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Assessment of Suspending Properties of Katira Gum: Formulation and Evaluation of Nimesulide Suspension

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Abstract There are several hydrophilic polymers that have been employed as suspending agents in pharmaceutical suspensions due to their ability to form colloidal gel in aqueous medium. In the present study, katira gum obtained from the bark of *Cochlospermum religiosum* has been evaluated as suspending agent in nimesulide suspension and compared with acacia gum at concentration of 1-5%. Sedimentation volume, rheology, particle size, degree of flocculation and in-vitro drug release were employed as assessment parameters. The result showed that at all concentrations, katira gum higher suspending capability compared acacia gum. The sedimentation volume was found to increase from 0.36 to 1 (A1-A3) and 0.26 to 0.56 (B1-B3). The viscosity of suspensions (A1 and A2) containing gum katira as suspending agent was found to be 1.35 and 2.4 centipoise and 0.63- 1.05 centipoise (B1-B3). Plots between shear stress and rate of shear were plotted using different concentrations indicates the obedience to newtonian behaviour. Degree of flocculation of gum katira and gum acacia suspension was established to be 1.69 and 1.05 respectively.

Keywords: Suspension, katira gum, acacia gum, sedimentation rate, rheology, particle size, degree of flocculation

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1. INTRODUCTION

Pharmaceutical suspensions are defined as heterogeneous systems made up of two phases - the continuous or external phase, generally a liquid or semisolid, and the dispersed phase, generally insoluble solids, dispersed throughout the continuous phase (Lloyd and Levinson, 2006). Pharmaceutical

suspensions are thermodynamically unstable systems that requires the use of stabilizer or suspending agent which reduces the rate of settling and permits redispersion of any settled particulate matter by increasing the consistency of suspending medium or by colloidal action (Subrahmanyam, 2000; Mbang *et al,* 2004) . Various polymers that have been used as suspending agents include the natural polymers e.g. acacia, tragacanth, xanthan; cellulose derivatives e.g. methylcellulose, carboxymethylcellolose; synthetic polymers e.g. polyvinylpyrrolidone, carbomer; and particulate colloids e.g. bentonite, veegum (Mahmud *et al*, 2010). There is the need for continuous search for cheaper and effective natural excipients that could be used in the formulation of pharmaceutical suspensions that could meet the needs of drug formulators.

Katira gum is an insoluble gum derived from the bark of *Cochlospermum religiosum*. The gum is sweet, semi-transparent, insoluble in water, but swells into a pasty transparent mass with water (Mann *et al*, 2010). It has thermogenic and sedative properties and has been found to be useful in cough, diarrhoea, dysentery, pharyngitis, gonorrhoea, syphilis and trachoma (Jain and Babbar, 2002). Katira gum has been used as a gelling agent in microbial tissue culture media (Kirtikar and Basu, 1998) and its drug release retardant in the matrix tablets has been established (Singh *et al*, 2010). Kitara gum has been reported to possess extensive degree of swelling (Singh *et al*, 2010). However, the suspending properties of Kitara gum have not been investigated.

Thus in the present study, the suitability of katira gum as a suspending agent in nimesulide suspension has been investigated in comparison with acacia. The suspension was evaluated in terms of sedimentation volume, viscosity, particle size analysis and in vitro drug release studies. The effect of storage on the stability of the suspension was also investigated.

2. MATERIALS AND METHODS

2.1 Materials

The materials used include nimesulide (Park Pharmaceuticals, Baddi, India), benzoic acid (Loba Chemicals, Mumbai, India), Katira and acacia gum (Yarrow Chem, Mumbai, India). Katita gum was powdered and passed through 60 mesh sieve. All other chemicals and reagents were of analytical grade and were used as such.

2.2 Preparation of suspension

Nimesulide and benzoic acid were finely triturated with the aid of mortar and pestle. Mucilage of the gums was prepared by hydration using some portion

of the distilled water. The mucilage of suspending agent was added in same increments to the powdered drug and triturated until homogeneous slurry was obtained. This was transferred to a 100 ml beaker and the remaining vehicle was used to rinse the mortar to make up the required volume. Details of the composition of the suspension formulations are given in Table 1. To observe the sedimentation rate and volume, the suspensions were transferred into measuring cylinders which were stoppered and placed on a vibration- free surface and stored at 29±2ºC.

Table 1. Formulation code table of the formulated suspension batches

Ingredients	A1	A2	A3	B1	B2	B3
Nimesulide (mg)	100	100	100	100	100	100
Katira gum (gm)	1	2.5	5	-	-	-
Acacia gum (gm)	-	-	-	1	2.5	5
Benzoic acid solution (ml)	1	1	1	1	1	1
Distilled water	q s					

2.3 Evaluation of suspension properties

2.3.1 Physical test

The suspensions were observed for physical changes such as aggregation, caking and crystal growth formation at weekly intervals for a period of 6 weeks.

