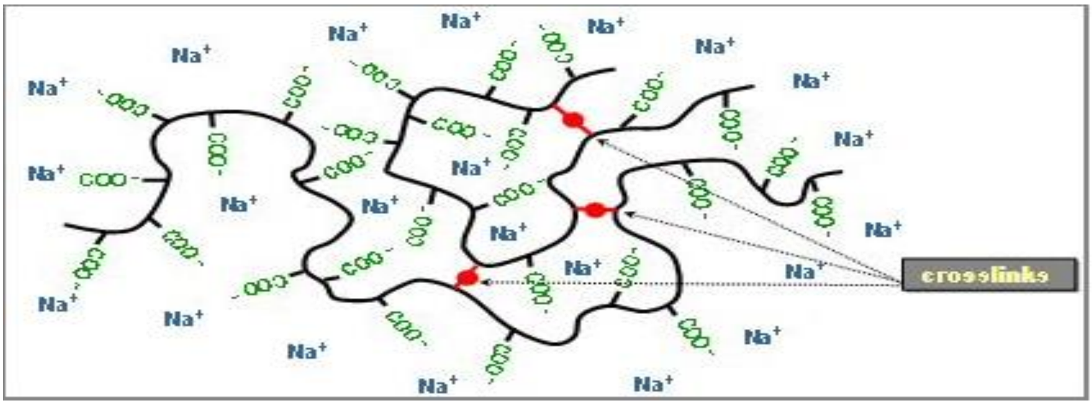

Fig. 1.1 Structure of Carbopol974p (Ref: https://www.chemicalbook.com)

Carbopol974p also has a major application as a drug carrier in controlled drug delivery. Specifically, it is used as a drug carrier in the administration of mangiferin ($C_{19}H_{18}O_{11}$) for increased absorption of mangiferin in the gastrointestinal tract- Wang et.al (2013). This is because therapeutic efficiency is limited by intestinal permeability of mangiferin. Investigations by Wang et al, (2013) involved combinations of mangiferin with Carbopol974p in a series of vivo experiments on Wistar rats: these revealed that when mangiferin was combined with Carbopol974p (100mg/kg) the oral bioavailability of mangiferin was increased by seven fold. This is due to adherence of Carbopol974p to the surface of intestinal tract which helps in localization of the drug and prolongs the residence time inside the tract (targeted site). The mechanism of increased absorption by the addition of Carbopol974p was described in three steps (see Wang et al. (2013)). A hydrogen bond formed between carboxyl groups of Carbopol974p and phenolic hydroxyl groups of mangiferin in gastric fluid. Carbopol974p adhered to the intestinal surface by formation of a strong hydrogel and released mangiferin through the channels of the gel structure. The hydrogen bond between Carbopol974p and mangiferin in the gastric fluid prevents the precipitation of mangiferin in it, and increase the bioavailability at the absorption site.

Carbopol974p also finds another application in drug delivery by incorporation into Eudragit($C_7H_7NO_3$), and use as a stabilizing agent for supersaturated levels of Itraconazole (ITZ: $C_{35}H_{38}Cl_2N_8O_4$)- see Miller et al. (2008). In this study in vivo experiments were carried out in male Sprague rats using 20% and 40% Carbopol974p formulations at acidic pH and neutral pH. Area under the dissolution curve (AUDC) calculations revealed that the adsorption of ITZ in small intestine was greater in 20% formulation than 40% formulation of Carbopol974p. Further, stabilization of supersaturated levels of ITZ were same with both the formulations, and was significantly higher than Eudragit carrier matrix. When Eudragit was used as a carrier of ITZ, precipitation occured immediately. Hence the residence time inside the intestinal tract was very less. However, when 20% Carbopol974p formulation was used there was a substantial decrease in release of ITZ from carrier matrix resulting in increased residence time favoring enhanced absorption. The mechanism for this phenomenon is the formation of a viscous gel of Carbopol974p due to its swelling behavior in neutral media, and thus retardation of the release of ITZ. This prolonged the contact time of drug with the intestinal tract. When the drug (along with carrier) is ingested, the carrier (Carbopol974p) is exposed to different pHs inside the body ranging from 1.5 (lower stomach) to 8.5(duodenum) as shown in Fig. 1.2. The carrier is also exposed to different temperatures of the body- 36.5 – 37.5°C (97.7 – 99.5°F) during normal condition and 37.5 –

39.5°C (99.5 – 102°F) during fever (see Marieb 2006). Rheological properties of a material are affected by changes in pH and temperature. This study records the rheological properties of Carbopol974p under conditions that are encountered when ingested, and summarize how they help in controlled drug delivery application.

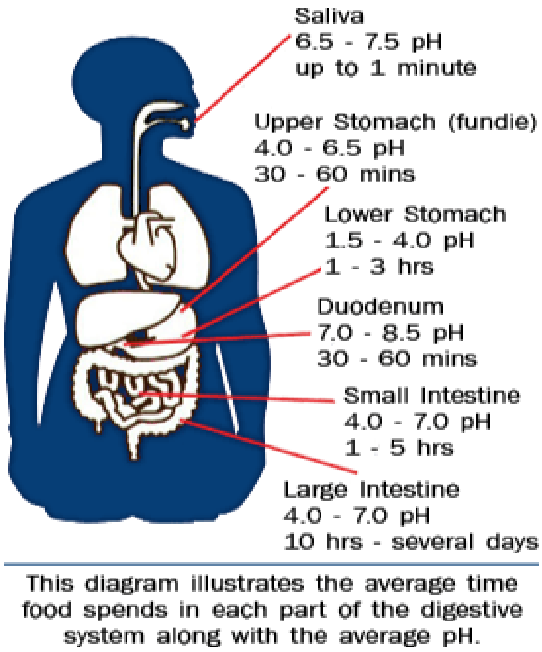

Fig. 1.2. average pHs recorded in each part of human digestive system
(Ref: Figure: www.homeschoolingforfree.org)

1.2 Rheometry

Rheometry is defined as an experimental technique used to study and analyze rheological properties of a material, or also as the study of flow of matter primarily in liquid state (sols, suspensions), but also of soft solids like gels-Mezger (2014). The primary rheological properties of a material are Viscosity, Yield Stress, and Shear Moduli (Storage and Loss Modulus).

The study of Rheology has relevance to practice of Chemical engineering, Civil engineering, Material Science engineering, Biomedical engineering, Physiology, and Geophysics. Some of the applications include benchmarking food and personal care products for ability to pump and spread, pre-formulation screening for therapeutics (especially biopharmaceuticals), evaluation of product application and final finish quality of paints and coatings.

1.2.1 Rheometer

Rheometer is the equipment used to record rheological properties of a material. Usually such equipment come along with software packages for processing the raw data recorded by the equipment and reporting it as meaningful material properties; examples of such software include Rheoplus, Rheocompass, Rheowin, Trios etc. There are two major types of mechanical rheometers, namely Shear rheometer and Extensional rheometer. The rheometer used in this study is the Anton Paar MCR301 rheometer which is a Shear rheometer.

1.2.2 Geometries

Geometry refers to the measuring device where the material sample is loaded, and which detects the material responses that are actually reported as rheological properties. Geometry is an important part of a rheometer because it acts as the interface between the instrument and the material. Any rheometer comes supplied with different types of geometries; we have to select one of these geometries based on the nature of the material (whether single-phase fluid, suspension, or gel, etc.) and the rheological properties to be measured. The geometries supplied with the MCR301 rheometer are Parallel plate (PP), Cone and Plate (CP), Concentric cylinder (CC), and Cup-and-Bob (CB): each geometry is described in detail below. The Parallel plate (PP) geometry is one wherein the sample is placed between two parallel plates with the bottom plate being stationary and top plate being rotated or oscillated. Cone and Plate(CP) geometry is one where the sample is placed between stationary plate (bottom) and a rotatable cone (top) which rotates or oscillates. Concentric Cylinder(CC) geometry is one where the sample is placed between two concentric cylinders, and the bottom/inner one is stationary and top/outer cylinder is rotating or oscillating. The last geometry is Cub and Bob type: in this geometry the sample is placed between stationary bottom Cup and moving top hollow Bob. Hence, the samples will be in contact with both sides of the bob. The rotation or oscillation of the geometries depends upon the input given in the software by the user.

1.3 Thixotropy

There are many definitions for Thixotropy, among which one found in Chhabra & Richardson (2008) is “It is a gradual decease in viscosity with time at constant shear rate until dynamic equilibrium is attained”. Barnes (1997) defines it as “a gradual decrease of viscosity when shear stress (shear rate) increases and gradual recovery of structure with different time scales when the stress or shear rate decreases or is removed leading to hysteresis”. Thixotropy arises because this microstructural changes itself takes time to occur due to local spatial rearrangement of the molecules- Barnes (1997).

Difficulty in understanding Thixotropy arises because some of the definitions confuse thixotropy with viscoelasticity (see Mewis and Wagner 2009), and some of the definitions confuse thixotropy with shear thinning behavior (see Goodeve 1939). The materials exhibiting Thixotropy are called Thixotropic materials. Few examples of such materials are molten chocolate, soap solutions, nail polishes and many polymer gels like carbopols, sodium alginate, chitosan etc. Thixotropic fluids have applications in pharmaceutical formulations for controlling drug delivery in ophthalmic, oral, nasal, dental, and sunscreen lotions. Thixotropic fluids are also applicable in process industries as thread locking fluids.

1.4 Literature survey

Lee et.al (2009) have studied application of thixotropic property in pharmaceutical formulations. They determined that pH, temperature, concentration of polymers, addition of anions and cations affected the rheological properties. This motivated us to study rheological characteristics of Carbopol974p at different pHs and temperatures which the material may encounter in controlled drug delivery and pharmaceutical formulations.

