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Research Article

Effect of Oppositely Charged Polymer and Dissolution Media on Rheology of Spray-Dried Ionic Complexes

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Abstract. The purpose of this research was to address the utility of rheological study in understanding the influence of oppositely charged polymers on release of naproxen sodium encapsulated in chitosan particles. The interaction between oppositely charged κ-carrageenan (κ-Ca) and chitosan leads to relatively higher gel strength, which is proportional to the ability to retard the drug release at acidic pH. The oscillatory tests within the linear viscoelastic range where the stress is proportional to the applied strain were performed on the hydrated sample matrices containing chitosan-naproxen sodium spray-dried complexes and k-Ca or hydroxypropyl methylcellulose (HPMC) in various ratios. It was observed that the effect of pH change on the dynamic moduli in spray-dried complexes containing κ-Ca was much stronger than that with HPMC reflecting presence of strong ionic interaction between κ-Ca and chitosan. The combination of oppositely charged polymers in different ratios proved to be useful in modulating the rheological properties of the hydrated formulations and their release-retarding properties. Dynamic moduli can be used to measure gel strength and are significant for the interpretation of oral sustained release spray-dried complexes.

KEY WORDS: gel strength; ionic complexes; rheology.

INTRODUCTION

The use of polyelectrolytes in the design of controlled release drug formulations has received increasing attention in the recent years. As excipients, polyelectrolytes have shown to affect the release of oppositely charged drugs due to formation of stable ionic complexes (1). Oppositely charged polyelectrolytes such as sodium alginate-chitosan (CH), polyacrylic acid-CH, and CH-carrageenan were utilized in the design of controlled release formulations (2–6). CH is a linear cationic polyelectrolyte in which degree of ionization of amine groups depends significantly on the pH of the media. At acidic pH, these groups are protonated, acquire positive charge, and coagulate upon addition of negatively charged drugs (7). Naproxen sodium (NS), a nonsteroidal anti-inflammatory weakly acidic drug, exhibits gastric toxicities, mucosal ulcerations, and hemorrhage due to inhibition of prostaglandin production. The severity of these side effects can be reduced by sustaining and lowering the peak plasma concentrations (8). With NS-CH complex (NSC), though, drug retardation to some extent was observed; further control was not achieved due to the lack of matrix integrity and strength. In such cases, release-retarding polymers were added to strengthen the matrices (7). The previous research from our laboratory has provided evidence to confirm the *in situ* complexation in the matrices containing CH, κ-carrageenan (κ-Ca), and NS (9). The possibility of ionic interactions in NSC prepared by different drying techniques was further explored with κ-Ca and hydroxypropyl methylcellulose (HPMC) (K4), and their effect on water uptake, matrix erosion, and drug release in the different dissolution media were correlated (10). The NSC complexes and NS-CH ratios in the complexes were quantified and optimized based on the dialysis studies. The average maximum binding capacity corresponds to 1:1 NS and CH that was maintained constant during drying processes. The NSC characterization, the evidence of charge presentation in the swollen gel matrices, and their dissolution profiles in the different media have been addressed. The drug dissolution of the NSC complexes at different pH was affected due to the addition of ionic and neutral release-retarding polymers in different concentrations (10). The literature reviews demonstrate the importance of polymer, the hydration, and interparticular forces on the drug dissolution at different pH. The rheological measurements can be an interesting tool to correlate the different factors

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ABBREVIATIONS: Chitosan, CH; Complex modulus, G*; Complex viscosity, η*; Compliance, J; Degree Celsius, °C; Drug release, DR; Gel strength, GS; Hertz, Hz; Hour, h; Hydroxypropyl methylcellulose, HPMC K4; κ-Carrageenan, κ-Ca; Linear viscoelasticity region, LVR; Loss tangent, Tan δ; Loss or viscous modulus, G″; Milligrams, mg; Milliliter, ml; Millimeters, mm; Naproxen sodium, NS; NS-CH complex, NSC; Oscillatory frequency sweep, OFS; Oscillatory stress sweep, OSS; Pascal, Pa; Percentage, %; Rotation per minute, rpm; Seconds, s; Spray dried, SD; Storage or elastic modulus, G′; US Pharmacopeia, USP; Viscosity, η; Volume/volume, *v/v*; Weight/volume, *w/v*; Weight/weight, *w/w*.

