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Rheological evaluation of thermoreversible and mucoadhesive nasal gels of Zolmitriptan

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Abstract. – BACKGROUND AND OBJECTIVES, Rheological evaluation of thermoreversible mucoadhesive nasal gel of zolmitriptan is done to determine the steady shear behaviour and gelation temperature. The thermoreversible mucoadhesive polymers are sucessesfully used to increase the contact time of the therapeutic compound in the nasal cavity as well as they cause enhancement in permeation of drug through the nasal mucosa.

MATERIAL AND METHODS, Pluronic (F127) and Pluronic (F 68) were used as thermoreversible polymers in combination with a mucoadhesive polymer obtained from natural resource Zolmiriptan anti migraine drug obtained from Cipla Ltd. Rheometer Brookfield R/S- CPS- PI having cone-and-plate geometry was used for steady shear behaviour study and the gelation temperature was determined by Brookfield R/S plus Rheometer (Brookfield viscometer Ltd, Harlow, Essex, UK) fitted with spindle and Eurotherm cone/plate geometry.

RESULTS, Steady shear behaviour study concludes as content of mucoadhesive polymer starts increasing subsequently the viscosity of the solution starts increasing in the same manner. Gelation temperature study suggests that as the mucoadhesive content was increased in formulation the gelation temperature of the formulation was decreased subsequently. So it was concluded from the study that gelation temperature of the formulation was influenced by the mucoadhesive content. Temperature increases the gelation time of the formulation.

CONCLUSIONS, Above studies indicate that even small difference in the composition of the thermoreversible mucoadhesives gel formulations may cause major change in the rheological behaviour. Although the gelation temperatures of all the three formulations L1, L2 and L3 were below the human nasal temperature, they show different responses to the varied shear rates at different temperatures below and above the temperature of nasal cavity.

Key Words:
Mucoadhesive, Thermoreversible, Nasal gel, Viscosity, Temperature.

Introduction

It is widely accepted that the most suitable and easy way of administrating the drug is the oral route. However, in some cases oral route is not followed because of significant degradation via first pass metabolism. Due to first pass effect, amount of drug available for systemic absorption is less; hence scientists are always in search of alternate routes of drug delivery like parenteral, intramuscular, subcutaneous, intranasal, transdermal etc.[1]. Among them intranasal (IN) administration is a needle free, painless, invasive method of administrating the drugs and it also do not require sterile preparations and hence it serves as an ideal alternative approach to the parenteral drug delivery system[2-4].

The nasal mucosa has a rich vasculature and, therefore, offers greater permeability than any other mucosal surfaces of the body. The nasal route offers faster drug absorption as it bypasses the hepatic first pass metabolism[5-6]. When drug is administered via inhalation the contact time is short and clearance half time is about 15 min[7-8]. Mucoadhesive drug delivery systems improve local and systemic delivery of therapeutic compound as they increase the absorption. Hence, mucoadhesive polymers are used to improve the bioavailability of several drugs[9]. The mucoadhesive polymers have advantage that these don't get absorbed and, therefore, did not show any systemic toxicity.

Mucoadhesive polymer when used as carrier for drug delivery, there is an increase in duration of contact between the drug and nasal mucosa. This augmented contact time increases drug concentration at the site of deposition and drug permeation also get facilitated. To imitate the biological conditions of the body like pH and temperature stimuli responsive polymers are used which leads to change in the formulation properties[10-13]. These changes can be found in conformation, solubility, hydrophilic/hydrophobic balance or in release be-

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haviour of the drug[14]. Temperature is the most predominant stimuli which would be responsible for *in situ* gel formation among the various stimuli like pH, electric field, light and magnetic field[15-24]. When mucoadhesive polymers are used in combination with thermoreversible polymers then this combination provides better drug administration as the mucoadhesive polymer get adhered to the nasal mucosa which increases the residence time of the formulation into nasal cavity. Thermoreversible polymers remain in solution form at storage temperature and convert into gel when administer into cavity at the body temperature. This mechanism minimizes administration difficulties and also improve the retention of formulation by low flow mechanism of gel. In this paper we are going to perform rheological studies on the nasal gel of zolmitriptan.

Materials and Methods

Materials

Pluronic (F127) was supplied from Sigma laboratories Mumbai, India. Pluronic (F 68) was supplied from Himedia laboratories Mumbai, India. Zolmitriptan was kindly provided by Cipla Ltd. (R&D centre, L.B.S.Marg, Vikhroli, Mumbai, Maharastra, India). All other chemicals were of reagent grade and used without further purification.