2.3.2 Sedimentation volume and rate

The sedimentation volume of the suspensions was determined by measuring the volume of the sediments in the suspension placed in the measuring cylinders at 5 days interval for duration of 40 days. The sedimentation volume (F) was calculated using the formula:

$$F = V_u / V_o$$

Where, V_u = volume of sediment at time t, and V_o = original volume of sediment before settling occurred. A graph of sedimentation volume, F, against time was plotted and the sedimentation rate was calculated.

2.3.3 Degree of flocculation

The degree of flocculation (β) was obtained from the expressed:

$$\beta = F / F_\infty$$

Where, F = sedimentation volume in flocculated suspension and F_∞= sedimentation volume in deflocculated suspension.

2.3.4 Rheological assessment

The viscosities of the prepared suspensions were determined using Brookfield viscometer (Model DV-2 +LV, Brookfield Laboratories, Massachusetts, USA). The suspension was placed in a 600 ml beaker, appropriate enough to immerse the spindle groove in the fluid. Speed of rotation was varied to determine its effect on the viscosity values since drag force is known to alter with changes on the spindle size and rotational speed. Viscosity values at rotational speeds of 10, 20, 50, and 100 rpm were determined at room temperature. The viscosity was determined at different rotation speed and the graphs of viscosity versus speed of rotation were plotted.

2.3.5 Flow rate

The time required for suspension sample to flow through a 10 ml pipette was determined and the flow rate calculated from the equation:

Flow rate = Volume of suspension in pipette (ml) / Flow time (seconds)

All determinations were made in triplicate and the results were expressed as mean values.

2.3.6 Particle size analysis

The particle sizes of the suspensions were measured using microscopic method. Drops of suspensions were separately placed on a slide and placed on the (pre-calibrated) stage of the microscope. The particle sizes of 500 particles were measured and the mean particle sizes was computed.

2.3.7 In vitro dissolution study

The USP Type 2 dissolution apparatus (DS 8000, Lab India, Mumbai, India) was used to determine the dissolution time of the suspension at 37±0.5ºC in 900 ml alkaline borate buffer, pH 8.4, at a paddle rotation speed of 50 rpm. The suspension was then carefully introduced to the bottom of the flask using 10 ml glass syringe. Aliquots of 10 ml dissolution medium were withdrawn at predefined time intervals and replaced with equal volume of fresh dissolution medium using a 10ml glass syringe. The sample was immediately filtered through Whatman filter paper and the drug content determined using UV-visible spectrophotometer (2202 Systronics, India) at wavelength of 397nm.

2.3.8 Stability studies

Accelerated stability testing was carried out as per ICH guidelines (40ºC/75% RH). Suspensions were packed in HDPE bottles and kept in a stability chamber with set temperature and relative humidity. The suspensions were evaluated at 0 days, 3 months and 6 months for pH, particle size, viscosity, sedimentation volume and degree of flocculation.

3. RESULTS AND DISCUSSION

In addition to therapeutic efficacy and chemical stability, a properly prepared pharmaceutical suspension should settle slowly and be readily redispersed by gentle shaking. Moreover the particle size of the suspension should remain fairly constant throughout the period of undisturbed standing and the suspension should easily pourable from the container. The suspending agent should be used at the optimum concentration such that it should maintain physical stability of the suspension in addition to not rendering the formulation to be too viscous to agitate or pour. At very low concentrations of suspending agent, a large number of sites remain available on the surface of dispersed solids leading to relatively lower particle polymer bridging. Intermediate levels of the polymer leads to optimum flocculation and sedimentation volume of the suspension as sufficient adsorption sites remain available for the formation of more inter-particulate bridges. At high polymer concentrations there will be complete coverage of the dispersed particles by the polymer and no more sites will be available for bridging of the particles leading to formation of deflocculated suspension. Hence suspending agent in optimum concentration would be required for formation of aesthetically stable suspension.

The sedimentation volume was 1 at 5 % concentration level of katira gum, but the formulated suspension was very viscous such that it viscosity could not be determined. Sedimentation volume or F values as shown in Table 2 indicates that 2.5 % concentration of katira gum was showing better result when compared with 5 % concentration of acacia gum (Figure 1 and 2). Hence, when compared with conventional suspending agent lower concentrations of katira gum were showing adequate suspending agent properties for formulating suspension dosage forms. The physicochemical properties of nimesulide suspension containing the different concentration of suspending agents are presented in Table 3. No sign of aggregation, caking and crystal growth formation was seen in any of the prepared batches of the suspension.