that monitor drug dissolution (11–17). Few rheological publications have addressed the rheological behavior of viscoelastic formulations (18–30). Rotational viscometric measurement does not have potential to measure the viscoelastic properties as material is tested in the ground state and is subjected to gross deformation during measurement. Analysis of viscoelastic materials by oscillatory methods is performed within linear viscoelastic region (LVR), confirming the measurement in rheological ground state of the material. However, the relationship between rheological responses, matrix integrity, and stability that determines the rate of drug release is still unexplored. The purpose of this research was to address the influence of oppositely charged polymers and dissolution media on rheology of hydrated matrices containing spray-dried NSC. The present manuscript describes the utility of rheological study in monitoring the effect of κ-Ca and HPMC on release of NS encapsulated in CH particles. The oscillatory tests within the LVR where the stress is proportional to the applied strain was performed on the hydrated sample matrices of NSC-κ-Ca and NSC-HPMC, respectively, in the various ratios.

MATERIALS AND METHODS

Materials

CH (87% deacetylation), molecular weight 80 KDa, κ-Ca (Gelcarin, GP911 NF), HPMC K4, and NS were procured as gift samples from Marine Chemicals, Chennai, India, FMC Corporation, USA (through Signet Chemicals, Mumbai, India), Colorcon Asia Pvt Ltd, Mumbai, India, and Divi Laboratories Pvt Ltd, Hyderabad, India, respectively. All other chemicals were purchased and were of analytical grade.

Methods

Preparation of NSC Complex by Spray Drying

Based on the average maximum binding capacity between CH and NS (10), 3 g CH was dissolved in 100 ml of 1% *v/v* acetic acid solution and was stirred continuously for 24 h at 50 rpm (Whirlmatic Motorless Magnetic Stirrer, Model: WS-MEGA, Spectra Lab, Mumbai, India) to ensure maximum swelling of CH. Equal amount of NS was mixed separately in 100 ml deionized water. Both the solutions were mixed together and were stirred on six station magnetic stirrer at 50 rpm for 24 h at room temperature. The resultant dispersion was then spray dried in a co-current spray system (Twin Cyclon Lab Spray Drier: LU-222 Advanced Model, Labultima, Mumbai), with nozzle size of 0.7 mm, two fluid spray nozzle at inlet temperatures of 165°C to 170°C and outlet temperature of 108°C to 115°C. The vacuum obtained at 45% aspirator was −110 mm WC. The sample was pumped through 0.25 cm annular air orifice at a rate of 2 ml/min (approximately 14.5%) with atomization air pressure of 2 Kg/cm^2. Obtained product was collected and stored in the desiccator.

Drug Content of Spray-Dried Complexes

The partition coefficient (pK_a) of NS is 4.2, and its solubility depends upon the pH of the dissolution medium. Ethanol was incorporated into medium A (30% *v/v* ethanol and 70% *v/v* hydrochloric acid buffer pH 1.2) to compensate for the low solubility of NS at acidic pH (7,9). Twenty-five milligrams of spray-dried (SD) complex was dissolved in 100 ml of the medium A with constant stirring for 24 h. After filtering the dispersion through Whatman filter paper 41 (Spring Field Mill, UK), the solution were assayed at 327.5 nm after appropriate dilutions on double beam UV–VIS Spectrophotometer, Model V-530 (Jasco International Co Ltd, Japan). The experiment was repeated thrice in order to establish accuracy and precision of the method, and the drug content was determined by using the formula:

$$\text{Drug content (\%)} = \text{observed drug content / spray dried complex)} \times 100$$