Preparation of Formulations

Thermoreversible-mucoadhesive gels were prepared by using the cold method[25]. The nasal solution was prepared using 0.65% NaCl, 0.04% KH_2PO_4, 0.09% K_2HPO_4 and 0.02% benzalkonium chloride. pH of this nasal solution was adjusted to 5.5 by 1N HCl. The concentration of drug in nasal solution was kept 2.5 mg/ml. After preparing the nasal solution thermoreversible polymers Pluronic F127 (PF127) and Pluronic F68 (PF68) were solubilized and optimisation of their concentration was done on the basis of gelation temperature.the optimised concentration of PF127 and PF 68were found 22% w/v and 5% w/v respectively. At those respective concentrations they get converted to gel at nasal temperature. Now natural mucoadhesive polymer was slowly added to the optimized thermoreversible formulation with continuous agitation to form three formulations L1, L2, L3 which varied in concentration of mucoadhesive polymer for L1 (0.5% w/v), L2 (1%w/v) and for L3 (1.5% w/v). Composition details are mentioned in the Table I.

Steady Shear Viscosity

The steady shear viscosity of thermoreversible mucoadhesives nasal gels of zolmitriptan was determined using Rheometer Brookfield R/S-CPS-PI having cone-and-plate geometry. The shear rate was varied from 1 to 100/s. Samples were applied to the plate using a spatula to ensure that formulation shearing did not occur. To find out the effect of temperature, the measurements were made at 20.0°C and 36.9°C. Each point is the average of at least nine readings[26].

Gelation Temperature

The sol/gel transition temperatures of all the three batches of zolmitriptan pluronic were determined using a thermostatically controlled Brookfield R/S plus Rheometer (Brookfield Viscometer Ltd, 1 Whitehall Estate, Flex Meadow, Pinnacle west, Harlow, Essex CM19 5TJ, United Kingdom) fitted with spindle and Eurotherm. The cone/plate geometry was used. The cone had a 1.2 cm radius and an angle of 3°C. As the rate gelation is determined simultaneously so temperature was increased in steps of 1°C, from 22°C to 45°C to lo-

Table I. Formulation composition.

Serial number	Ingredients	Formulations		
		L1	L2	L3
1	NaCl	0.65% w/v	0.65% w/v	0.65% w/v
2	KH_2PO_4	0.04% w/v	0.04% w/v	0.04% w/v
3	K_2HPO_4	0.09% w/v	0.09% w/v	0.09% w/v
4	Benzalkonium chloride	0.02% w/v	0.02% w/v	0.02% w/v
5	Pluronic F127	22% w/v	22% w/v	22% w/v
6	Pluronic F 68	5% w/v	5% w/v	5% w/v
7	Mucoadhesive polymer	0.5% w/v	1.0% w/v	1.5% w/v

cate the solution/gel transition point[25]. The gelling temperature was determined graphically as the inflection point on the curve of the apparent viscosity (mPa s) as a function of the temperature (°C).

Effect of pH on the Viscosity

The effect of pH on the viscosity of the formulation L1, L2 and L3 solution was studied at different pH values ranging from 6.8 to 7.8. As the pH of the nasal mucosa lies in this range under different pathological conditions, the solution of these pH was prepared with HCl and NaOH and required amount of nasal gel was dispersed. The apparent viscosity measured at shear rate of 60 s^{-1} using Rheometer Brookfield R/S-CPS PI having cone-and-plate geometry. A graph of apparent viscosity vs pH was plotted.

Effect of Moist Heat Sterilisation

The effect of moist heat sterilisation on the viscosity of all the three formulations L1, L2 and L3 was studied. All the formulations were sterilised at 121°C at 15 psi pressure for 30 min in an autoclave. The viscosity of all the formulations were recorded using Rheometer Brookfield R/S-CPS PI having cone-and-plate geometry at 60 s^{-1} shear rate before, immediately after sterilisation and after a relaxation period of 1 hour till 4 hours.

