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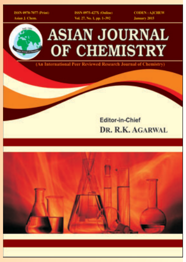

Synthesis, Characterization and Rheological Studies of Novel Acrylic Acid-co-Acrylonitrile-co-*N*-Isopropylacrylamide Terpolymeric Hydrogels

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The primary objective of this research work is the extensive rheological characterization of novel *N*-isopro-pylacrylamide (NIPAAM) based hydrogels. *N*-isopropylacrylamide being a temperature sensitive component can alter flow behaviour and drug release characteristics of topical gels in the form of change in their viscosities with temperature and variation in the network structure with their composition. Terpolymeric hydrogels of acrylic acid-co-acrylonitrile-co-*N*-isopropylacrylamide (AA-AN-NIPAAM) with different concentrations of *N*-isopropylacrylamide were synthesized by free radical polymerization method. Oscillatory and transient shear measurements were carried out to study viscoelastic properties, effect of temperature on flow behaviour and yield strength of novel pharmaceutical gel formulations. Results indicate a remarkable temperature dependency of the *N*-isopropylacrylamide based physically cross linked hydrogels. Flow curves plotted at a range of temperature point out a reasonable pseudoplastic behaviour, the most facilitating property of topogels. The hydrogels have acquired a suitable yield strength requisite to rupture their polymeric network structure. The trends of dynamic moduli (G' and G") and relaxation time with *N*-isopropylacrylamide contents indicate presence of necessary mechanical strength required for the settlement of the gels and controlled release of the drug. Conclusively the rheological behaviour of these novel gels is found to be favourable for applying as controlled and sustained targeted drug delivery.

Keywords: *N*-isopropylacrylamide based polymers, Rheology, Hydrogels, Ostwald model, Bingham model.

INTRODUCTION

Hydrogels are vivacious polymeric materials capable to captivate water akin to living tissues. Due to this property they have attracted many imperious applications in biotechnology, biomedicine and pharmacy as protein and drug delivery vehicles[1] soft contact lenses, hair gel, plant water crystals and in tissue engineering[2], *etc*. Hydrogels may be cross linked either chemically or physically[3]. Covalently bonded linkage imparts high mechanical strength and stability to the chemically cross linked hydrogels. Therefore, these hydrogels are less suitable for active release of enclosed bioactive substances as reported earlier[4]. Moreover, being undesirable and toxic to living environment, they need to be slayed very shortly after *in vivo* drug application. Countering these possible threats are physically cross linked (non-covalently bonded) hydrogels whose fugacious linkages assure safe release of drug without any intervention with activity of biomolecules[5]. Such systems can be administered either by injection as liquid formulations or topically after jellifying *in situ*. Later mode of application is considered more appropriate with some careful adjustments according to the type and content of polymeric materials in a delivery system.

Objective of the present work is to synthesize a unique tercopolymeric hydrogel system having successful application in drug delivery systems. In this regard rheological aspects were studied to pave degree of compatibility of the prepared hydrogels. *N*-Isopropylacrylamide and acrylic acid were used as constituent monomers.

Among the topically applied gels, anionic hydrogels are highly recommended due to their spreadibility, skin compatibility and friendly desorption. In this regard physically cross linked derivatives of acrylic acid have been reported[6]. Acrylonitrile being polar and reactive monomer can be copolymerized with a wide range of other vinyl monomers such as styrene, methylacrylate, acrylic acid and *N*-isopropylacry-lamide *etc*.[7]. These acrylonitrile containing gels are considered to be useful candidates in the fields of textile treatments, cross linking agents, solvents, viscosity modifiers, artificial organs, insecticides and medicines *etc*.[7]. *N*-Isopropylacry-lamide based hydrogels are thermo sensitive polymers exhibiting volume phase transition at its lower critical solution temperature

(LCST) *i.e.* swells below lower critical solution temperature and deswells above lower critical solution temperature. This volume phase transition has been attributed to the disruption of hydrophilic and hydrophobic balance of *N*-isopropylacrylamide based polymeric materials[8]. Interestingly lower critical solution temperature of *N*-isopropylacrylamide polymers (33 °C)[9,10] is close to human body temperature (37 °C) due to which these hydrogels seek more opportunities in biomedical field.

The processing of any polymer system for drug delivery requires complete knowledge of their rheological characteristics. For example, therapeutic effects of a drug are technically optimized for manufacturing processes, alterations occurring during transportation and packing and mode of drug administration by rheological determinations[11,12].

Literature claims little booms of rheological characterization of terpolymeric *N*-isopropylacrylamide based hydrogels. Therefore, in the present studies acrylic acid-co-acrylonitrile-co-*N*-isopropylacrylamide (AA-AN-NIPAAM) terpolymeric hydrogels have been prepared and their rheological properties (flow curves, complex viscosity and viscoelastic properties) are discussed.