Preparation of Matrices

Drug content of the spray-dried NSC (SD) was 50% *w/w*± 0.11 that corresponds to 125 mg of NS in the 250 mg of NSC. The SD equivalent to 125 mg of NS was mixed separately with release-retarding polymers κ-Ca and HPMC in the concentration range from 50% to 70% *w/w* of the total mixture. Powder admixtures were compressed with tablet weight of 250±2.3 mg using ten-station Minipress II "D" tooling, tableting machine (Rimek, Karnavati Engineering Ltd, Gujarat, India) fitted with 11-mm diameter flat faced punches on both sides. For comparison purpose, matrices containing SD, physical mixtures of κ-Ca-CH (PM-κ-Ca), and HPMC-CH (PM-HPMC) at 1:1 ratio were also compressed separately in the similar manner. For each batch, 60 matrices were produced with thickness and hardness in the range of 2.6±0.1 mm and 6±0.5 kg/cm^2, respectively. The composition of matrices is given in the Table I.

Free Chitosan Estimation in SD, SD±κ-Ca, and SD±HPMC

Accurately weighed 10 mg plain SD and that with 50%, 60%, and 70% κ-Ca/HPMC (SD15, SD25, SD16, SD26, SD17, and SD27) were added separately to 100 ml of 1% acetic acid solution to give a concentration of 100 μg/ml in calibrated 100-ml volumetric flasks. All the solutions were stirred on six station magnetic stirrer at 40 rpm for 24 h at room temperature. Ten-milliliter samples were withdrawn from each solution after time interval of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h and were filtered through Whatman filter paper 41 (Spring Field Mill, UK). The sink condition was

Table I. Formulation of Spray Dried Matrices

Batch code	% *w/w* Carrageenan	% *w/w* HPMC	Matrix weight (mg)[a]
SD	–	–	250±2
SD15	50	–	375±2
SD16	60	–	400±1.5
SD17	70	–	425±2
SD25	–	50	375±2.5
SD26	–	60	400±2.5
SD27	–	70	425±2

[a] All values represent mean of three batches±standard deviation (n=3)

maintained by replacing equal volume of 1% acetic acid solution. To 5 ml of each filtered solution, equal volumes of acetic acid/acetate buffer (pH5.5) and ninhydrin reagent were added with vigorous shaking and were boiled for 20 min. After the solutions had cooled down, their absorbances were noted at 555 nm in a UV–VIS spectrophotometer for free CH.

Sample Preparation and Rheological Analysis

The preweighed SD, SD15/SD25, SD16/SD26, and SD17/SD27 matrices were placed in 900 ml of medium A (30% *v/v* ethanol and 70% *v/v* hydrochloric acid buffer pH 1.2) for the first 2 h followed by 4 h in 900 ml of medium B (phosphate buffer pH 6.8) of US Pharmacopeia (USP) XXIV Type II dissolution test apparatus (Dissolution Tester Model TDT-08L, Electrolab, Mumbai, India). The studies were performed in triplicate for six matrices from each batch. The temperature of the dissolution medium was maintained at 37±0.5°C and stirred continuously at 100 rpm. The hydrated matrices were removed at an interval of 60 min up to 6 h (6). The dissolution medium A was decanted carefully after 2 h and was replaced by 900 ml of the medium B. Rheological studies were performed at 37±0.5°C with a controlled stress rheometer (Viscotech Rheometer, Rheologica Instruments AB, Lund, Sweden) on the swollen matrices withdrawn from the dissolution bath at various time intervals using a cone and plate sensor with 40 mm diameter and the cone angle 4°, taking care that the sample should occupy full circumference of the plate so that its maximum area will be exposed to the cone and also to reduce the noise level during measurements. The fresh samples of hydrated matrices were used for each measurement. The following tests were carried out after optimizing the parameters, and the data analysis was done with Stress Rheologic Basic software, version 5.0.

Oscillation stress sweep. LVR was determined in the stress range of 1–100 Pa at a constant frequency of 1 Hz.

Oscillation frequency sweep. The samples were exposed to stepwise increasing frequency (0.1–5 Hz) at a central stress value in the LVR range. The behavior of elastic (G′) and viscous (G″) moduli was studied against applied frequency. The complex viscosity of hydrated matrices was plotted against time for 6 h at a frequency of 5 Hz.