Kim.et.al (2003) have studied rheological properties of polymer gels and effect of changes in microstructure on rheological properties using steady and oscillatory rheometry. They studied Carbopol941 of different concentrations dissolved in triethanolamine (TEA) as solvent. They conducted micro structure analysis using scanning electron microscopy(SEM). The results from rheological characterization were compared with different constitutive models.

Islam et al. (2004) have studied the rheological properties of Carbopol980 at different pHs (up to neutral pH 7.0) using oscillatory measurements like shear sweep, and frequency sweep, and determined yield stress using low shear rate extrapolation method.

Rheological studies of carbopols were performed by Tamburic and Craig (1995): they have characterized Carbopol934, Carbopol974p, NoveonAA-1, and CarbopolEX-214 by using controlled stress shear rheometer. They performed oscillatory measurements, creep test and hysteresis test to choose any of these polymers for usage in bio-adhesives and other dosage forms. In our study of Carbopol974p, our application is for controlled drug delivery by ingestion using the advantage of bio-adhesiveness of Carbopol974p. Further, we perform flow test, constant shear test, and temperature ramp in addition to the hysteresis test performed in Tamburic and Craig (1995).

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Chapter 2

Materials and Methods

Our aim is to record the Rheological properties of Carbopol974p between pH 1.5 and pH 8.5, and between temperatures of 36.5C and 39.5C. We use the Anton Paar MCR301 Rheometer (which is a shear rheometer) to perform the experiments. The preparation of samples, and experimental protocols are detailed below.

2.1 Chemicals and Equipment

Chemicals used for preparing the samples are Carbopol974p, Distilled water, and Acid-based Buffer solutions of pH 9.2, and pH 11. The key equipment for studying rheological properties is the shear rheometer (model Physica MCR301 built by Anton Paar) supplied with Rheoplus software for data interpretation. The rheometer setup includes a measuring system, attached geometry, measuring cell, and supporting accessories include a compressor, air dryer/filter, and chiller. The Anton Paar rheometer has also been supplied with camera module, which contains a microscope objective of 20x magnification, glass Plate-Peltier temperature device, microscopy tube, polarizer, analyzer, optical fiber, camera and a light source. Other minor equipment used in the course of experiments include a pH meter (range 0 to 14, EI Make), weighing balance (range 10mg to 300gm, CONTECH Make), and Magnetic stirrer (max. speed 2000 rpm, REMI Make).

2.1.1 Preparation of Samples

Carbopol974p is procured in powder form from Bangalore Fine Chemicals Ltd. It is a very soft powder, and cannot instantly dissolve in distilled water; if we add the powder directly to water, the powder will form clumps and not form a homogeneous solution. Hence, we used a magnetic stirrer to agitate 100ml of distilled water at high speed (2000 rpm), and added 1.7gm of Carbopol974p powder at the vortex to form hydrogel. This mixture is stirred for 24hrs and the measured pH is 3-3.5. For preparing Carbopol974p samples of pHs 4.5, 6.5, 7.5, and 8.5, we added 5 to 15 ml of acid-buffer solutions of pH 9.2, and pH 11. Each of the samples thus prepared is characterized using the rheometer by the following procedure.

2.2 Experimental Procedure

The operation of the MCR301 rheometer requires continual operation of the air compressor with attached air filter dryer unit and operation of the water chiller/circulator unit. The air compressor can generate air with pressure up to 300lb/in^2: this pressurized air, after purification, is used to operate the air-bearings, and measuring systems attached to the rheometer. We have used cone and plate geometry with plate diameter 75mm and cone angle of 2°: the notation of this geometry is CP75. The bottom plate in this configuration is connected with Peltier temperature device (called measuring cell) to control the temperature. The water necessary for heating and cooling in the measuring cell is circulated by the chiller/circulator.

Carbopol974p samples of 3.9ml volume are placed between the measuring cone and the bottom plate for characterization. Each test is repeated three times, and results are plotted with error bars. In order to identify and quantify the rheological behavior of the sample (whether Newtonian or non-Newtonian, whether time-independent or time dependent, nature of non-Newtonian behavior), we performed three different tests as detailed below. Each test is initially carried out for Carbopol974p of 3.38pH (pH at concentration of 1.7g/100ml) at a constant temperature of 36.5°C; later, the required tests are performed for other temperatures and pHs of Carbopol974p.

2.2.1 Flow test

Flow test is carried out to identify whether the material is Newtonian or non-Newtonian. In this test shear rate is increased monotonically from $0.01s^{-1}$ to $1000s^{-1}$. The time for the test is 300sec, and a measuring point is taken at every 30sec: the viscosity and shear stress are measured. Protocol of this test is plotted in Fig. 2.1.

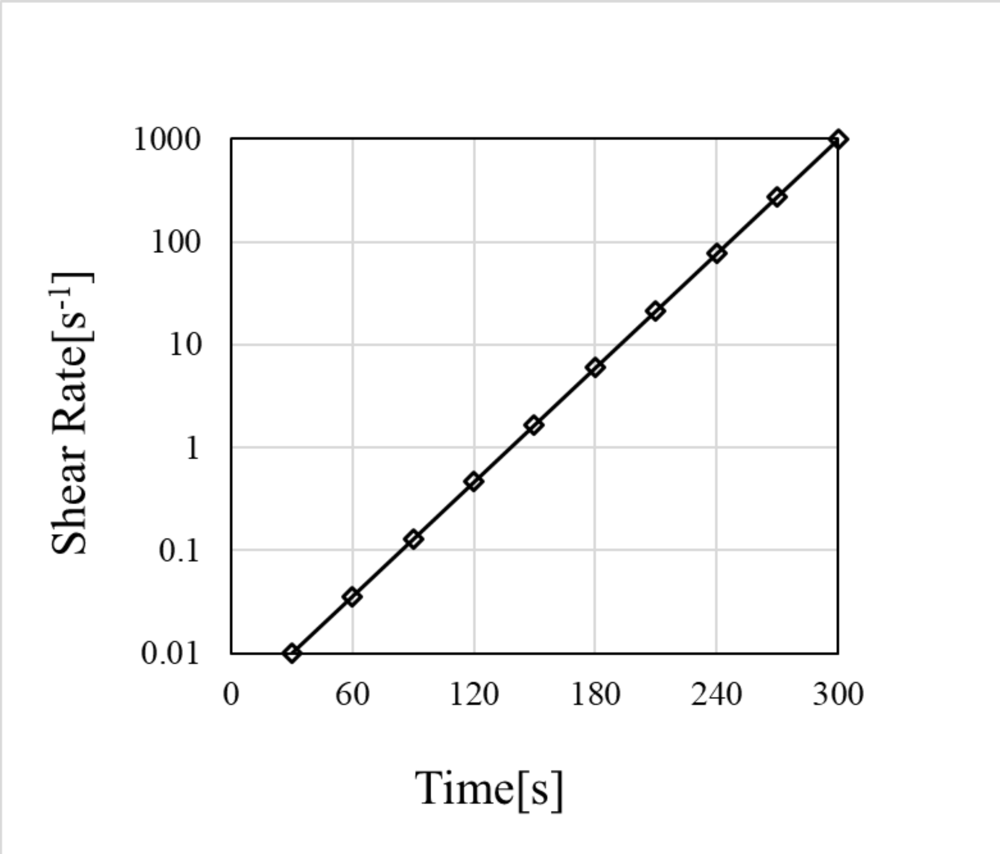

Fig.2.1 Protocol for Flow test

2.2.2 Constant Shear test

After observing the behavior (non-Newtonian) in Flow test, we have to perform constant shear test for identifying whether the material exhibits time- dependent behavior. Constant shear test is conducted by applying a constant shear rate of $0.1s^{-1}$ for 1200sec and measuring corresponding viscosity in time. Measuring point is taken at every 120sec. The protocol for this test is plotted in Fig. 2.2. This test is repeated for constant shear rate of $10s^{-1}$, and protocol is shown in Fig. 2.3.