EXPERIMENTAL

Materials used in these studies were *N*-isopropylacrylamide (97 %, Aldrich), acrylic acid (99 %, Fluka), acrylonitrile (99 %, DAE Jung), ethyl alcohol (99.8 %, BDH) and benzoyl peroxide (100 % Merck).

Synthesis of hydrogels: The gels NR1, NR2, NR3 and NR4 were prepared by free radical polymerization. The two monomers acrylonitrile and acrylic acid were used in equal volume ratio and the amount of *N*-isopropylacrylamide (0.25 g in NR1, 0.50 g in NR2, 0.75 g in NR3, 1 g in NR4) was varied to synthesize these gels. Ethyl alcohol (100 % v/v of monomeric solution) was added as a solvent. The contents were mixed thoroughly and the nitrogen gas was bubbled through the reaction mixture to avoid the interference owing to oxygen. In nitrogen saturated reaction mixtures, the benzoyl peroxide (1 % w/v) was added as an initiator. The sample tubes were capped tightly and treated with ultrasonic agitation for 14 min. The tubes were then, placed in a water bath preset at 40 °C. The temperature of the reaction mixture was gradually raised to 70 °C where the polymeric gels started to form. The reaction mixture was kept at this temperature for 24 h to ensure the completion of the polymerization reaction. The synthesized gels were washed with ethanol and were used for further investigations.

Thermogravimetric analysis: Thermal characterization of the synthesized hydrogel (NR4) was carried out by using Perkin Elmer TG/DTA Diamond instrument in the temperature range 30 to 600 °C at 10 °C/min.

Fourier transform infrared (FTIR) spctroscopy: FTIR spectrum was obtained by FTIR spectrometer NICOLET 6700 thermoscientific USA for structural elucidation of the synthesized gel (NR4).

Rheological measurements: The rheograms (FC and FS) of the synthesized gels NR1, NR2, NR3 and NR4 were recorded in the temperature range of 20 to 60 °C using MCR 301 Rheometer Anton paar, Germany.

RESULTS AND DISCUSSION

Thermal analysis: Thermogram of the synthesized hydrogel NR4 is shown in Fig. 1. It demonstrates the degradation pattern in three stages *i.e.* 30-140, 140-410 and 410-560 °C. The 56 % weight loss in first step may be related to the evaporation of moisture and ethanol which was used as solvent in the polymerization reaction. The second stage (27 % weight loss) corresponds to the degradation of polymer backbone which is completed in last step. The negative value of residue indicates the absence of any carbonaceous material beyond 560 °C.

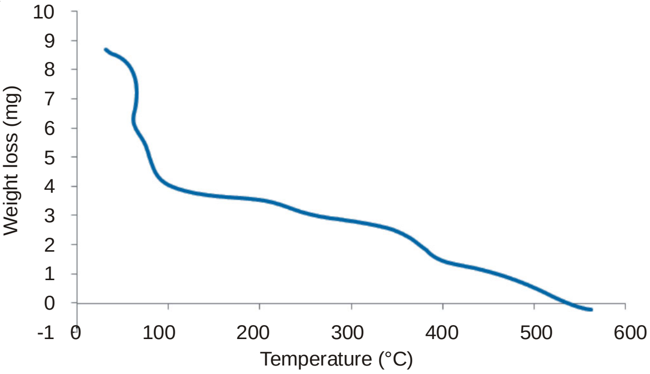

Fig. 1. Thermogravimetric curve of the hydrogel NR4

FTIR analysis: Fig. 2 demonstrates the FTIR spectrum of the synthesized hydrogel NR4. A broad band at 3319 cm^{-1} is attributed to the stretching vibrations of hydrogen bonded -OH of acrylic acid. The peaks at 2931 and 2856 cm^{-1} may be ascribed, respectively to the methylene (CH_2=) C-H asymmetric and symmetric stretching vibrations of vinyl group present in all the monomers used for the synthesis. The band in the region 2280-2200 cm^{-1} may correspond to the nitrile (-C=N) of acrylonitrile. The carbonyl group (=C=O) of acrylic acid and amide group (-NH-) of *N*-isopropylacrylamide are located at 1727 and 1651 cm^{-1}, respectively. The C-H bending vibrations of methylene (CH_2=) in vinyl group is observed at 1450 cm^{-1}. The peak at 1365 cm^{-1} may be related to iso dimethyl (isopropyl) group in *N*-isopropylacrylamide. All the peaks appear in 1300-700 cm^{-1} region owing to the C-C skeletal vibrations. The peaks in the region 700-590 cm^{-1} may be due to the out of plane bending vibrations of -OH of ethanol used as solvent in the synthesis process[13].

Rheological properties

Flow curves: In these studies, the shear stress and viscosity of the hydrogels (NR1, NR2, NR3 and NR4) are recorded as a function of shear rate at 20, 30, 40, 50 and 60 °C. The shear stress of all the gels increases with shear rate at all the temperatures studied. For convenience, a representative plot of shear stress dependence on shear rate for NR1 at all the temperatures studied is shown in Fig. 3.