Results and Discussion

Steady Shear Behaviour

The steady shear behaviour of thermoreversible mucoadhesive polymer based formulations was influenced by the temperature and the content of mucoadhesive polymers. At 20.0°C, all the three formulations L1, L2 and L3 did not shown any notable changes in the viscosity by changing the shear rate from 1 to100 s^{-1}. The viscosity of formulation L3, which contains 1.5% of mucoadhesive polymer, was found greater than the rest formulation. It may be due to the higher concentration of mucoadhesive polymer in the formulation the viscosity of L3 formulation was found 1.5 times more from L1. At 36.9°C the viscosity of nasal gel formulation was found decreased since it increases the shear rate unlike the shear viscosity pattern. At 20.0°C the remarkable shear-thinning behaviour is observed in nasal gel. Newtonian behaviour was showed by all the formulations at 36.9°C and regardless of the measurement conditions, all the shear viscosity curves showed relatively constant slope. It was concluded from the graph plotted that viscosity of the formulation L1 was lower than the other two as it has the lowest concentration of the mucoadhesive polymer. However, as content of mucoadhesive polymer starts increasing form L1 (0.5%) to L2 (1.0%) to L3 (1.5%) subsequently the viscosity of the solution starts increasing in the same manner. Graph obtained is shown in Figure 1 between viscosity and shear rate.

Gelation Temperature

The gelation temperature is the criteria for analysing the properties of a thermoreversible gel. The gelation temperature corresponds to the temperature at which the solution converts to gel temper shear rates. All the formulations exist as liquids at 20.0°C, and exhibit Newtonian coefficient of solubility of block copolymer mi-

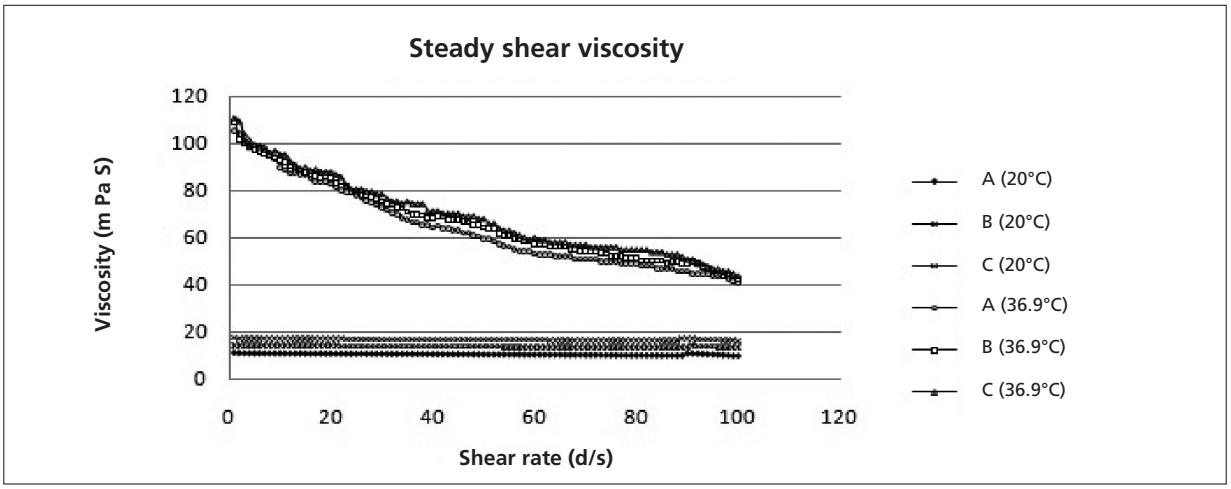

Figure 1. Viscosity *vs* shear rate graph at 36.9°C and 20°C.

Table II. Observation table for gelation temperature.

Serial number	Temperature (°C)	Formulations		
		L1	L2	L3
1	22	60 ± 0.57	69 ± 0.78	96 ± 1.6
2	23	109 ± 0.59	102 ± 0.58	159 ± 0.98
3	24	154 ± 0.79	187 ± 0.47	207 ± 1.46
4	25	207 ± 0.85	243 ± 0.57	298 ± 1.45
5	26	268 ± 1.02	312 ± 0.56	978 ± 0.57
6	27	348 ± 0.95	1008 ± 1.15	1246 ± 0.33
7	28	996 ± 0.57	1276 ± 1.08	1457 ± 1.09
8	29	1435 ± 0.86	1458 ± 1.2	1689 ± 1.57
9	30	1867 ± 0.95	1689 ± 1.6	1879 ± 0.56
10	31	2011 ± 0.49	1998 ± 0.98	2145 ± 0.87
11	32	2258 ± 0.33	2159 ± 1.46	2435 ± 1.56
12	33	2465 ± 1.09	2598 ± 1.45	2765 ± 0.85
13	34	2789 ± 1.57	2875 ± 0.96	3091 ± 1.02
14	35	3018 ± 0.56	3123 ± 0.98	3345 ± 0.95
15	36	3279 ± 0.87	3387 ± 1.01	3567 ± 0.78
16	37	3509 ± 1.56	3619 ± 0.85	3876 ± 0.67
17	38	3865 ± 1.78	3978 ± 0.47	4235 ± 0.97
18	39	4103 ± 0.95	4210 ± 0.37	4456 ± 0.47
19	40	4336 ± 0.67	4468 ± 0.45	4678 ± 0.68
20	41	4573 ± 0.97	4653 ± 0.67	4897 ± 0.47
21	42	4756 ± 0.47	4879 ± 0.86	5098 ± 0.68
22	43	4876 ± 0.68	4907 ± 0.58	5234 ± 0.29
23	44	5097 ± 0.29	5123 ± 0.38	5467 ± 1.07
24	45	5188 ± 1.07	5325 ± 0.46	5598 ± 0.95