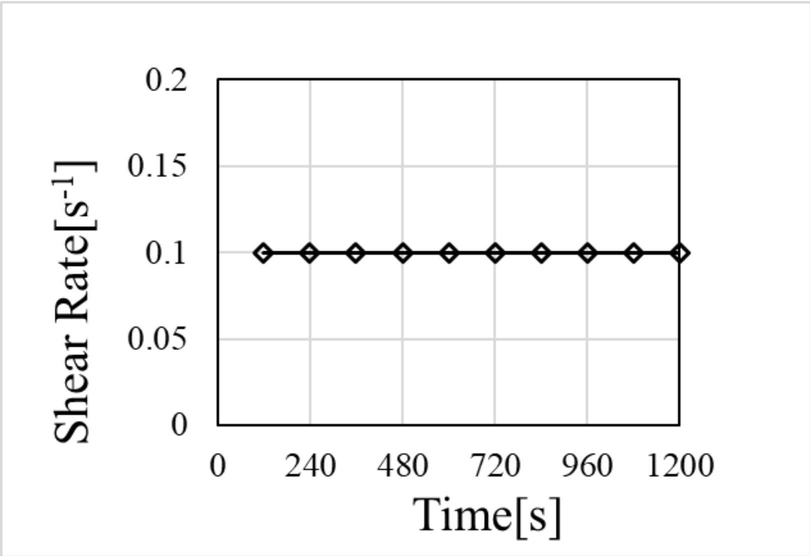

Fig. 2.2 Protocol for Constant shear test at constant shear rate of $0.1s^{-1}$

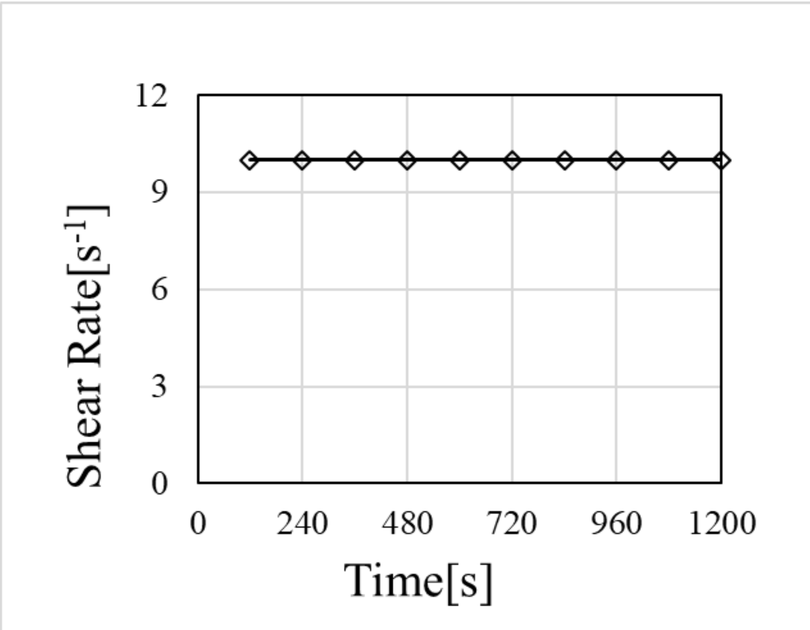

Fig. 2.3 Protocol for Constant shear test at constant shear rate of $10s^{-1}$

2.2.3 Hysteresis test

The results for Constant shear test on Carbopol974p samples indicates time dependent viscosity (thixotropy). Hysteresis test is carried out to record the structure recovery characteristic, which is essential to characterize a thixotropic material. In this test shear rate is increased linearly from $0.01s^{-1}$ to $100s^{-1}$ and then decreased from $100s^{-1}$ to $0.01s^{-1}$ at the same rate at constant temperature. The corresponding viscosity and shear stress are measured. Protocol for this test is plotted in Fig. 2.4. Area under the hysteresis loop so recorded indicates the structure loss because of shear history that the material is subjected to.

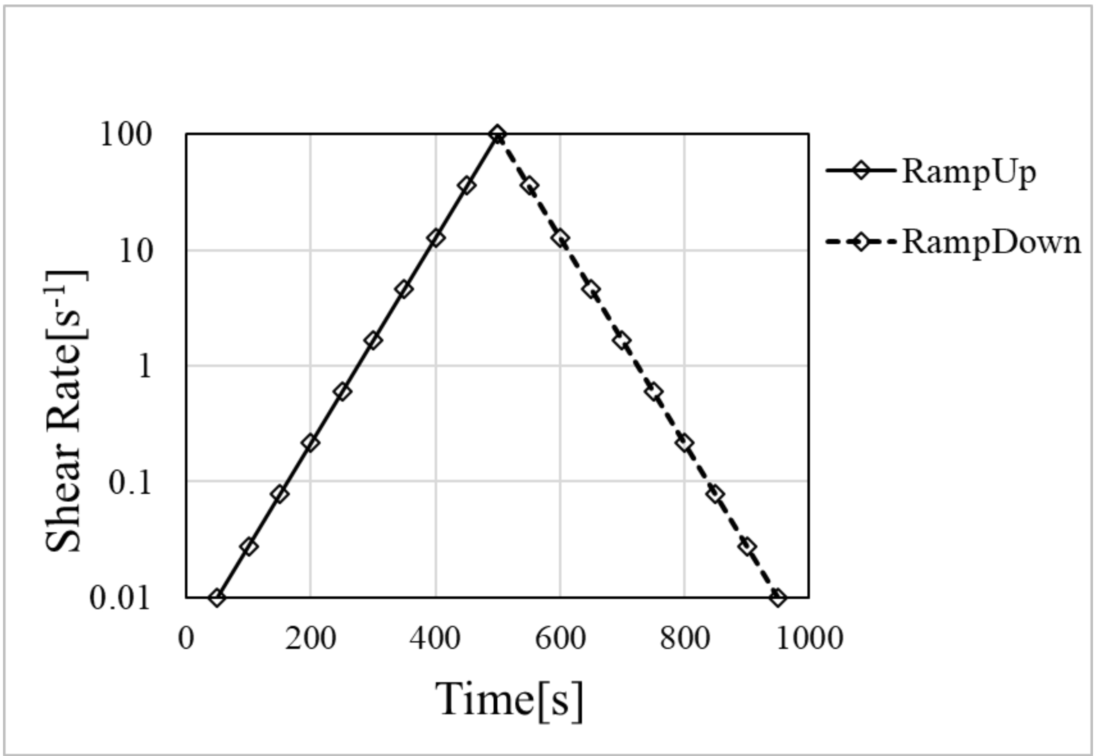

Fig. 2.4 Protocol for Hysteresis test

2.2.4 Temperature Ramp

Temperature ramp test is conducted on Carbopol974p to record the changes in viscosity due to temperature. The viscosity referred to is equilibrium viscosity i.e. the changes in viscosity observed in this test are only because of the changes in temperature. Temperature is increased from 36 to 40°C, at a constant shear rate of $50s^{-1}$ at which the structure of Carbopol974p is in equilibrium. Protocol for this test is plotted in Fig. 2.5.

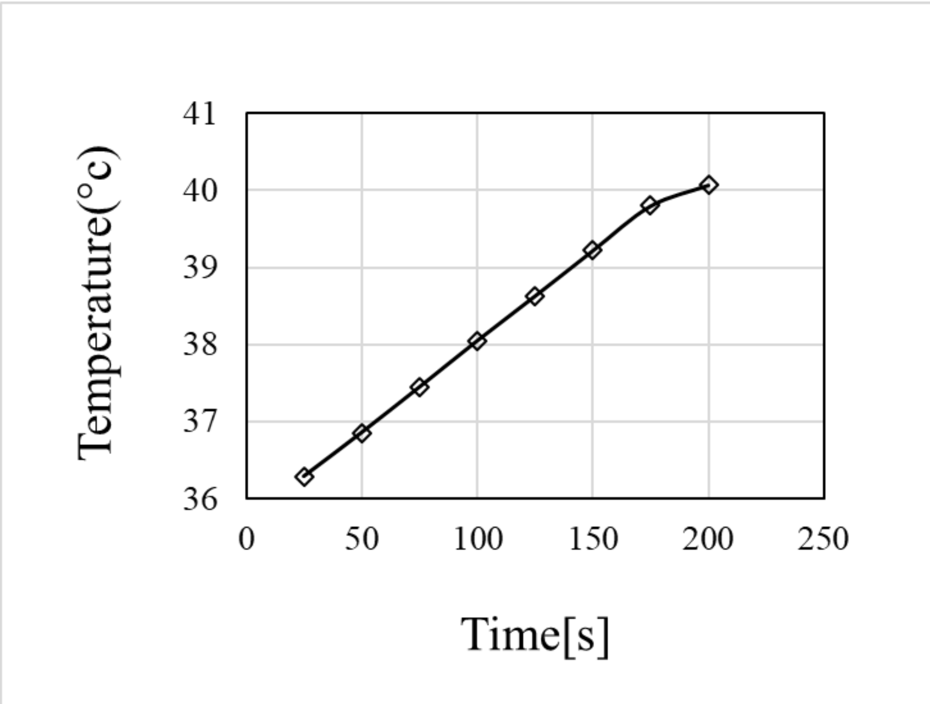

Fig. 2.5 Protocol for Temperature ramp test

Chapter 3

Results

The results obtained from each rheological test are shown in respective figures.

3.1 Viscosity versus shear rate (Flow test)

The result of flow test is data on viscosity (and shear stress) variation with shear rate. Viscosity data obtained are plotted in Fig.3.1(i) for Carbopol974p samples of pH 3.38: data for temperatures of 36.5°C, 37°C, 37.5°C, 38°C, 38.5°C, 39°C, and 39.5°C are plotted in the same figure. The corresponding shear stress is plotted in Fig.3.1(ii) for all the temperatures (see legend). Viscosity versus shear rate data, and shear stress versus shear rate data are also plotted for Carbopol974p samples of pH 8.5 (the maximum pH we tested for) in Figs. 3.2(i) and (ii) so as to give an overview of data.

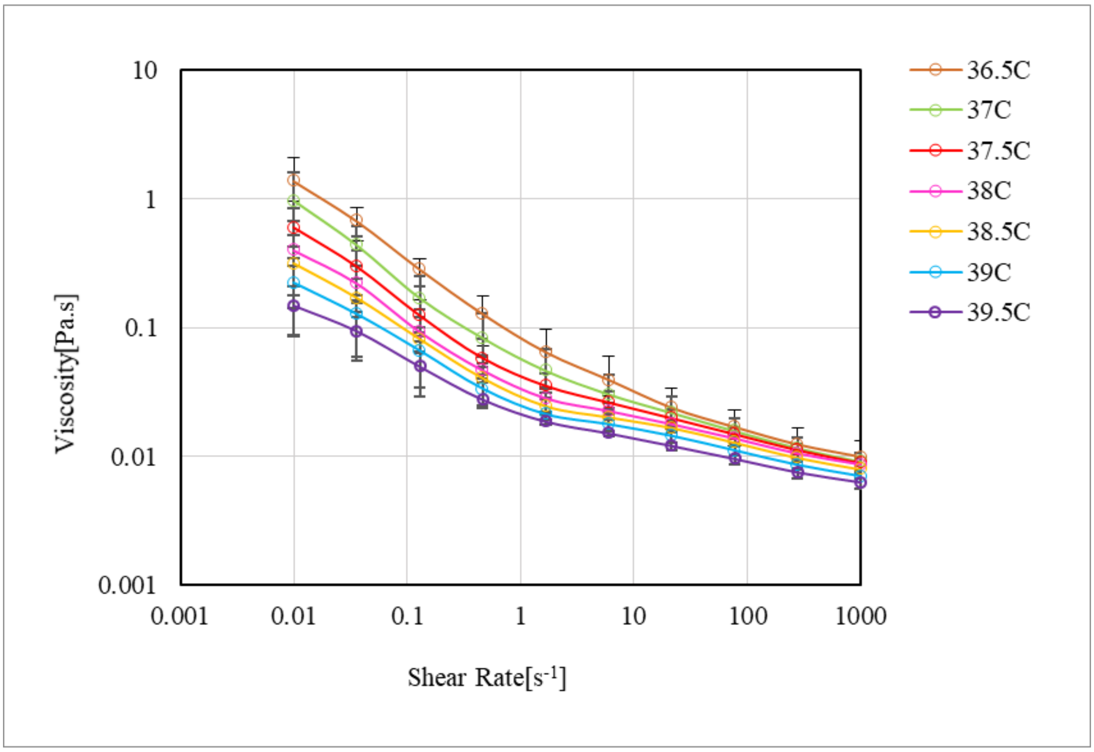

Fig.3.1(i) Variation of viscosity with shear rate at different temperatures for Carbopl974p (pH=3.38).