The characteristic rheograms of the synthesized gels are illustrated in Figs. 4 and 5. It is obvious from these plots that at lower shear rate measured viscosity of each hydrogel initially increases then drops with increasing shear rate at all the temperatures studied. However, at 20 °C in NR1, at 30 °C in

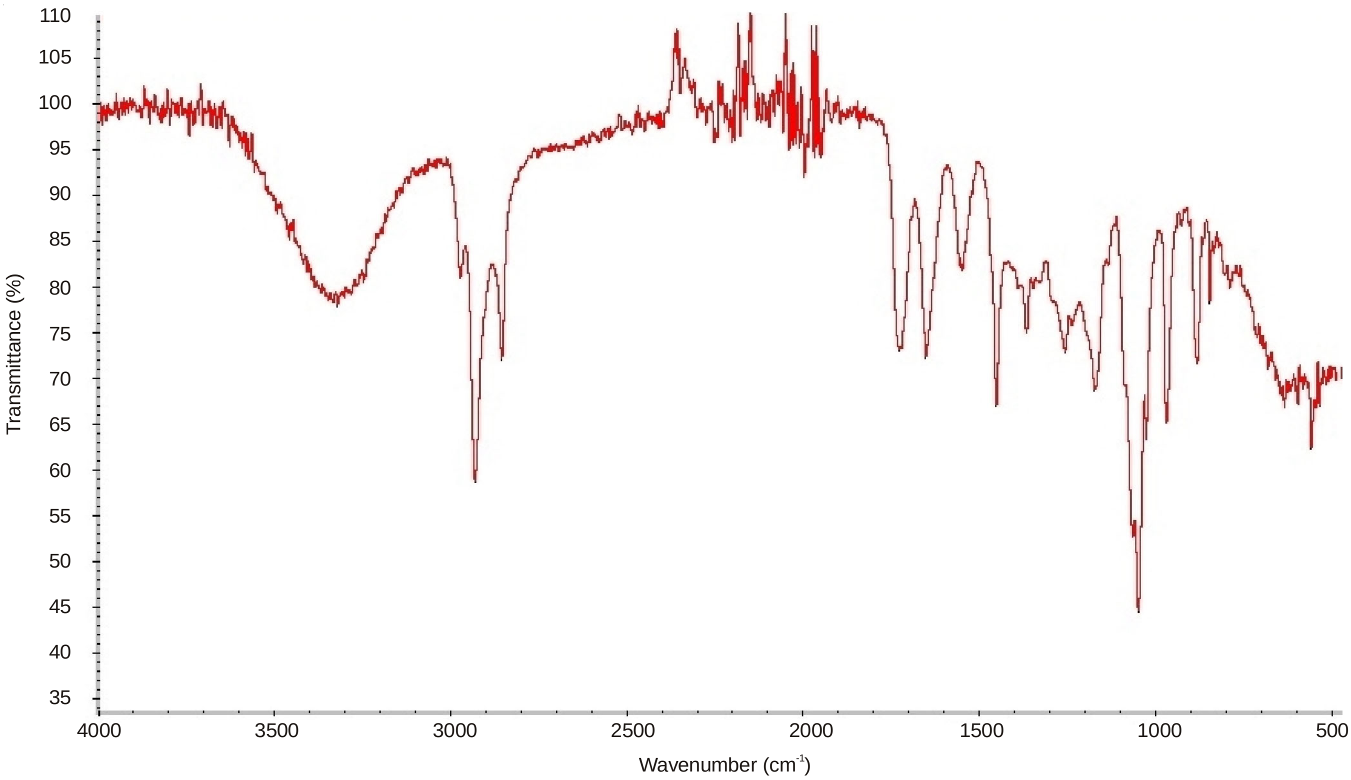

Fig. 2. FTIR spectrum of the gel NR4

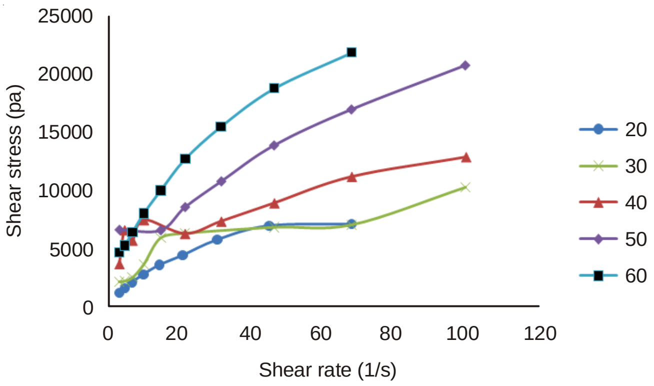

Fig. 3. Graph between shear rate and shear stress for NR1 at 20, 30, 40, 50 and 60 °C

NR3 and at 40 °C in NR4 viscosity only decline with shear rate. It indicates that each system show strong tendency of shear thinning in low shear rate region. This variation of viscosity with shear rate can be explained on the basis of random coil model of macromolecules. Owing to the difference in chain lengths as well as branched structure of *N*-isopropylacrylamide, the monomers acrylic acid, acrylonitrile and *N*-isopropylacrylamide may copolymerize as random coils with no specific geometry and having statistical distribution of shapes of all the chains of polymer molecules. A slight initial increase in viscosity (Fig. 4a) may be due to the fact that the initial shear rate may produce compactness in these coils by propelling water molecules entrapped in them thereby causing slight shear thickening. However, when sufficient shear rate is applied then elongation starts and the molecules align themselves along the direction of flow. This alignment causes decrease in viscosity of the polymeric gels and shear thinning takes place[14,15]. The observed increase in shear stress and decrease in viscosity with shear rate reflects pseudoplastic nature of these hydrogels.