Creep recovery. The samples were exposed to the creep for 200 s at a stress of 10 Pa, followed by zero stress recovery for 100 s. The creep compliance *J* (1/Pa) was plotted against time (seconds).

Drug Release Studies

The preweighed six matrices of each batch of SD, SD15/SD25, SD16/SD26, and SD17/SD27 were subjected to 6 h drug release studies in 900 ml of medium A for the first 2 h followed by same volume of medium B for 4 h (USP XXIV Type II, dissolution test apparatus: Dissolution Tester Model TDT-08L, Electrolab, Mumbai, India) at 37±0.5°C and 100 rpm paddle speed. Aliquot of 5 ml samples were withdrawn at predetermined time intervals and replenished with fresh dissolution medium. The aliquots were filtered through Whatman filter paper 41 (Spring Field Mill, UK), and drug concentration was determined spectrophotometrically at wavelengths of 327.5 and 229.4 nm (10).

RESULTS

Free Chitosan Estimation in SD, SD±κ-Ca, and SD±HPMC

The present experiment was designed in order to assess quantitatively the amount of free CH available in the presence of NS and κ-Ca in the spray-dried complexes. Solutions containing SD (100 μg/ml) in 1% *v/v* acetic acid solutions with and without release-retarding polymers were prepared. The quantitative assessment of free CH in the selected batches (SD, SD15, SD25, SD16, and SD26) has been depicted in Fig. 1. Increase in the κ-Ca/HPMC content above 60% did not significantly affect the availability of free CH in the solution and, therefore, the results of SD17/SD27 are not emphasized. The influence of pH of dissolution fluids and concentration of release-retarding polymers on the rheological behavior and thus the structural stability of hydrated SD matrices were studied during 6 h dissolution at 37°C in media A and B, respectively, and the rheological measurements were performed on the swollen tablets to have an insight of the micro- and macrostructure of the CH-NS swollen gel system. Two types of oscillatory measurements were performed in triplicate for each sample. The first one was oscillation stress sweep that was used to investigate the influence of the stress on dynamic moduli G′ and G″ at a constant frequency of 1 Hz and a stress range of 1–100 Pa. LVR was determined by plotting G′ *versus* stress in logarithmic scale. In the linear region of LVR, the G′ response of a material is characteristic for its microstructure at rest, and for the stress above the linear limit, the structure is affected or even destroyed during the measurement and is therefore defined as the maximum stress that could be applied without affecting the dynamic moduli. This stress was then used to perform the other oscillatory tests such as frequency sweep at a constant stress within LVR, and the frequency was varied from 0.1 to 5 Hz. Loss or viscous and storage or elastic moduli are connected by Tan δ, a ratio between G″ and G′ during frequency sweep. An inverse value of Tan δ represents the gel strength (GS) of matrices. In the present study, it was calculated by taking the moduli values at frequency of 5 Hz. Table II records LVR and Tan δ of matrices at the end of the second and sixth hour during dissolution. Table III depicts the

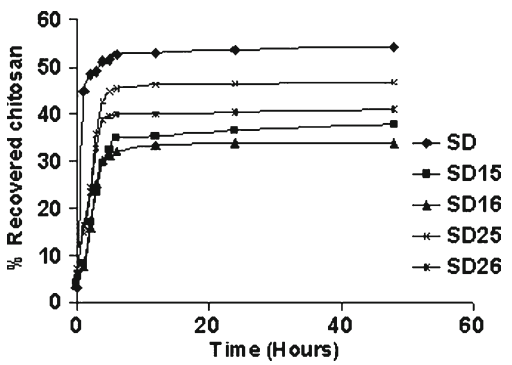

Fig. 1. Free chitosan estimation in SD, SD15, SD25, SD16, and SD26

Table II. Linear Viscoelasticity Region and Gel Strength of Different Hydrated Matrices