celles. Consequently, the micelles become so tightly packed that the solution becomes immobile and gel was formed. The readings obtained for gelation temperature were tabulated as Table II and respective graph obtained was given as Figure 2.

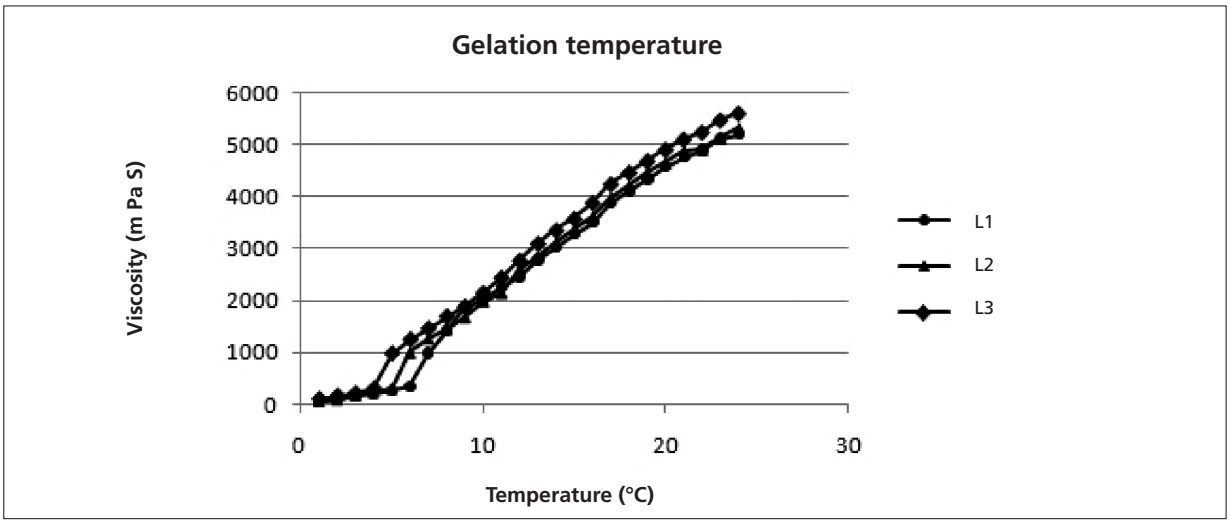

Figure 2. Viscosity vs temperature graph showing gelation temperature.