Sensitivity of shear gradient of viscosity to temperature: Effect of temperature on shear gradient of viscosity of

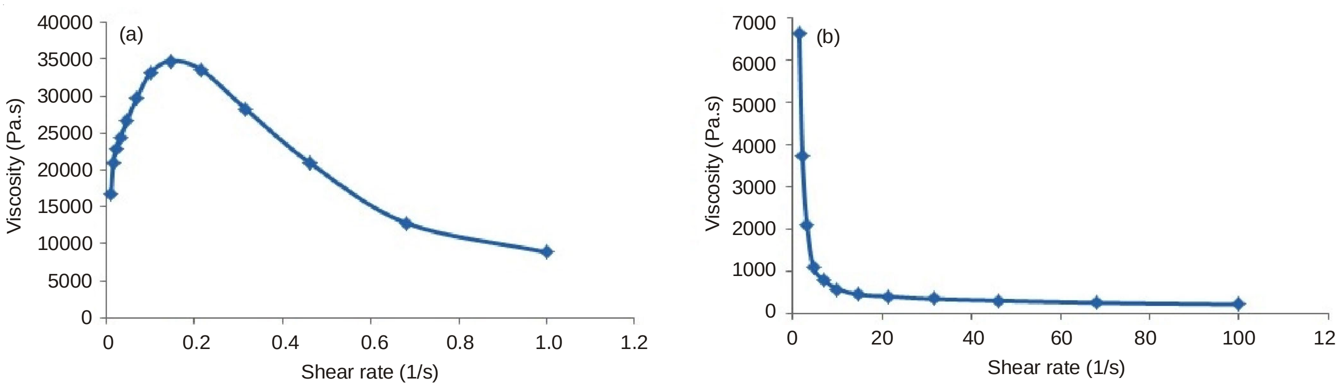

Fig. 4. Rheogram of NR1 at 50 °C (a) at low shear rate (b) at high shear rate

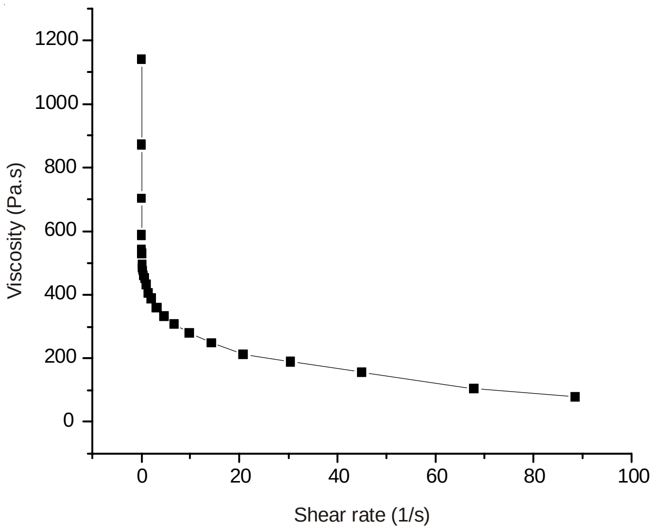

Fig. 5. Rheogram of NR1 at 20 °C

the gels NR1, NR2, NR3 and NR4 at 30, 40 and 50 °C are shown in Table-1. It is clear from this table that viscosity change increases with temperature from 30 to 50 °C. Higher sensitivity of viscosity gradient at higher temperature may be due to the fact that increase in temperature increases the free volume around the molecules and also provide threshold thermal energy to decrease flow inhibiting barriers. Due to this reason, Brownian motions of chains become rapid thus, making the flow easy. It is interesting to note that the temperature sensitivity of viscosity gradient in these gels is 6 folds as temperature is raised from 30 to 40 °C and about 2.5 folds from 40 to 50 °C. The higher sensitivity in the former case may be due to the fact that the behaviour of N-isopropylacrylamide gels change dramatically when transition in temperature is caused from below lower critical solution temperature to above lower critical solution temperature which is about 33 °C.