		Stress sweep		Frequency sweep					
		LVR (Pa)		Second hour		Sixth hour		Tan δ	
Sr. number	Matrix	Second hour	Sixth hour	G′(Pa)	G″ (Pa)	G′(Pa)	G″ (Pa)	Second hour	Sixth hour
1	SD	0.14–0.20	–	64,550±7.51	98,000±5.29	–	–	1.52±0.0015	Structure breakdown
2	SD15	1.62–20.22	4.43–15.36	16.14±0.005	2.01±0.019	6,765±3.21	1,169±2.29	0.12±0.0023	0.17±0.0025
3	SD16	0.43–5.73	0.36–1.60	16.22±0.014	1.92±0.017	12,500±3.40	1,982±3.68	0.11±0.0012	0.16±0.0022
4	SD17	0.36–7.20	4.1–100	24.03±0.026	4.30±0.029	26,150±3.81	3,653±2.24	0.17±0.0015	0.14±0.0026
5	SD25	0.08–0.77	2.03–21.89	10.19±0.012	22.39±0.03	15,060±4.63	3,400±1.22	0.49±0.0027	0.22±0.0032
6	SD26	0.01–0.10	0.75–12.64	15.03±0.011	31.86±0.023	5,180±4.11	1,060±2.67	0.21±0.0011	0.20±0.0045
7	SD27	0.3–3.40	2.09–18.58	18.7±0.014	65.47±0.037	16,380±3.98	3,921±2.76	0.41±0.0021	0.24±0.0013
8	PM-κ Ca	0.15–0.2	0.91–0.11	42.1±0.019	6.09±0.042	136.2±3.65	13.75±0.11	0.14±0.0034	0.10±0.0036
9	PM-HPMC	0.25–6.03	0.05–0.17	15.51±0.02	7.61±0.034	17,370±3.11	3,383±2.14	0.5±0.0012	0.19±0.0041

All values represent mean of three batches±standard deviation (n=3)

relation between percentage of *w*/*v* drug release and Tan δ after 6 h dissolution from NSC matrices with different concentration of κ-Ca/HPMC. Figure 2(a, b) presents the effect of frequency on the storage modulus or elastic (G′) loss or viscous (G″) modulus for the hydrated optimized matrices at the end of the second hour. The recoverable and non-recoverable part of the samples was interpreted with the help of creep curve. Figure 3 presents relationship between compliance (*J*) and time for the hydrated optimized matrices at the end of the second hour during dissolution. Figure 4 relates Tan δ with percentage of *w*/*w* concentration of κ-Ca or HPMC. The drug release and Tan δ data for SD15/SD25, SD16/SD26, and SD17/SD27 after 6 h at n=3 were substituted in Graph Pad Prism 5 software to quantify the correlation between the two variables (XY pair).

DISCUSSION

Quantitative assessment of free CH in NSC was performed to confirm and elucidate the drug −CH/CH-κ-Ca or HPMC binding. Studies were conducted on 10 mg of SD15/SD25, SD16/SD26, and SD17/SD27 powder samples, respectively, with 50–70% κ-Ca or HPMC, and the rest (50–30%) being NSC complex that contained 50% CH. Ten milligrams of SD15/SD25 would contain 5 mg of NSC, with 25 μgm/ml of CH theoretically. For plain SD, 10 mg of samples contained 50 μgm/ml of CH. The percentage of CH recovered during the experiment has been expressed graphically in Fig. 1 for the selected batches SD, SD15, SD25, SD16, and SD26. It was observed that SD15, SD25, SD16, and SD26 released 37.8%, 46.78%, 33.88%, and 40.93% CH, respectively, in 48 h, whereas SD released 54.2% CH during the same period suggesting increased release of free CH in plain SD due to its ionization in 1% acetic acid. Reduced availability of free CH in SD15 and SD16 indicated probable presence of CH-κ-Ca ionic interaction. It seems that due to the formation of viscous

Table III. Percentage of Drug Release (DR) and Tan δ After 6 h Dissolution

S.N	Batch	TAN δ	% DR
1	SD	1.52±0.0015	60±3.6
2	SD15	0.17±0.0025	33±1.00
3	SD16	0.16±0.0022	32±1.16
4	SD17	0.14±0.0026	32±0.70
5	SD25	0.22±0.0032	40±0.57
6	SD26	0.20±0.0045	38±1.50
7	SD27	0.24±0.0013	36±1.52