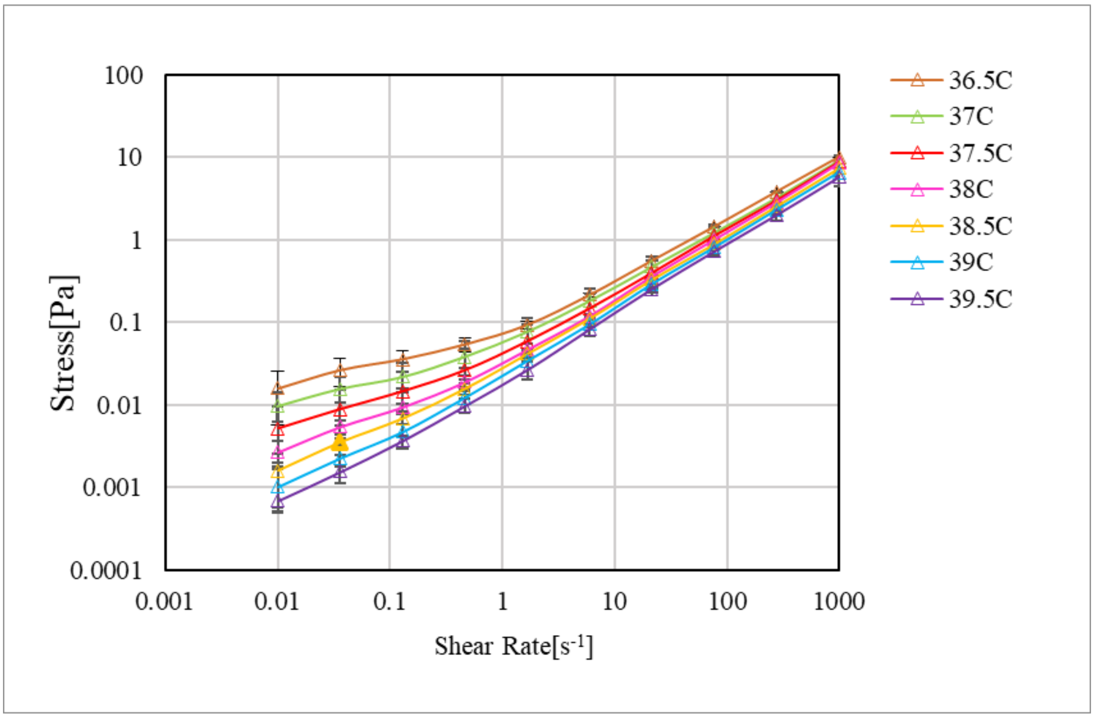

Fig.3.1(ii)Variation of shear stress with shear rate at different temperatures for Carbopl974p (pH=3.38).

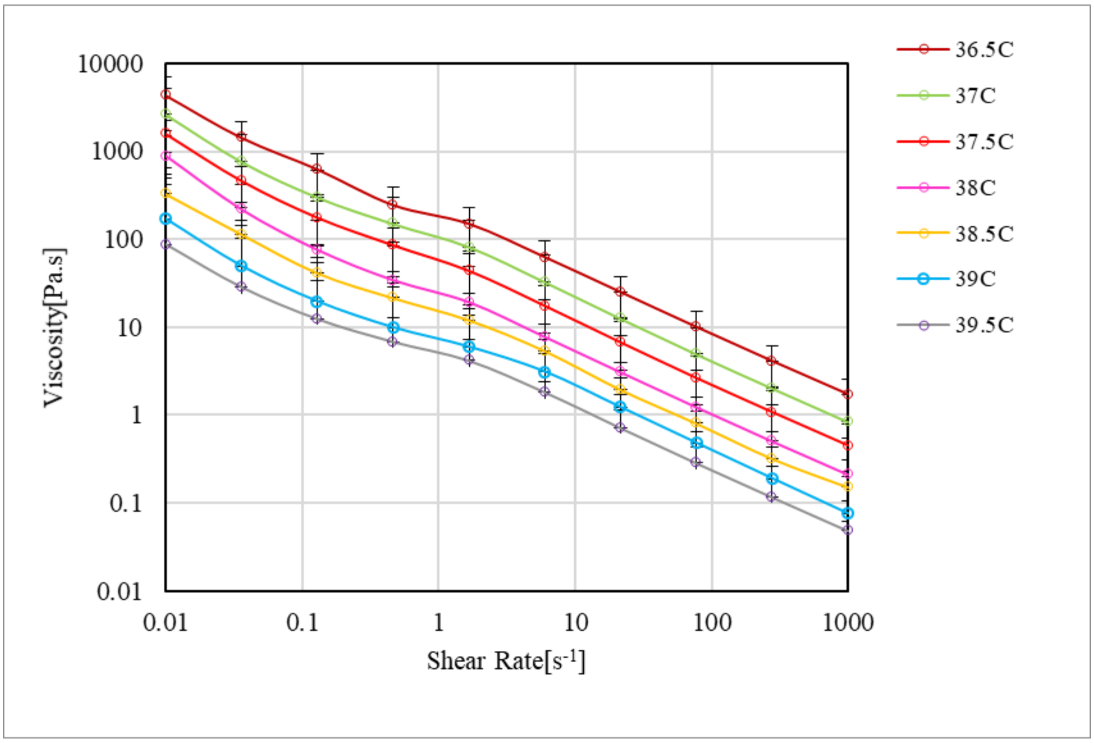

Fig.3.2(i) Variation of viscosity with shear rate at different temperatures for Carbopl974p (pH=8.5).

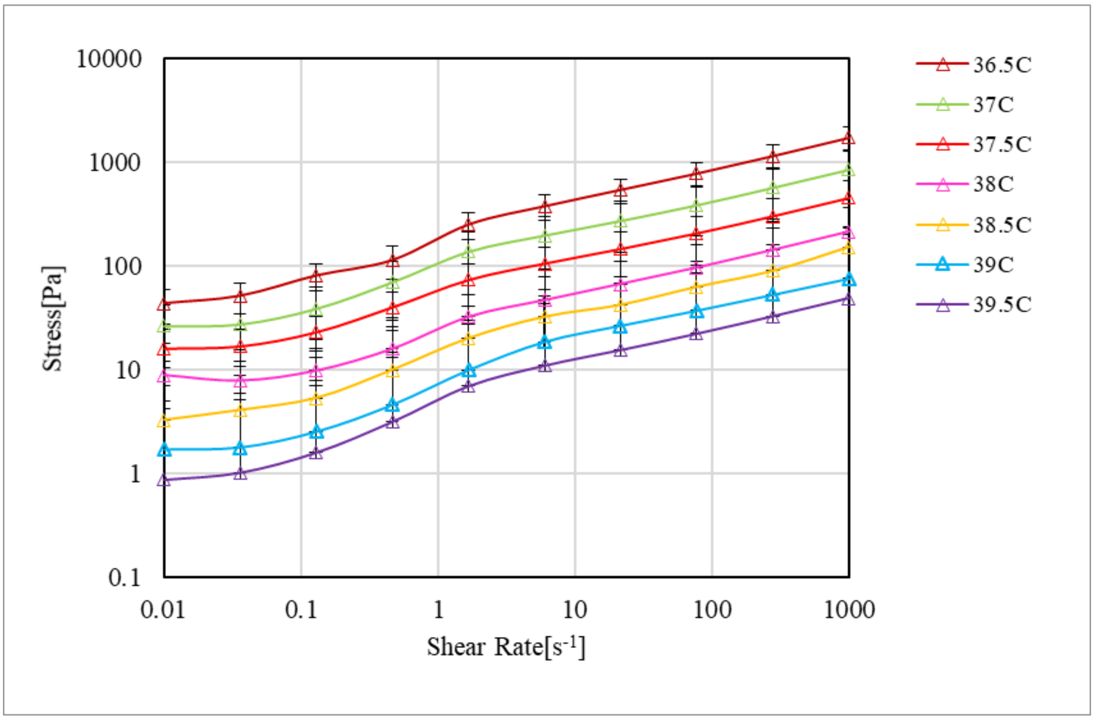

Fig.3.2(ii)Variation of shear stress with shear rate at different temperatures for Carbopl974p (pH=8.5)

3.2 Viscosity versus time (Constant Shear test)

The result from constant shear test is data for viscosity versus time at a shear rate of $0.1s^{-1}$: these are plotted in Fig. 3.3(i) for pH 3.38, and Fig. 3.3(ii) for pH 8.5. The sample in consideration is held at fixed pH (3.38, and 8.5), and results are also plotted for all remaining temperatures in the same figure. Viscosity versus time data obtained at shear rate of $10s^{-1}$ are plotted for all temperatures in Fig. 3.4(i) for pH 3.38, and Fig. 3.4(ii) for pH 8.5.