TABLE-1
SENSITIVITY OF SHEAR GRADIENT OF VISCOSITY TO TEMPERATURE FOR ALL THE GELS

Gels	$\Delta\eta/\Delta\gamma$		
	30 °C	40 °C	50 °C
NR1	730	11990	25960
NR2	454.4	4460	1396
NR3	324	540	9450
NR4	83.51	1.087	3232

Sensitivity of shear gradient of viscosity to shear rate: Sensitivity of shear gradient of viscosity to shear rate for all the gels calculated at 20, 30 and 40 °C are given in Table-2. It is apparent from the table that sensitivity of viscosity change to shear rate of all the gels decreases as contents of *N*-isopropylacrylamide are increased which means that *N*-isopropylacrylamide being branched monomer is creating higher inhibition barrier to flow of the gel in the shear rate range upto 1.0 s^{-1}. If we look at this sensitivity at different temperatures for the gel NR1, the increase in viscosity gradient from 20 to 30 °C is 2.6 folds whereas this increase from 30 to 40 °C (just below LCST to just above LCST) is approximately 10.8 folds. This behaviour also confirms the substantial change in properties of *N*-isopropylacrylamide gels below and after its LCST. However, the gels containing higher amount of *N*-isopropylacrylamide show random behaviour.

TABLE-2
SENSITIVITY OF SHEAR GRADIENT OF VISCOSITY TO SHEAR RATE FOR ALL THE GELS

Gels	$\Delta\eta/\Delta\gamma$		
	30 °C	40 °C	50 °C
NR1	830	855.8	14056.2
NR2	75.96	532.7	5228.6
NR3	90.62	37.983	633.05
NR4	22.86	97.901	1.274

Zero shear viscosity: The values of zero shear viscosity for the gels NR1, NR2, NR3 and NR4 at all the temperatures studied are given in Table-3. It is seen from the table that by lowering the shear rate viscosity of the hydrogel increases and approaches to a limiting value as shear rate approaches zero. This limiting value is larger for each gel at higher temperature indicating greater degree of entanglement at higher temperature. These trends are random at other temperatures studied. Deviation of NR4 from this trend at 30 °C may be attributed to balanced amount of *N*-isopropylacrylamide in the gel. Greater value of η_o at higher temperature for all the gels suggests that these pseudoplastic gels enter into the Newtonian region at higher temperature.

Rheological models: Various rheological models were applied to the experimental data to calculate the rheological parameters such as fluidity index (n), consistency coefficient (k) and yield stress (τ_o).

Ostwald model: Ostwald model[16] commonly known as power law describes flow behaviour of non-Newtonian liquid and is given by the expression (eqn. 1).

$$\tau = k\dot{\gamma}^n \qquad (1)$$

here k is flow consistency and n is fluidity index, τ is shear stress and $\dot{\gamma}$ is shear rate.

For the systems with n < 1 the power law suggests that effective viscosity will decrease with increasing shear rate approaching zero at infinite shear rate. However, real fluids exhibit some minimum and maximum effective viscosities depending upon physical chemistry of the fluids at molecular level. The fluids exhibiting n < 1 are classified as pseudo plastic, n =1 are Newtonian fluids and those having n > 1 are called dilatant fluids. In the present studies, the values of

TABLE-3
ZERO SHEAR VISCOSITY (η_o) OF ALL THE GELS AT ALL THE TEMPERATURES INVESTIGATED

Gels	(η_o (Pa.s)				
	20 °C	30 °C	40 °C	50 °C	60 °C
NR1	842.3	1328	7367	17295	6712
NR2	117.4	372.4	1587	1493	6824
NR3	125.5	54.95	212.1	4526	33401
NR4	766.3	1331	2.093	1331	766.3

fluidity index (n) obtained from this model (Fig. 6) are less than 1 in all the cases revealing the pseudoplastic nature of all the hydrogels. The values of consistency coefficient (k) rise with *N*-isopropylacrylamide concentration which is indicative of increased entanglement in the polymer structure with increase of *N*-isopropylacrylamide contents. However, k shows random behaviour with temperature.

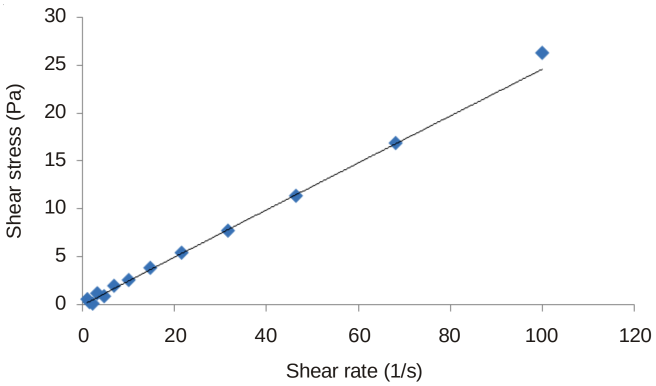

Fig. 6. Fit of Ostwald model for NR4 at 40 °C

This model cannot be fitted well for most polymer systems in the low and high shear range which are the ranges for zero shear viscosity and infinite shear viscosity, respectively. It is well suited for medium shear range. In the present polymer system, deviations can be observed in Fig. 5 in low and high shear rate region.

Ostwald Dewaele model: Ostwald Dewaele model (modification of power law) is given by the expression (eqn. 2).

$$\eta = k\dot{\gamma}^{n-1} \tag{2}$$

The values of n obtained from this model for all the gels at all the temperatures investigated are less than unity again showing pseudo plastic nature of these hydrogels[14].