Viscosity is a vital factor that determines the stability and pourability of the suspension formulation. The optimum concentration of the suspending agent imparting thickening of the suspension has to be identified such that

Table 2. Sedimentation volume of nimesulide suspension using different concentrations of suspending agents

Batch No.	Sedimentation volume Time in days								
	0	**5**	**10**	**15**	**20**	**25**	**30**	**35**	**40**
A1	1	0.6	0.38	0.38	0.36	0.36	0.36	0.36	0.36
A2	1	0.84	0.8	0.76	0.76	0.76	0.76	0.76	0.76
A3	1	1	1	1	1	1	1	1	1
B1	1	0.6	0.32	0.28	0.28	0.28	0.28	0.26	0.26
B2	1	0.8	0.4	0.4	0.36	0.36	0.36	0.36	0.36
B3	1	0.9	0.76	0.59	0.59	0.56	0.56	0.56	0.56

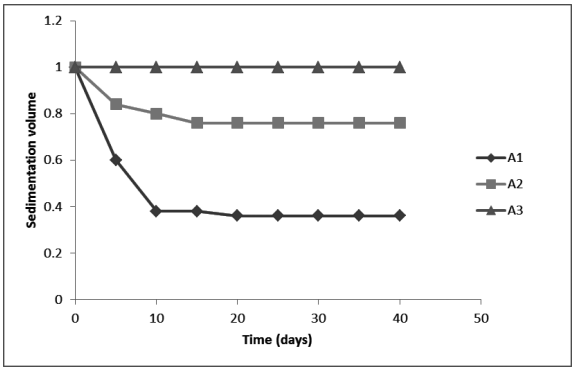

Figure 1. Sedimentation rate of different concentrations of katira gum

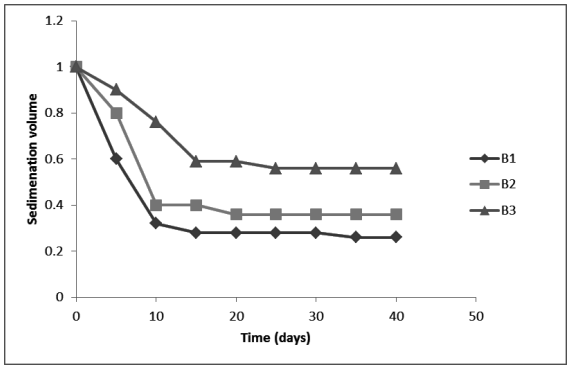

Figure 2. Sedimentation rate of different concentrations of gum acacia

Table 3. The physicochemical properties of nimesulide suspension containing the different concentration of suspending agents

Batch No.	Viscosity (centipoise)	Flow rate (ml s^{-1})	Degree of flocculation	Mean particle size (µm)
A1	1.35±0.13	0.96	1.69 ± 0.26	3.9 ± 0.25
A2	2.4±0.24	0.82	3.26 ± 0.15	4.2 ± 0.15
A3	Too viscous, indeterminable		5.15 ± 0.25	4.4 ± 0.22
B1	0.63±0.34	1.65	1.05 ± 0.12	5.2 ±0.12
B2	0.84±0.45	1.45	2.87 ± 0.25	5.3 ± 0.21
B3	1.05±0.57	0.92	4.20 ± 0.21	5.5 ± 0.15

the stability is maintained alongside the dispensability of the suspension. Viscosity of katira gum was found to be 1.35 and 2.4 centipoise at 0.2 and 2.5 % concentration levels whereas for acacia gum the values are 0.63, 0.84 and 1.05 centipoise respectively for 0.2, 2.5 and 5 % concentrations of the suspending agent (Table 3). Katira gum was found to offer more stable suspension at lower concentrations compared to acacia gum. Inverse relationship was observed between concentration of suspending agent and the flow rate of the formulation. Flow rate was found to be 0.96 and 0.82 for A1 and A2 and 1.65, 1.45 and 0.92 for B1, B2 and B3 batches of suspensions respectively. Plots between shear stress and rate of shear were plotted using different concentrations indicates the obedience to newtonian behaviour (Figure 3 and 4).