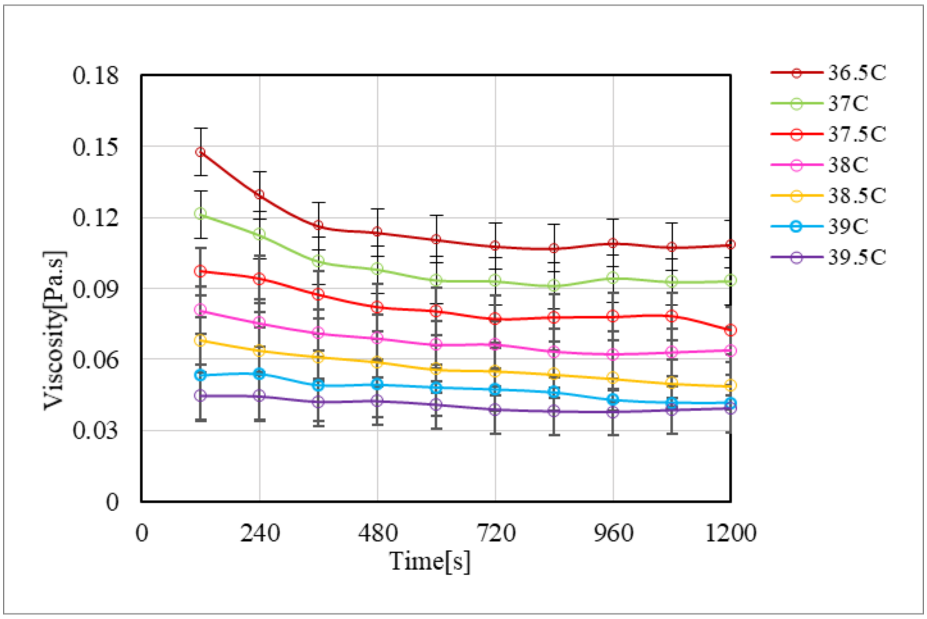

Fig.3.3(i) Variation of viscosity with time at shear rate of $0.1sec^{-1}$ (different temperatures) for Carbopl974p (pH=3.38).

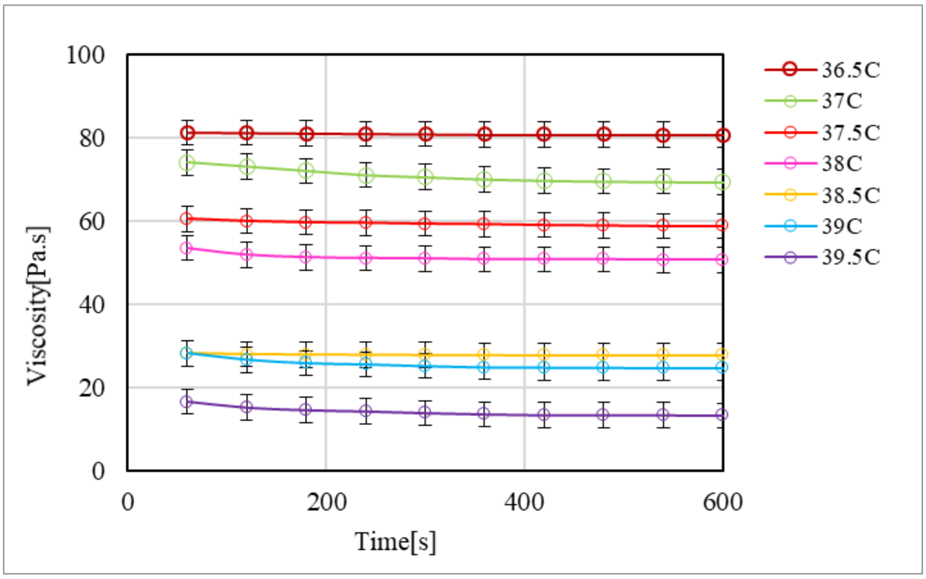

Fig.3.3(ii) Variation of viscosity with time at shear rate of $0.1sec^{-1}$ (different temperatures) for Carbopl974p (pH=8.5)

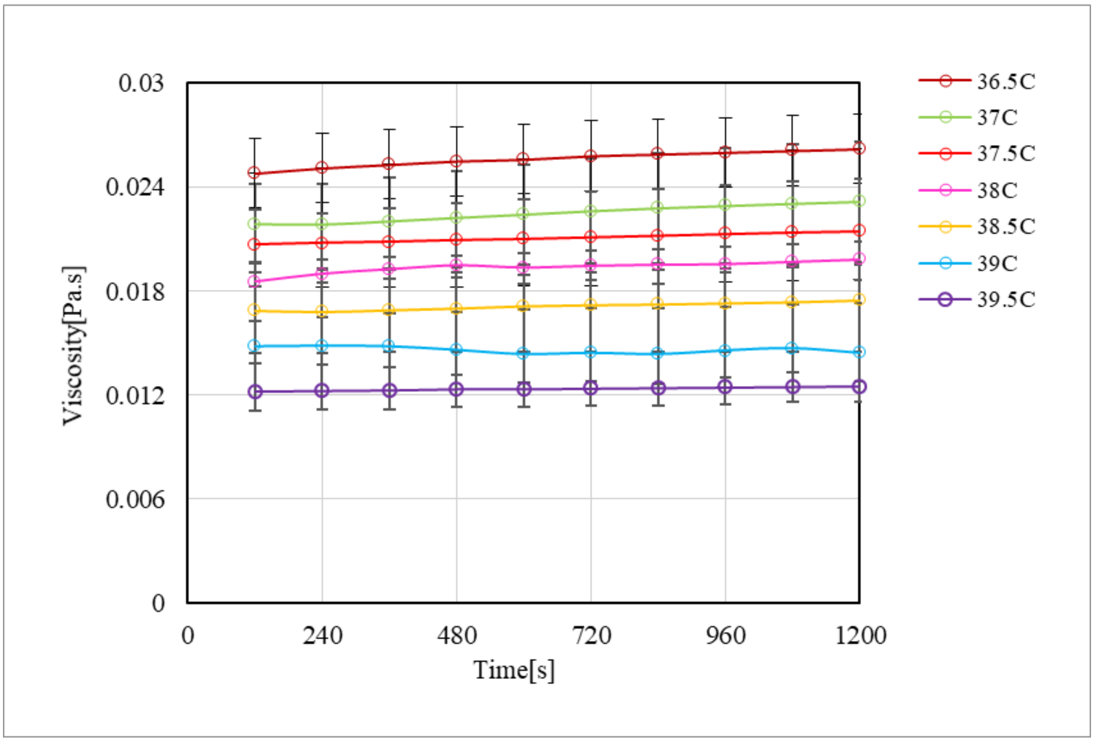

Fig.3.4(i) Variation of viscosity with time at shear rate of 10sec^{-1} (different temperatures) for Carbopl974p (pH=3.38)

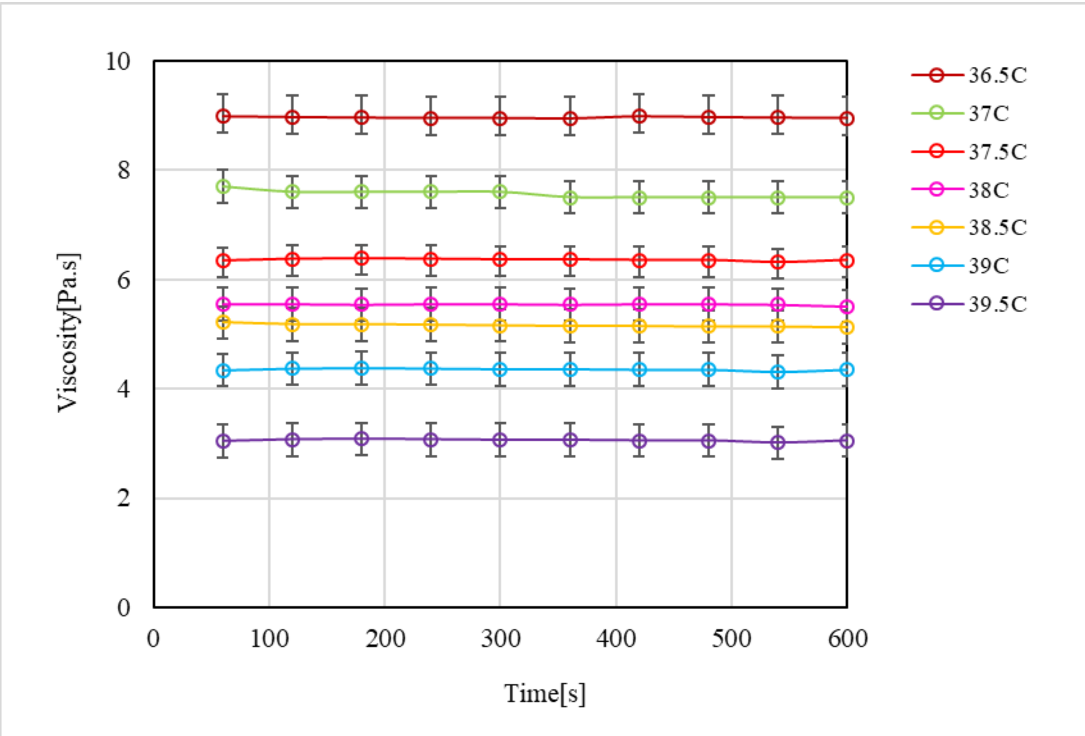

Fig.3.4(ii) Variation of viscosity with time at shear rate of 10 sec^{-1} (different temperatures) for Carbopl974p (pH=8.5)

3.3 Hysteresis test

The result of hysteresis test is data for viscosity versus shear rate and shear stress versus shear rate (with ramp up and ramp down). Data for Carbopol974p of pH 3.38 and temperatures of 36.5°C and 39.5°C are plotted in Figs. 3.5 and 3.6, respectively. Data for samples at pH 8.5 and temperatures of 36.5°C and 39.5C are shown in Figs. 3.7 and 3.8, respectively. Solid line indicates data collected during ramp up of shear rate from $0.01s^{-1}$ to $100s^{-1}$ and dashed line indicates data collected during ramp down of shear rate from $100s^{-1}$ to $0.01s^{-1}$.