By comparing the values of R^2 of these two models, it is inferred that the experimental data is better described by Ostwald model which designates flow behaviour for shear thinning without a yield point. The representative plot of Ostwald model for NR4 at 40 °C is shown in Fig. 6. The values of n and k obtained from this model for all the gels at all the temperatures studied are given in Table-4.

Bingham Model: Bingham model is the simplest model to describe flow behaviour of viscoplastic materials. The mathematical form of this model is given as (eqn. 3).

$$\tau = \tau_0 + \mu\dot{\gamma} \tag{3}$$

here τ, τ_0 to and $\dot{\gamma}$ are shear stress, yield stress and shear rate, respectively.

The values of yield stress (τ_o) obtained from this model are in the range of 0.012-239.8 Pa that are comparable to those already reported in literature[17].

Bingham modified model: Bingham modified model was also used for calculation of yield stress in all the gels (NR1, NR2, NR3 and NR4) at all the temperatures studied. The mathematical expression of this model is given in (eqn. 4).

$$\tau = \tau_0 + \mu\dot{\gamma} + c\,\dot{\gamma}^2 \tag{4}$$

here, τ, τ_o and $\dot{\gamma}$ have the same meaning as described above. The values of yield stress obtained in the present studies are in the range of 0.061-4.246 Pa. These values are within the range already reported in literature[18] for other such gels.

Casson model: This model is mathematically expressed as (eqn. 5).

$$\sqrt{\tau} = \sqrt{\tau_o} + \sqrt{\mu\dot{\gamma}} \tag{5}$$

In the current studies, the values of yield stress (τ_o) obtained from this model are in the range of 0.005-0.871Pa.

By comparing the values of R^2 for all the three models, it is concluded that the experimental data for NR1, NR2, NR3 and NR4 are well described by Bingham model at all the temperature studied. Thus, the representative plot of Bingham model for NR2 at 50 °C is shown in Fig. 7. The values of yield stress (τ_o) and R^2 obtained from Bingham model for all the gels at all the temperature studied are given in Table-5. The negative values of yield stress obtained in the current studies have no physical significance and are excluded from the discussion.

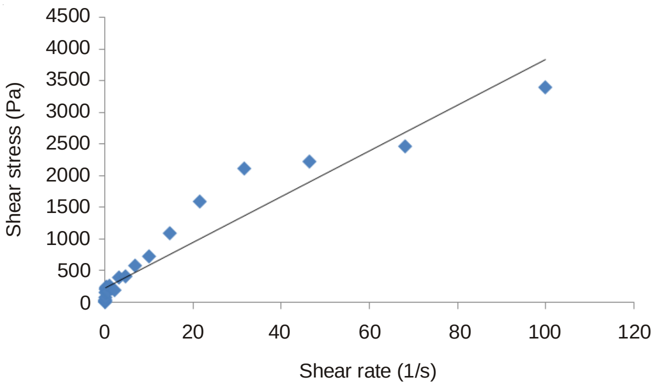

Fig. 7. Fit of Bingham Model for NR2 at 50 °C

Frequency sweep test

Complex viscosity: In the present studies, complex viscosity of the gels NR1, NR2, NR3 and NR4 were measured as a function of angular frequency at different temperatures. It was seen that the complex viscosity of all the gels decreased as the angular frequency increased showing good shear thinning

TABLE-4
VALUES OF n AND k OBTAINED FROM OSTWALD DEWAELE MODEL
FOR ALL THE GELS AT ALL THE TEMPERATURE STUDIED

Temperature (°C)	NR1		NR2		NR3		NR4	
	k	n	k	n	k	n	k	n
20	14.645	0.773	67.62	0.848	90.83	0.922	360.8	0.831
30	0.986	0.748	34.64	0.630	224.7	0.827	1049	0.938
40	1.126	0.866	287.45	0.799	1391	0.963	19569	0.156
50	1043	0.904	2024	0.494	4162	0.244	18629	0.303
60	1494	0.114	2645	0.445	9556	0.998	19783	0.743

TABLE-5
VALUES OF R^2 AND τ^0 (Pa) OF ALL THE GELS AT ALL THE TEMPERATURE STUDIED OBTAINED FROM BINGHAM MODEL

Temperature (°C)	NR1		NR2		NR3		NR4	
	R^2	τ^o (pa)	R^2	τ^o (pa)	R^2	τ^o (pa)	R^2	τ^o (pa)
20	0.999	4.785	0.985	0.968	0.961	1.539	0.998	-0.111
30	0.992	8.066	0.912	6.779	0.995	0.358	0.975	0.447
40	0.999	-102.8	0.993	-68.1	0.969	-3.224	0.995	0.012
50	0.998	-275.3	0.919	239.8	0.990	-170.3	0.974	-54.92
60	0.998	-46.11	0.998	-99.04	0.991	69.69	0.997	-1.675

behaviour at all the temperatures studied. A representative rheogram showing the complex viscosity as a function of angular frequency for NR1 at 40 °C is illustrated in Fig. 8.