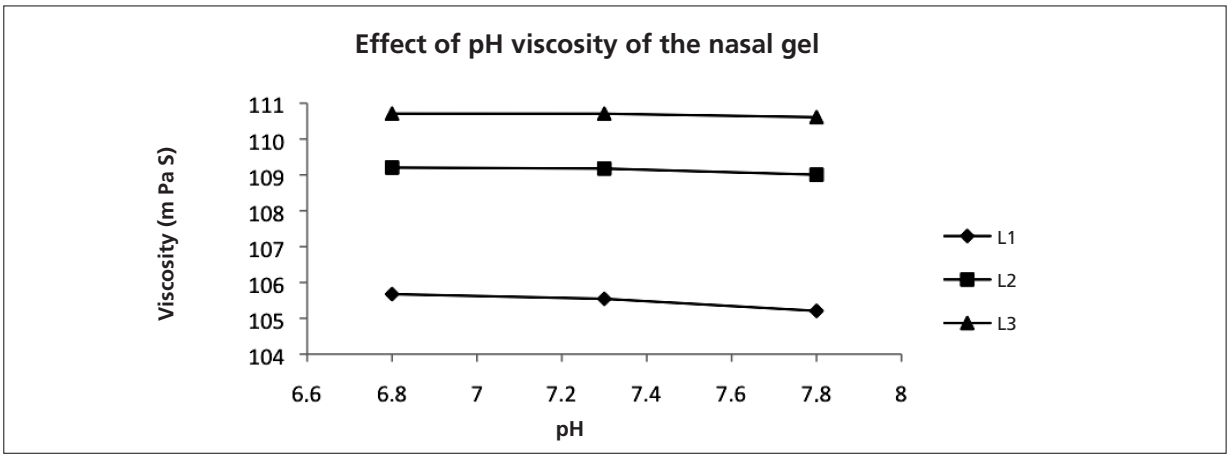

Figure 3. Viscosity *vs* pH graph at 60 s^{-1}shear rate.

Viscosity Behavior Influenced by Change of pH

Nasal mucosa is a very sensitive part of our body and its pH changes between 6.8 and 7.8 under the influence of climatic conditions and in the presence of some sort of allergic conditions like rhinitis. The effect of change of pH was measured on all the three formulations L1, L2 and L3.

From the graph above (Figure 3) it was recorded that the pH of nasal mucosa did not significantly affect the viscosity of the nasal gel.

Effect of Moist Heat Sterilization on Viscosity

Sterilization is a very important part of any pharmaceutical preparation as they are to be sterilized before packaging, so it was essential to test the effect of sterilization on viscosity of nasal gel. For this the formulation was kept in autoclave for 30 minutes at a temperature of 121°C at 15 psi pressure and its viscosity was determined before autoclaving and immediately after autoclaving a sharp downfall in the viscosity was recorded and then the viscosity was measured after every one hour. A complete recovery of the gel with respect to viscosity was obtained in a duration of 4 hours[27-28], as shown in Figure 4.

Conclusions

Above studies indicate that even small difference in the composition of the thermoreversible mucoadhesive gel formulations may cause major change in the rheological behaviour. Although the gelation temperatures of all the three formulations L1, L2 and L3 were below the human

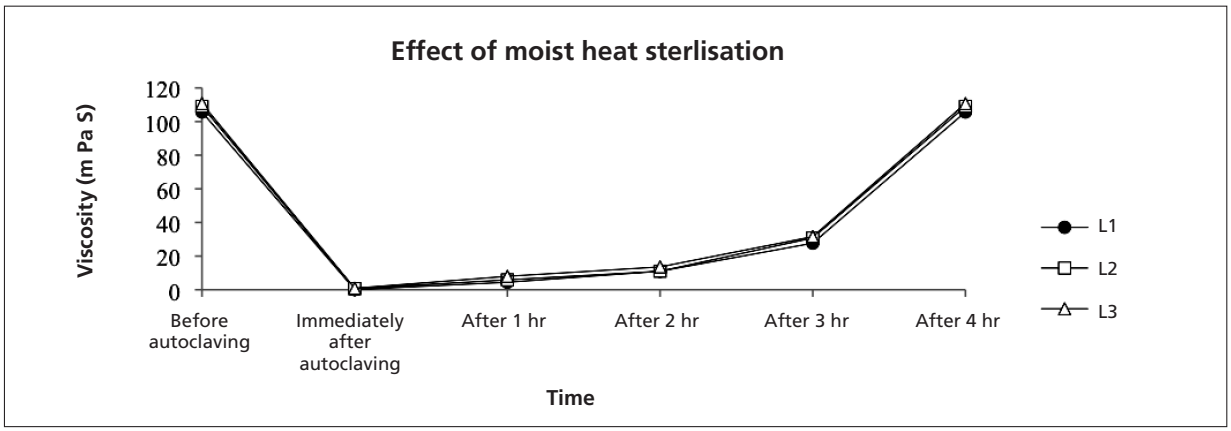

Figure 4. Viscosity *vs* time graph at 60 s^{-1}shear rate.

nasal temperature, they show different responses to the varied shear rates at different temperatures below and above the temperature of nasal cavity. Furthermore, our results suggest that the rheological studies at different temperature and shear rates would be a useful application for the predicting the behaviour of gel and its drug efficacy after intranasal application.