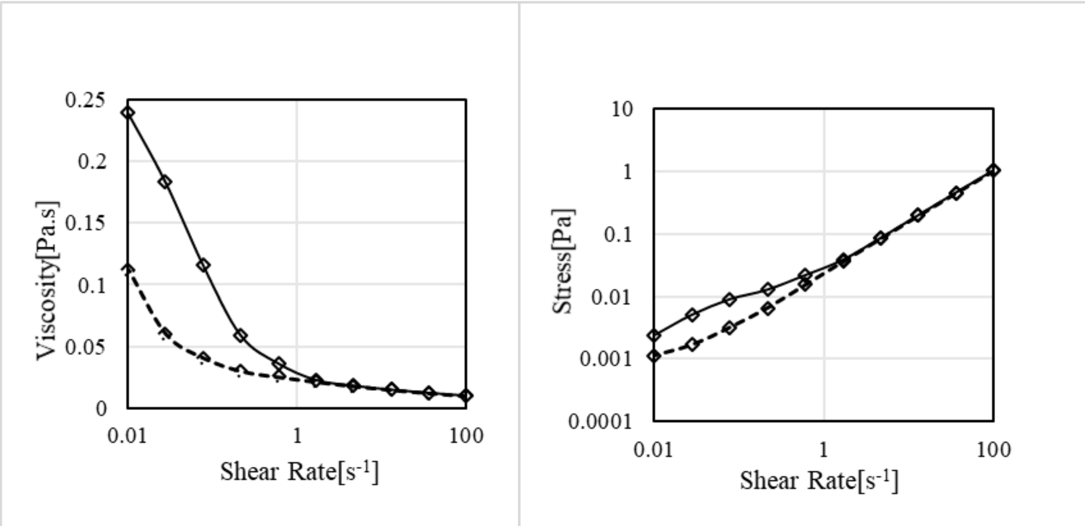

Fig.3.5 Hysteresis data at temperature 36.5°C for Carbopol974p (pH 3.38).

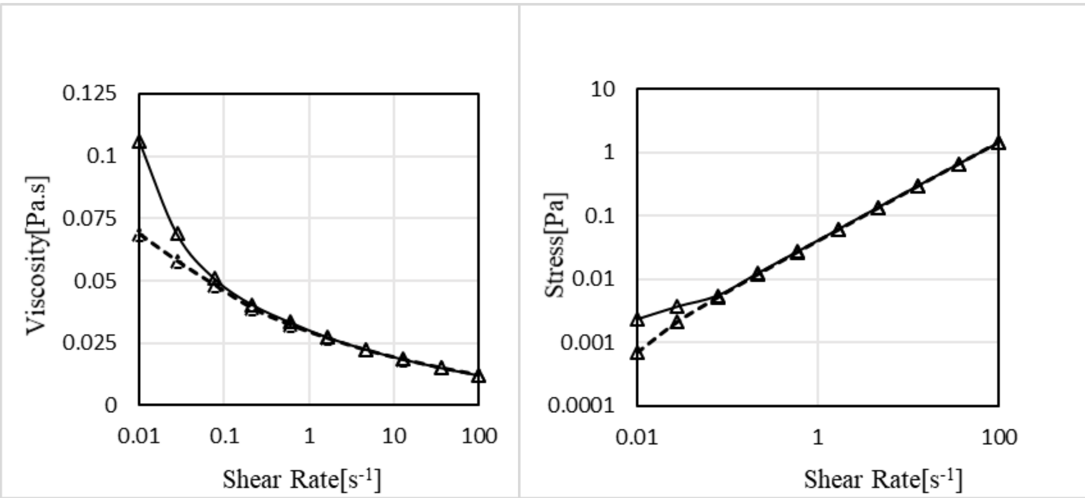

Fig.3.6 Hysteresis data at temperature 39.5°C for Carbopol974p (pH 3.38)

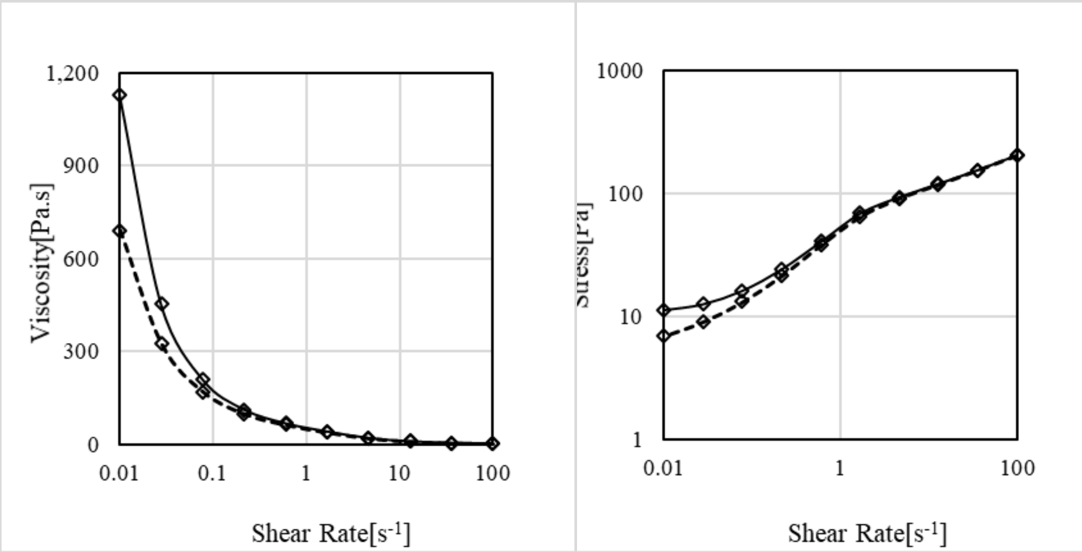

Fig.3.7 Hysteresis data at temperature 36.5°C for Carbopol974p (pH 8.5)

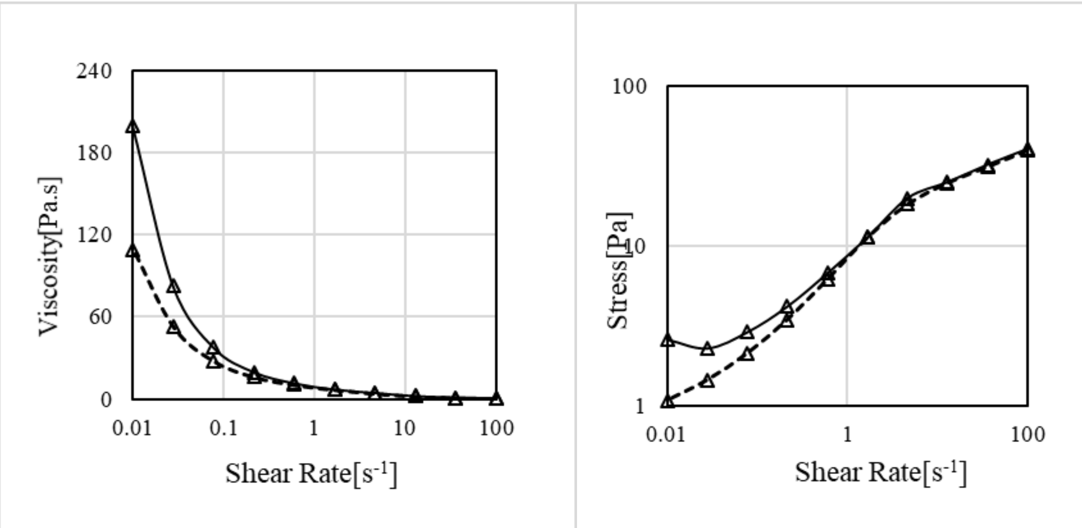

Fig.3.8 Hysteresis data at temperature 39.5°C for Carbopol974p (pH 8.5)

3.4 Viscosity versus Temperature (Temperature Ramp test)

The result of temperature ramp test is variation of viscosity with increase in temperature. It is shown in Fig. 3.9 for different pHs of Carbopol974p at $50s^{-1}$.

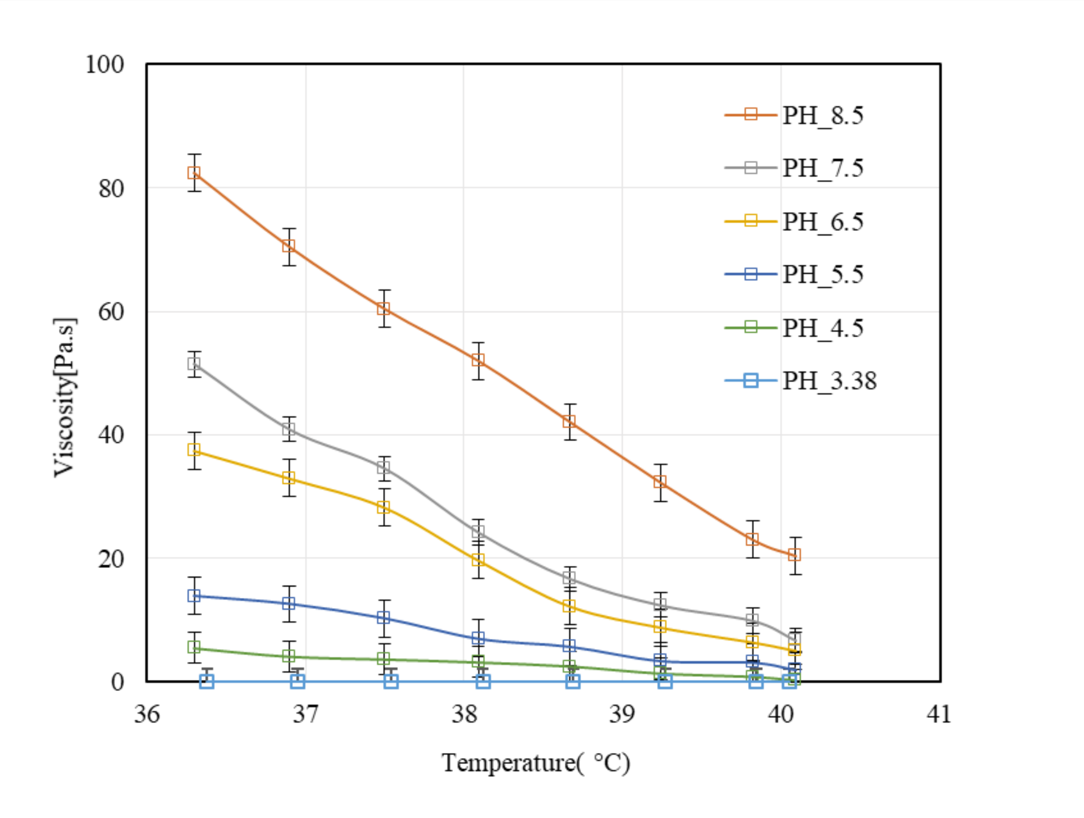

Fig.3.9 Viscosity variation of Carbopol974p w.r.t temperature at different pHs

3.5 Microscopic Analysis

Fig.3.10 shows the images of Carbopol974p of pH 3.38 at 36.5°C, captured by the microscopic objective of 20x magnification (resolution = 0.2mm/20 = 0.01mm). Fig.3.11 shows the result obtained from Dynamic Light Scattering (DLS), which is particle size distribution of Carbopol974p pH 3.38 at 36.5°C.