All values represent mean of three batches±standard deviation (n=3)

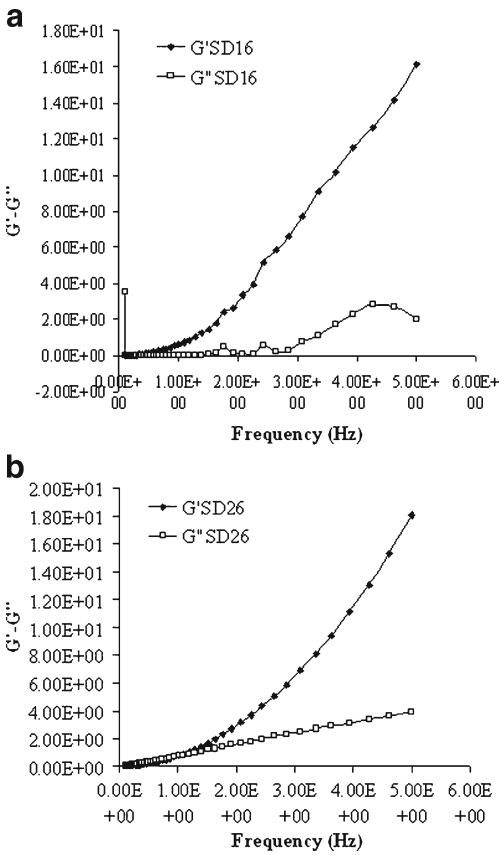

Fig. 2. **a** Frequency sweep of hydrated SD16 matrices after 2 h dissolution. **b** Frequency sweep of hydrated SD26 matrices after 2 h dissolution

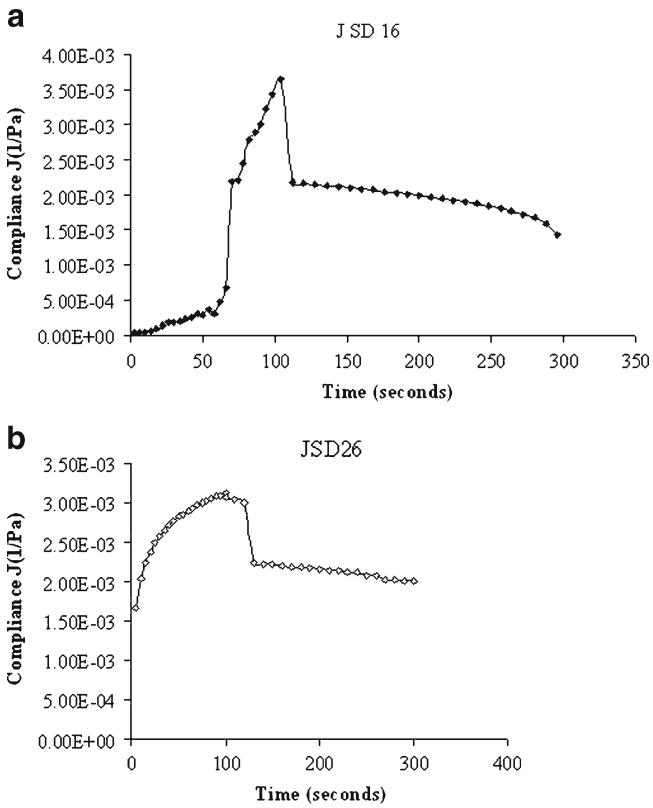

Fig. 3. **a** Creep curves of hydrated SD16 matrices after 2 h dissolution. **b** Creep curves of hydrated SD26 matrices after 2 h dissolution