References

1) Behl CR, Pimplaskar HK, Sileno AP, De MJ, Romeo VD. Effects of physicochemical properties and other factors on systemic nasal drug delivery. Adv Drug Deli Rev 1998; 29: 89-116.
2) Chein YW. Novel drug delivery systems. 2nd ed. New York: Marcel Dekker; 1992.
3) Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: Physicochemical and therapeutic aspects. Int J Pharm 2007; 337: 1-24.
4) Turker S, Onur E, Ozer Y. Nasal route and drug delivery systems. Pharm World Sci 2004; 26: 137-142.
5) Chien YW. Biopharmaceutics basis for transmucosal delivery. S.T.P. Pharma Science 1995; 4: 257-275.
6) Illum L, Furraj N, Critcheley H, Davis SS. Nasal administration of gentamicin using a novel microsphere delivery System. Int J Pharm 1988; 46: 261-265.
7) Illum L, Jorgensen H, Bisgaard H, Krogsgaard O, Rossing N. Bioadhesive microspheres as a potential nasal drug delivery system. Int J Pharm 1987; 39: 189-199.
8) Gizurarson S. The relevance of nasal physiology to the design of drug absorption studies. Adv Drug Deli Rev 1993; 11: 329-347.
9) Lueben HL, Lehr CM, Rentel CO, Noach ABJ, Boer de AG, Verhoef JC, Junginger HE. Bioadhesive polymers for the peroral delivery of peptide drugs. J Cont Rel 1994; 29: 329-338.
10) Barker SLR, Ross D, Tarlov MJ, Gaitan M, Locascio LE. Control of flow direction in microfluidic devices with polyelectrolyte multilayers. Anal Chem 2000; 72: 5925-5929.
11) Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. Adv Drug Deli Rev 2002; 54: 53-77.
12) Cunliffe D, De Las Heras Alarcon C, Peter V, Smith JR, Alexander C. Langmuir 2003; 19: 2888-2899.
13) Hoffmann J, Ploner M, Kuckling D, Fisher WJ. Actuators 1999; 77: 139-144.
14) Schmaljohann D. Thermo- and pH responsive polymers in drug delivery. Adv Drug Deliv Rev 2006; 58: 1655-1670.
15) Tanaka H, Tomita H, Takasu A, Hayashi T, Nishi T. Morphological and kinetic evaluation of surface patterns in gels during the swelling process: Evidence of dynamic pattern ordering. Phys Rev Lett 1992; 68: 2794-2797.
16) Hirokawa Y, Tanaka T. Volume phase transition in a nonionic gel. J Chem Phys 1984; 81: 6379-6380.
17) Amiya T, Hirokawa Y, Hirose Y, Yong Li, Tanaka T. Reentrant phase transition of nisopropylacrylamide gels in mixed solvents. J Chem Phys 1987; 86: 2375-2379.
18) Chen G, Hoffman AS. Graft copolymers that exhibit temperature induced phase transitions over a wide range of pH. Nature 1995; 373: 49-53.
19) Tanaka T, Nishio I, Sun ST, Ueno-Nishio S. Collapse of gels in an electric field. Science 1982; 218: 467-469.
20) Osada Y, Okuzaki H, Hori H. A polymer gel with electrically driven motility. Nature 1992; 355: 242-244.
21) Tanaka T, Fillmore D, Sun ST, Nisio I, Swislow G, Shah A. Phase transition in ionic gels. Phys Rev Lett 1980: 45: 1636-1639.
22) Irie M. Stimuli-responsive poly (N-isopropylacrylamide). Photo and chemical induced phase transition. Adv Polym Sci 1993; 110: 49-65.
23) Suzuki A, Tanaka T. Phase transition in polymer gels induced by visible light. Nature 1990; 346: 345.
24) Szabo D, Szeghy G, Zrinyi M. Shape transition of magnetic field sensitive polymer gels. Macromolecules 1998; 31: 6541-6548.
25) Majithiya RJ, Ghosh PK, Umrethia ML, Murthy RSR. Thermoreversible-mucoadhesive gel for nasal delivery of Sumatriptan. AAPS Pharm Sci Technol 2006; 7: E1-7.
26) Kim CK, Chang JY, Oh YK, Choi HG, Kim YB. Rheological evaluation of thermosensitive and mucoadhesive vaginal gels in physiological conditions. Int J Pharm 2002; 241: 155-163.
27) Arslan E, Yener ME, Esin A. Rheological characterization of tahin/pekmez (sesame paste/concentrated grape juice) blends. J Food Eng 2005; 69: 167-172.
28) Woolfe ML, Chaplid MF, Otchere G. Studies on the Mucilages Extracted from Okra Fruits (Hibiscus esculentus L.) and Baobab Leaves (Adansonia digitata L.). J Sci Food Agric 1917; 28: 519-529.