Before shearing After shearing

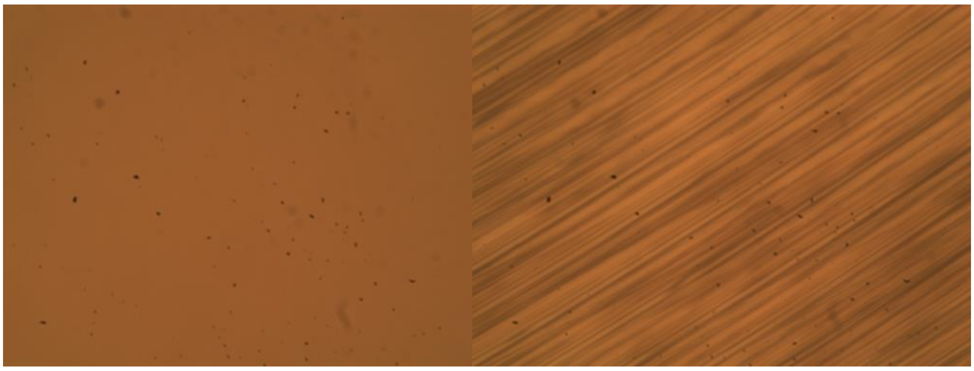

Fig. 3.10 Images of Carbopol974p at pH 3.38 and 36.5°C

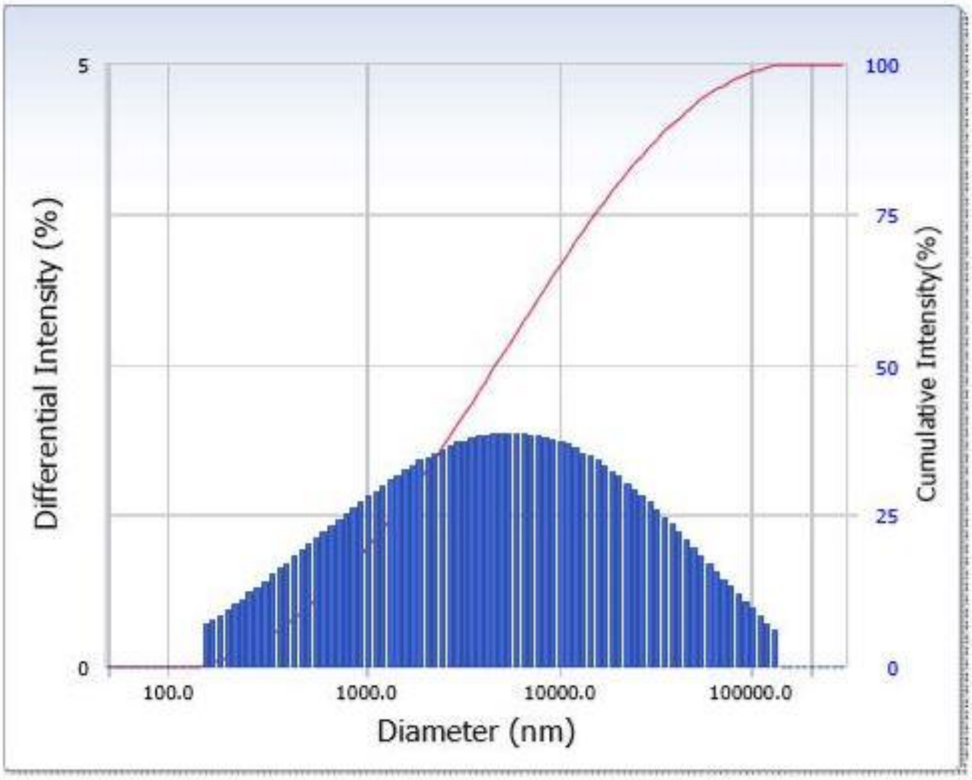

Fig. 3.11 Particle size distribution of Carbopol974p at pH 3.38 and 36.5°C

Chapter 4

Discussion

In this chapter, the results listed in Chapter 3 are summarized and discussed.

4.1 Viscosity versus shear rate (Flow test)

Data for viscosity versus shear rate (Fig 3.1(i)) for Carbopol974p (at pH 3.38) show that viscosity decreases as shear rate increases. This is due to microstructure breakdown of Carbopol974p: the cross links in the poly acrylic acid hydrogel get removed when shear rate increases, and the polymer chains get separated from each other and straighten. With the breakdown of the microstructure as shear rate increases, viscosity of Carbopol974p decreases. This behavior is the characteristic of non-Newtonian shear thinning fluid.

Fig.3.1(ii) contains the corresponding plots of shear stress versus shear rate of Carbopol974p (pH 3.38): these are called flow curves, and they follow the trend of a pseudo-plastic (shear-thinning) material.

Fig.3.2(i) shows the viscosity variation with respect to shear rate of Carbopol974p (at pH 8.5) at different temperatures. Fig.3.2(ii) contains corresponding plot of shear stress vs shear rate at pH 8.5 for all the temperatures. Viscosity decreases as shear rate increases because of microstructure breakdown of Carbopol974p. Here Carbopol974p (of pH 8.5) is prepared by mixing Carbopol974p (of pH 3.38, which is acidic in nature) with buffer solution of pH 11.0 which is a base. Because of large acid-base attraction between Carbopol974p and the buffer solution, viscosity of the sample (Carbopol974p of pH 8.5) is much higher than the viscosity of Carbopol974p of lower pHs (7.5, 6.5, 5.5, 4.5, and 3.38) at the same temperature. However, Carbopol974p exhibits non-Newtonian shear thinning behavior at all these pHs (obtained but not plotted).

Hence, Carbopol974p material exhibits non-Newtonian shear-thinning behavior at all temperatures and pHs studied. This can be attributed to breakdown of microstructure of Carbopol974p with application of shear rate.

4.2 Viscosity versus time (Constant Shear test)

Fig.3.3(i) shows variation of viscosity with time for Carbopol974p (pH 3.38) at a constant shear rate of $0.1s^{-1}$: this shows viscosity decreases continuously with time. This behavior is displayed because of the removal of crosslinks at a constant shear rate: hence the polymer molecules align in the direction of rotation of the cone. At the same time, some of the removed crosslinks reform again and microstructure builds up slowly. We have eliminated any buildup of structure from past shear history $>0.1s^{-1}$ (either during loading or handling the sample) of the material by ensuring that the sample is kept at rest for 24hrs after preparation. Hence any microstructure buildup is attributed only to the reforming of the crosslinks broken during shearing. However, the rate of breakdown of structure is higher than the rate of buildup of structure. Hence viscosity decreases continuously until the structure of Carbopol974p reaches dynamic equilibrium. Dynamic equilibrium is attained when the rate of breakdown of structure equals the rate of buildup of structure; after that, the viscosity does not change further with time. Viscosity at this stage is called equilibrium viscosity. Decrease in viscosity with time at constant shear rate is the characteristic of a thixotropic material. Hence Carbopol974p (pH 3.38) exhibits thixotropic behavior at 36.5°C.

Fig.3.3(i) also shows that Carbopol974p (pH 3.38) exhibits thixotropic behavior at all other temperatures. Further, at higher operating temperature, the slope of viscosity vs time curve decreases. This may be because, at higher temperature the polymer molecules are already separated and hence the further decrease in viscosity with respect to time has a lesser effect.

Fig.3.3(ii) is variation of viscosity of Carbopol974p (pH 8.5) with respect to time at a constant shear rate of $0.1s^{-1}$ also shows viscosity decreases continuously until dynamic equilibrium is attained. Hence Carbopol974p is thixotropic at pH 8.5 for all the temperatures. Carbopol974p exhibits same behavior at $0.1s^{-1}$ for pHs 4.5, 5.5, 6.5 and 7.5 also, and hence the plots for these pHs are not shown in this thesis.

Fig.3.4(i) shows variation of viscosity of Carbopol974p (pH 3.38) with respect to time at a constant shear rate of $10s^{-1}$: this shows that viscosity is constant w.r.t time, and this holds for all temperatures. This is because the structure of Carbopol974p is in equilibrium all the time at $10s^{-1}$, i.e. rate of buildup of structure and rate break down of structure are always equal at $10s^{-1}$, and hence no changes in viscosity occur. Hence, Carbopol974p is only shear thinning (pseudo-plastic) at $10s^{-1}$. A similar observation is made regarding Carbopol974p (pH 8.5) also whose viscosity does not vary with time at $10s^{-1}$ for all temperatures studied. These data are shown in Fig.3.4(ii). Carbopol974p exhibits same behavior at pHs 4.5, 5.5, 6.5 and 7.5 at other temperatures also. Hence the plots for these pHs are not shown in this thesis.