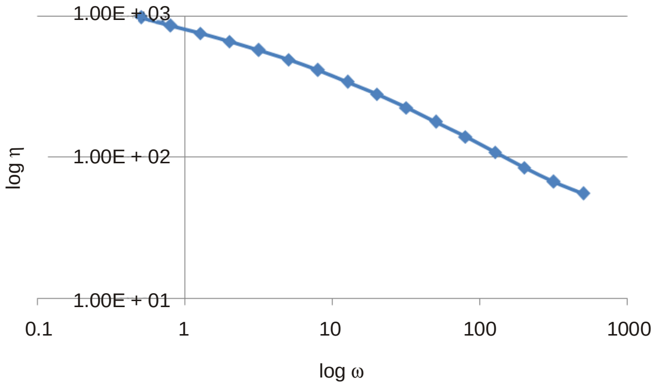

Fig. 8. Angular frequency dependence of complex viscosity of NR1 at 40 °C

Viscoelastic properties: Dynamic moduli G' and G" are the measure of reversible stored and irreversible dissipated energies in the gels, respectively. In other words, G' and G" reflect the elastic and viscous behaviour of the hydrogels, respectively[19].

The present studies of NR1, NR2, NR3 and NR4 revealed that both the G′ (storage modulus) and G″ (loss modulus) increase with angular frequency in all the gels at all the temperatures investigated. The representative angular frequency (ω) dependence of linear viscoelasticity of NR1 at 40 °C is depicted in Fig. 9.

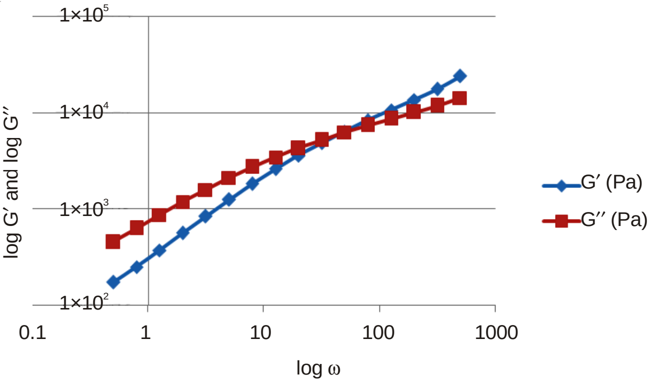

Fig. 9. Angular frequency dependence of dynamic moduli (G' and G") of NR1 at 40 °C

In the explored range of frequency, the values of G" for all the gels at all the temperatures studied are greater as compared to G'. This demonstrates a typical behaviour of liquid like material for all these hydrogels[20].

Cross over frequencies ω_C (intersection point of G' and G") observed in NR1, NR2, NR3 and NR4 hydrogels in the frequency range 0.5-500 s^{-1} are tabulated in Table-6. The shift in ω_C of storage modulus (G') and loss modulus (G") is considered to be indicative of entanglement degree in the polymer structure[21]. It is evident from the Table-6 that ω_C falls as the concentration of *N*-isopropylacrylamide is increased. This may, therefore, be interpreted in terms of increased entanglement in the polymer structure[21]. The crossover frequency can be used for evaluation of the relaxation time t* (The lifetime of the association of the polymer network)[22] by the following eqn. 6.

$$t^* = \frac{2\pi}{\omega_C} \tag{6}$$

where ω_c = cross over frequency.

When the network disturbs, the polymer must need this relaxation time (t*) to reach equilibrium and to form close packed entangled network again. Table-6 reveals that the relaxation time rises as the *N*-isopropylacrylamide contents are increased. This may be due to the fact that as the amount of *N*-isopropylacrylamide rises, entanglement increases owing to which the required time for the attainment of equilibrium and formation of network structure again is increased.

TABLE-6
VALUES OF CROSS OVER FREQUENCIES (ω_C) AND RELAXATION TIME (t*) OF ALL THE GELS AT 30 °C

Samples	ω_c (1/s)	t* (s)
NR1	126	0.049
NR2	50	0.125
NR3	25	0.251
NR4	0.5	12.56

In order to test behaviour of these gels as Maxwellian fluids, Cole-Cole plots[23] were drawn between storage modulus G' and loss modulus G" for all the gels at 30 °C and are shown in Fig. 10(a-d). The shape of these plots has been considered as criterion for Maxwellian fluids. A perfect Maxwellian fluid should exhibit a semicircular shape[24]. The hydrogel NR1 having minimum amount of *N*-isopropylacrylamide did not yield semicircle pattern but as the amount of *N*-isopropylacrylamide increases, the shape of plot turned to form semicircle. In case of NR4 the complete semcircular arc pattern of Cole-Cole plot was observed which advocates perfect maxwellain behaviour of this gel. Semicircular shape of the Cole-Cole plots has also been deliberated to identify the degree of entanglement in the hydrogels[25]. Development of better semicircular shape of Cole-Cole plots in case of gels containing greater amount of *N*-isopropylacrylamide confirms higher degree of