barrier, the availability of free CH in the SD25 and SD26 was less as compared to that in the plain SD sample. SD15 and SD16 released less amount of free CH after 48 h probably due to CH-NS and CH-κ-Ca interactions as confirmed by Fourier transform infrared spectroscopy and powder X-ray diffraction studies, and the results have been presented in our previous work (9). The difference in the molecular weight of polymers can be one more potential confounding factor as it affects the charge density and hence the ionic interactions between two oppositely charged polymers in NSC. The molecular weights of CH, κ-Ca, and HPMC are 80,000, 400,000–600,000 (with minimum 100,000), and 10,000–1,500,000 Da, respectively. The rheological tests were performed in triplicate on all the hydrated matrices of NSC with and without release-retarding polymers. These measurements gave information about (1) structure and the energy stored in elastic bonds of a sample (storage or elastic modulus, G′), (2) viscosity of the material or the amount of energy dissipated in the sample (loss or viscous modulus, G″), and (3) the zero viscosity and elastic (recoverable)/viscous (irreversible) deformation of a material. The parameters characterizing the rheological behavior of the SD matrices with and without release-retarding polymers are G′, G″, and Tan δ. The stress range over which G′ is independent of the applied stress is known as the LVR. The end of linear region is called the critical stress, beyond which the structure of the material gets disturbed. It is well established in the literature that a shortened LVR and a lower critical stress indicates weaker gel structure (lower G′). Over the LVR, the material structure is not broken (31,32). G′ reflects the solid-like component of the viscoelastic behavior of the formulation, and it is required to determine the stored and recovered energy per cycle of deformation. Tan δ is a measure of the ratio of energy lost to the energy stored in a cyclic deformation that describes the viscoelastic nature or GS of semisolids and polymer solutions. A lower value for Tan δ indicates a higher degree of elasticity and thus GS of the sample (32). To obtain information about viscous and the elastic behavior of an investigated system and the network structure formed by particle–particle interactions, oscillation frequency sweep test has to be conducted. If performed within the LVR, a frequency sweep provides a fingerprint (consistency spectra) of a viscoelastic system under non-destructive conditions (32). Thus, the systems are examined in their rheological ground state without disrupting the structure like continuous shear techniques do. The interpretation of data from oscillatory studies on viscoelastic materials can be conveniently visualized by considering a number of elastic elements or springs coupled in series with a number of viscous dashpots or pistons. At very low frequencies, the springs can elongate, and dashpots have time to move to extensions which significantly exceed those of the springs. The deformation of the springs will not continue indefinitely and will reach an equilibrium, at which point, no further deformation will take place, whereas the dashpots will deform continuously under the imposed oscillatory shear. During this phase, energy is dissipated, and the sample behaves as a liquid (η will be high and G′ will be low). At high frequencies, the springs can elongate and contract under the imposed oscillatory shear, but the dashpots have little time to react to the high frequencies. Energy is stored in each cycle of deformation, and the material will behave as an elastic solid (G′ will be high and η will be low). At intermediate frequencies, both springs and dashpots will provide contribution, and viscoelastic behavior is observed (32). Data in Table II provides a comparative measure of both the elastic and viscous contributions after oscillatory stress sweep and oscillatory frequency sweep. The oscillatory test within the LVR was performed on the hydrated SD with and without release-retarding polymers. Tan δ was highest in the plain SD matrices at the end of the second hour at acidic pH accounting for their poor GS. It decreased with an addition of the release-retarding polymers up to certain optimum concentration. This suggests that the poor GS of plain SD may improve in the presence of the moderate concentrations of the added polymers. However, above 60% *w*/*w* concentration, no improvement in the GS was noted for SD2# matrices indicating that beyond a certain limit, the addition of