The two tests discussed so far, i.e. flow test and constant shear test, are not sufficient to fully describe the thixotropic behavior of Carbopol974p. This is because whenever we speak about a thixotropic material, we need to report the structure recovery behavior of the material also. Structure recovery behavior of Carbopol974p is described in the next section (4.3).

4.3 Hysteresis test

Fig.3.5(i) shows viscosity variation of Carbopol974p for ramp up and ramp down of shear rate. This shows that as shear rate increases viscosity of Carbopol974p decreases, and later viscosity increases as shear rate decreases to form a hysteresis loop. This happens because, during shear rate increase, there is microstructure breakdown until the shear rate reaches $100s^{-1}$. Rebuilding of the microstructure follows when shear rate decreases from $100s^{-1}$ to $0.01s^{-1}$. During ramp-up, Carbopol974p has undergone microstructure breakdown continually from $0.01s^{-1}$ and $100s^{-1}$ but it has recovered this microstructure during ramp-down only between $100s^{-1}$ and $2s^{-1}$. In other words, the rate of recovery matches the rate of structural breakdown only between $100s^{-1}$ and $2s^{-1}$: hence, the viscosity recorded at these shear rates is same during ramp-up and ramp-down, and there is no area under the hysteresis loop between $2s^{-1}$ and $100s^{-1}$. However, the rate of microstructure recovery is slower than rate of structure breakdown between shear rates of $2s^{-1}$ to $0.01s^{-1}$, and we can observe a non-zero area under hysteresis loop between $0.01s^{-1}$ and $2s^{-1}$: this indicates the time-dependent nature of the microstructure in the material, and the extent of the area indicates the degree of thixotropy of Carbopol974p.

Carbopol974p could not recover complete structure at lower shear rates ($2s^{-1}$ to $0.01s^{-1}$) hence viscosity during ramp down is less than viscosity during ramp up. Carbopol974p (pH 3.38) needs more time to recover its complete structure at lower shear rates, hence it is thixotropic at lower shear rates ($0.01s^{-1}$ to $2s^{-1}$) at 36.5°C. Corresponding Stress of Carbopol974p (pH 3.38) at temperature 36.5°C is plotted in Fig.3.5(ii).

Fig.3.6(i) shows viscosity variation of Carbopol974p (pH 3.38) at a higher temperature of 39.5°C than the 36.5°C for Fig 3.5(i). These data show that Carbopol974p could recover its original structure between $0.2s^{-1}$ to $100s^{-1}$, but there is insufficient structure recovery from $0.2s^{-1}$ to $0.01s^{-1}$. Hence Carbopol974p (pH 3.38) at 39.5°C is a thixotropic material for a lower range of shear rates ($0.01s^{-1}$ to $0.2s^{-1}$) than at 36.5°C ($0.01s^{-1}$ to $2s^{-1}$). Fig. 3.6(ii) shows the corresponding stress of Carbopol974p (pH 3.38) at temperature 39.5°C during the hysteresis test, and the thixotropy is seen between the same shear rates ($0.01s^{-1}$ to $0.2s^{-1}$) as in the viscosity data.

Fig.3.7(i) shows variation of viscosity for Carbopol974p (pH 8.5) at temperature 36.5°C during the hysteresis test between shear rates of $0.01s^{-1}$ and $100s^{-1}$. Area under hysteresis loop which denotes the region where thixotropic behavior is noticed is observed at lower shear rates ($0.01s^{-1}$ to $1s^{-1}$) as compared to ($0.01s^{-1}$ to $2s^{-1}$) for Carbopol974p (pH 3.38) at temperature 36.5°C. Thus, the data suggests that thixotropic behavior of Carbopol974p becomes less prominent at higher pH. Fig.3.7(ii) shows recorded stress of Carbopol974p (pH 8.5) and temperature 36.5°C during the hysteresis test.

Fig.3.8(i) reports the variation of viscosity with time during hysteresis test of Carbopol974p (pH 8.5) at temperature 39.5°C. Carbopol974p's thixotropic behavior is noticed at same range of shear rates ($0.01s^{-1}$ to $1s^{-1}$) as Carbopol974p (pH 8.5) at temperature 36.5°C, which is slightly surprising as one would expect it to decrease further at higher temperature like for Carbopol974p (pH 3.38). Carbopol974p (pH 8.5) at temperature 39.5°C shows only shear- thinning behavior at higher shear rates ($1s^{-1}$ to $100s^{-1}$). Fig.3.8(ii) shows corresponding stress of Carbopol974p (pH 8.5) at temperature 39.5°C.

4.4 Viscosity versus Temperature (Temperature Ramp test)

Data for variation of viscosity with respect to temperature (Fig. 3.9) show that viscosity of Carbopol974p decreases as temperature increases. This is because energy level of the liquid molecules increases when temperature increases, and they move far away from each other: hence, intermolecular attraction decreases and viscosity decreases. Note that in some polymers viscosity can increase as temperature rises because the increase in energy leads to formation of new crosslinks between monomers. However, in the present case, the temperature change is very small (36.5°C to 39.5°C), and hence the monomers of Carbopol974p did not form any new cross links.

The slope of viscosity versus temperature curve decreases dramatically from value of -11.2 Pa.s/°C at higher pH of 8.5 to value of -1.37 Pa.s/°C at lower pH of 4.5. A possible explanation is that, at pH 8.5, the molecules of Carbopol974p are tightly packed due to large acid-base attraction between buffer solution (pH 11) and Carbopol974p (pH 3.38) than at lower pHs. Hence a small change in temperature results in a large change in viscosity. The same change in temperature, however, leads to a much lesser change in viscosity for the sample at pH 3.38 because the molecules in the solution are not tightly packed and the change in temperature does not change the intermolecular distances significantly.

4.5 Effect of pH on viscosity

Carbopol974p has pH 3.38 when prepared using distilled water (as already stated in chapter 2). Carbopol974p of pH 4.5, pH 5.5, and pH 6.5 are prepared by adding buffer solution of pH 9.2 (5ml, 10ml, and 15ml, respectively), and Carbopol974p of pH 7.5, and 8.5 are prepared by adding buffer solution of pH 11 (5ml, and 10ml, respectively). The magnitude of acid base attraction increases from pH4.5 to 5.5 and to 6.5 as the amount of base added is increasing; further acid base attraction is higher in Carbopol974p (pH7.5) than in Carbopol974p (pH 6.5) because the base added is stronger (pH 11). The acid base attraction is highest in Carbopol974p of pH8.5. Hence the structure of Carbopol974p of pH8.5 is tightly packed and the molecules are closer to each other, than the other pHs. Hence the viscosity of Carbopol974p increases as pH increases from 3.38 to 8.5: this is seen in the data.

4.6 Microscopic Analysis

We can validate the results obtained from flow test- which are decrease in viscosity due too application of shear- by capturing the microstructure of Carbopol974p during shearing. We have installed the camera module set up of rheometer and captured the images of Carbopol974p before and after shearing. However, the microscope available with the setup is 20x magnification which can resolve the images up to 0.01mm (0.2mm/20, where 0.2mm is the resolution limit of the human eye in white light), whereas the size of the particles of Carbopol974p is much lower and in the range of 100nm to 0.1mm. The range of particle size is known from Dynamic Light Scattering (DLS) studies which is shown in fig.3.11. Hence the images shown in fig.3.10 are the macro structures of Carbopol974p of 3.38pH at 36.5°C before and after shearing at a shear rate of $0.1s^{-1}$. The microscope could resolve the Carbopol974p particles greater than 0.01mm, but it could not capture the microstructure of Carbopol974p which is of much smaller size.

4.7 Conclusions

- ✓ Results from flow test lead us to conclude that Carbopol974p is non-Newtonian in nature at all the pHs (3.38 to 8.5) and temperatures (36.5°C to 39.5°C) studied.
- ✓ Results from constant shear test lead us to conclude that Carbopol974p is thixotropic material at $0.1s^{-1}$ for all the pHs (3.38 to 8.5) and temperatures (36.5°C to 39.5°C) studied. Additionally, rate of decrease of viscosity with time decreases as temperature increases.
- ✓ Carbopol974p is a purely shear thinning (pseudo-plastic) material at $10s^{-1}$ at all the pHs (3.38 to 8.5) and temperatures (36.5°C to 39.5°C) studied.

- ✓ Results from hysteresis test show that Carbopol974p at pH 3.38 and temperature 36.5°C exhibits thixotropic behavior at low shear rates ($0.01s^{-1}$ to $2s^{-1}$) and only shear thinning behavior at high shear rates ($2s^{-1}$ to $100s^{-1}$).
- ✓ Carbopol974p at pH 3.38 and temperature 39.5°C exhibits thixotropic behavior at a lower range of shear rates ($0.01s^{-1}$ to $0.2s^{-1}$) as compared to that at 36.5°C.
- ✓ Carbopol974p at pH 8.5 and temperatures 36.5°C and 39.5°C exhibits thixotropic behavior at low shear rates ($0.01s^{-1}$ to $1s^{-1}$) and only shear thinning behavior at high shear rates ($1s^{-1}$ to $100s^{-1}$).
- ✓ Result from temperature ramp test lead us to conclude that viscosity of Carbopol974p decreases as temperature increases and viscosity increases as pH increases.

Our study has extended the rheological data for Carbopol974p over what is available in the literature in Tamburic and Craig (1995). We performed flow test, constant shear test, and temperature ramp test as well as hysteresis test (which was also performed in Tamburic and Craig (1995)). Importantly, we have obtained the data over the entire range of conditions that Carbopol974p is likely to encounter if used as a drug carrier, and summarized its rheological properties in the above bullet points. These results can thus serve as a useful reference when considering Carbopol974p as a potential drug carrier.

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