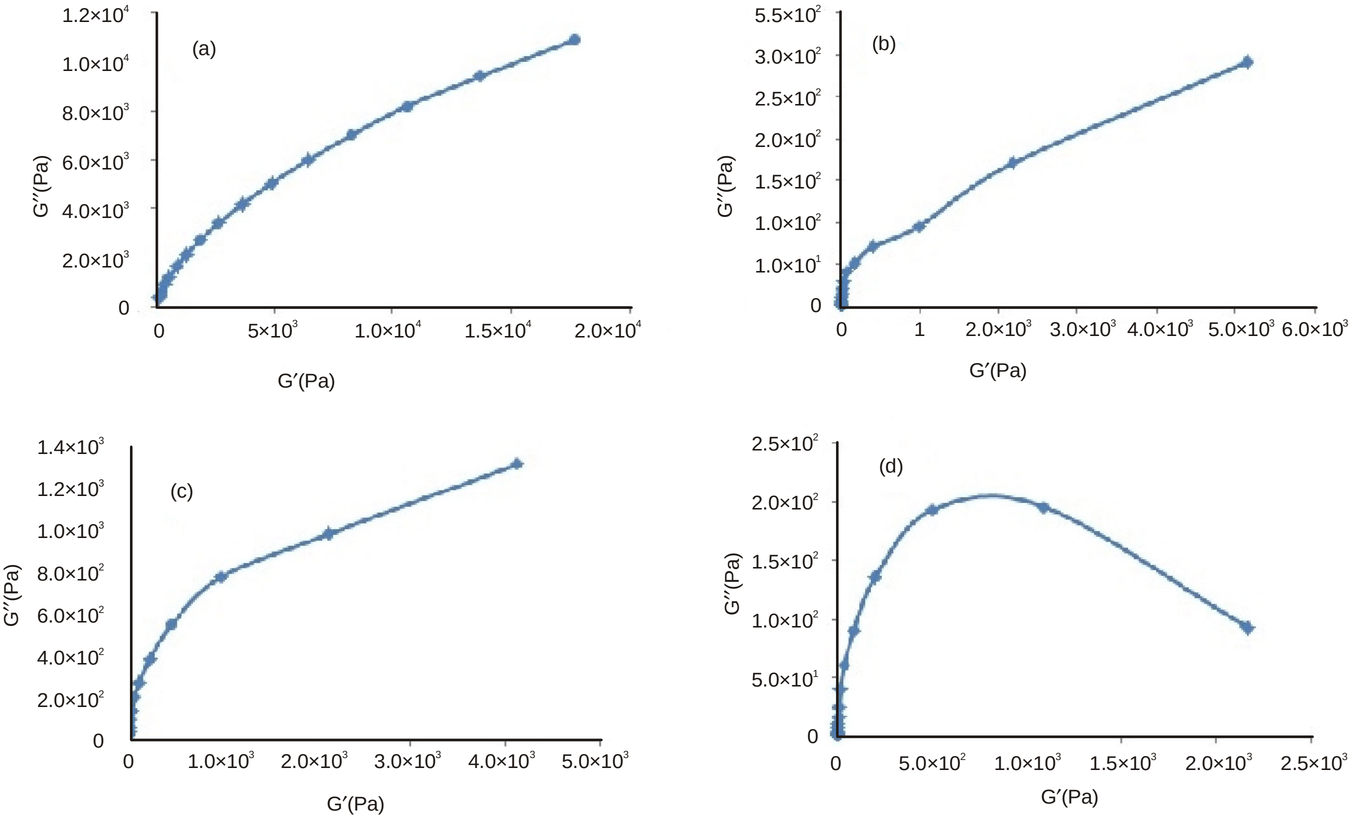

Fig. 10. Cole-Cole plot of (a)NR1 (b) NR2 (c) NR3 (d) NR4 at 40 °C

entanglement in these gels. This could be correlated to branched nature of *N*-isopropylacrylamide which may enhance the interaction and inter chain coupling in the polymer network.

Conclusion

Rheological data for the gels NR1, NR2, NR3 and NR4 is well described by Ostwald model. The value of fluidity index (n) obtained for all the gels is less than 1 reflecting pseudoplastic nature of all the hydrogels. Bingham yield stress obtained for all these gels is in the range comparable to that reported in literature. Fall of measured viscosity with shear rate and complex viscosity with angular frequency represents shear thinning behaviour of all the hydrogels at all the temperature studied. The greater value of storage modulus (G') than loss modulus (G") of these gels in lower frequency range indicates their liquid like viscoelastic behaviour. Shift in cross over frequency towards lower frequency side points out higher degree of entanglement as the *N*-isopropylacrylamide contents increases in the synthesized gels. Perfect semicircular shape of Cole-Cole plot for the gel NR4 (with maximum *N*-isopropylacrylamide content) designates it as Maxwellian fluid whereas the gels with lower *N*-isopropylacrylamide contents (NR1, NR2 and NR3) show deviation from Maxwellian behaviour.

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