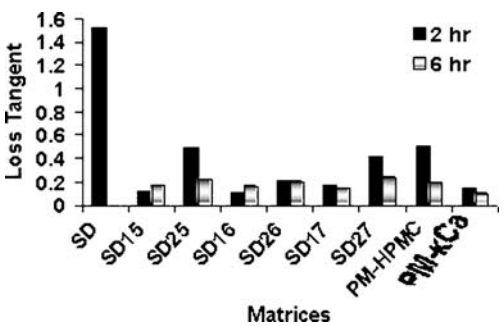

Fig. 4. Comparative representation of Tan δ for different formulations

HPMC will simply increase the bulk and viscosity of the mixture. Due to the satisfactory GS, SD16 and SD26 were selected as optimized batches for further studies. Figure 2(a, b) presents the relation between moduli (G″ and G′) and frequency (ν) of the optimized batches at the end of the second hour during drug dissolution. The values of G′, G″, and Tan δ for the hydrated NSC matrices at the end of 5 Hz in the frequency range of 0.1 to 5 Hz are presented in the Table II. The creep recovery data also support the above observations as no structural recovery was detected in the plain SD matrices. In SD1# matrices, G′ was much higher than G″ in both the dissolution fluids. Increased GS of SD15, SD16, and SD17 matrices suggest the domination of elastic responses. The ionic interaction between CH-κ-Ca in the acidic medium could be one of the reasons for such behavior. However, contrast observations were noted in SD25, SD26, and SD27 matrices, wherein viscous behavior was dominant with higher Tan δ values and poor GS at the acidic pH, confirming absence of ionic interactions between CH-HPMC. The elasticity and hence the GS of these matrices were improved in the alkaline environment. An addition of the release-retarding polymers to the SD affected the dynamic moduli considerably. As evident from Tan δ, the hydrated SD1# matrices were more rigid than that of hydrated SD2# compacts, probably due to the swelling and *in situ* complexation of the gel network in the former one. At acidic pH, the polyelectrolyte effect between protonated CH and κ-Ca is expected to be strong due to the electrostatic forces thereby promoting gel swelling. HPMC being nonionic does not ionize in the alkaline solution in contrast to κ-Ca which is highly ionized in the alkaline environment and is expected to entangle more in the alkaline pH. The extension of the ionized κ-Ca chains in the alkaline environment may facilitate the formation of entanglements resulting in a stronger gel network. Increase in the G′ values at alkaline pH for all matrices support strengthening of gel network that approached towards elasticity. The increased degree of change in tan delta of SD2# samples was induced due to the swelling of nonionic HPMC in the alkaline medium. As evident from Table II, G′ was greater than G″ probably due to ionic interactions between CH-κ-Ca and *vice versa* for CH-HPMC samples. Figure 2 also support that at the acidic pH, G′ was always higher than G″ for hydrated SD16 matrices and *vice versa* in SD26 samples, depicting viscous behavior of the later one at lower frequencies. However, after crossover frequency, SD26 presented an elastic behavior. Crossover shift towards higher frequency is a sign of more elastic properties. The moduli were constant in the alkaline medium at higher frequency range and therefore the plots are not included in the present study. The above observations were supported by the creep recovery data. Figure 3(a, b) illustrates a typical creep behavior of SD16 and SD26 samples. Elastic nature of SD16 was supported by the smaller compliance (J) values. The relation between drug release and GS has been presented in Fig. 4. Ethanol was incorporated into the dissolution media 0.1 N HCL to compensate for the low solubility of NS at acidic pH (7,9). The values of percentage of drug release obtained after 6 h dissolution for SD matrices with and without release-retarding polymers were related with the Tan δ values. Slower drug release from SD1# as compared to SD2# was observed in all the media. The NS-CH and CH-κ-Ca ionic interactions contributed in sustaining the drug release (10). Overall release of NS at the acidic pH was less. As can be observed from Table III and Fig. 4, Tan δ and drug release of plain SD matrices were highest indicating their poor GS as compared to other matrices. Presence of release controlling external polymers not only improved the matrix integrity of SD but also retarded drug release by forming highly viscous barrier along the periphery of the compacts. In order to measure the association between the two variables, i.e., drug release and GS (Tan δ), the SD1# and SD2# matrices were subjected to correlation analysis after 6 h *in vitro* dissolution at n=3. At 95% confidence interval, the Spearman "r" coefficient amongst SD1# and SD2# matrices was 0.5026 with P value <0.0001, indicating a moderate correlation between the GS and drug release of SD1# and SD2# matrices. The electrostatic interactions between CH-κ-Ca leads to relatively higher GS that controls the drug release from sustained release dosage forms.

CONCLUSION

Dynamic moduli are excellent tool to measure the GS and are significant for the interpretation of drug release from oral sustained release formulations.

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