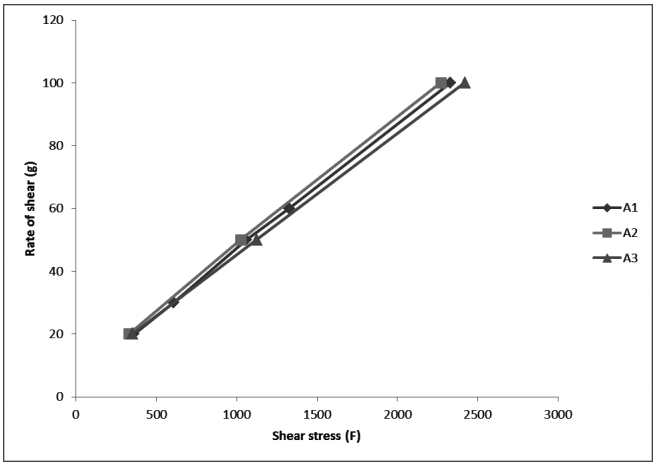

Figure 3. Shear stress versus rate of shear plot of katira gum suspension

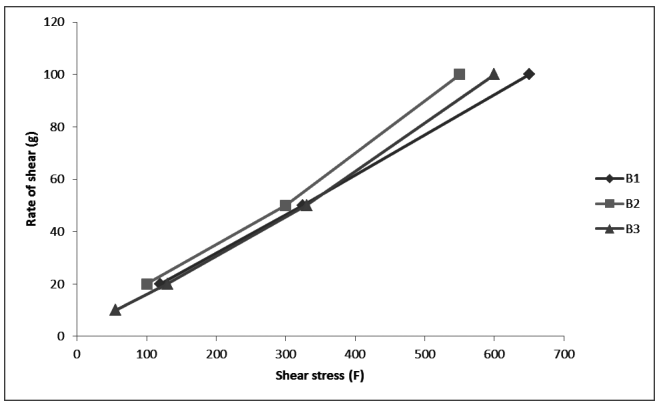

Figure 4. Shear stress versus rate of shear plot of acacia gum suspension

The degree of flocculation was found to increase from 1.69 ± 0.26 to 5.15 ± 0.25 from A1 to A3 and 1.05 ± 0.12 to 4.2 ± 0.21 from B1 to B3 formulated batches of the suspension (Table 4). The incremental increase in degree of flocculation with the increase in the concentration of suspending agent is an indicator of formation of more stable suspension. The higher values of degree of flocculation with katira gum indicates it to be a better suspending agent compared to acacia gum. For physical stability of suspensions, it is important to consider particle size of dispersed phase. Mean particle size was 3.9 ± 0.25, 4.4 ± 0.22, 5.2 ± 0.12, 5.5 ± 0.15 for A1, A3, B1 and B3 respectively (Table 4).

The in vitro release of nimesulide from the formulated batches of suspension are shown in figure 5. The profiles depict concentration (suspending agent) dependent reduction in the release of drug from the suspension. The release after 5 minutes was found to be 77.74%, 69.57% and 56.77% for A1, A2 and A3 and 97.20%, 78.06% and 50.01% for B1, B2 and B3 respectively. All prepared batches of suspensions released more than 80% of the drug with 30 minutes of in vitro release study.

Table 5 shows the effect of accelerated storage conditions on pH, particle size, viscosity, sedimentation volume and degree of flocculation. It is evident from the stability testing results that there was no significant change in pH, particle size, viscosity and degree of flocculation. of any batch of the prepared suspensions. However a concentration dependent increase in sedimentation volume was observed in all the prepared batches of suspension.

Table 4. Accelerated stability testing data of formulated batches of suspension

Batch	Parameters (months)														
	pH			Particle size			Viscosity			Sedimentation volume			Degree of flocculation		
	0	3	6	0	3	6	0	3	6	0	3	6	0	3	6
A1	6.2± 0.1	6.28± 0.2	6.30± 0.22	3.9± 0.25	4.13± 0.38	4.96± 0.22	1.35± 0.13	1.31± 0.56	1.26± 0.34	1	0.36	0.35	1.69± 0.26	1.65± 0.23	1.63± 0.16
A2	6.21± 0.15	6.25± 0.21	6.26± 0.23	4.2± 0.15	4.28± 0.32	4.33± 0.19	2.4± 0.24	2.32± 0.46	2.25± 0.31	1	0.76	0.75	3.26± 0.15	3.22± 0.23	3.02± 0.32
A3	6.25± 0.24	6.31± 0.35	6.33± 0.19	4.4± 0.22	4.42± 0.32	4.42± 0.24	-	-	-	1	1	0.9	5.15± 0.25	5.10± 0.13	5.03± 0.19
B1	5.24± 0.45	5.29± 0.53	5.30± 0.23	5.2± 0.12	5.88± 0.34	6.10± 0.28	0.63± 0.34	0.70± 0.24	0.65± 0.67	1	0.28	0.26	1.05± 0.12	1.01± 0.33	0.99± 0.10
B2	5.31± 0.37	5.37± 0.55	5.40± 0.34	5.3± 0.21	5.62± 0.64	5.86± 0.76	0.84± 0.45	0.80± 0.56	0.76± 0.33	1	0.36	0.34	2.87± 0.25	2.82± 0.29	2.79± 0.15
B3	5.35± 0.37	5.36± 0.34	5.38± 0.24	5.5± 0.15	5.52± 0.43	5.59± 0.23	1.05± 0.57	1.01± 0.39	0.96± 0.32	1	0.56	0.53	4.2± 0.21	4.13± 0.14	4.03± 0.23

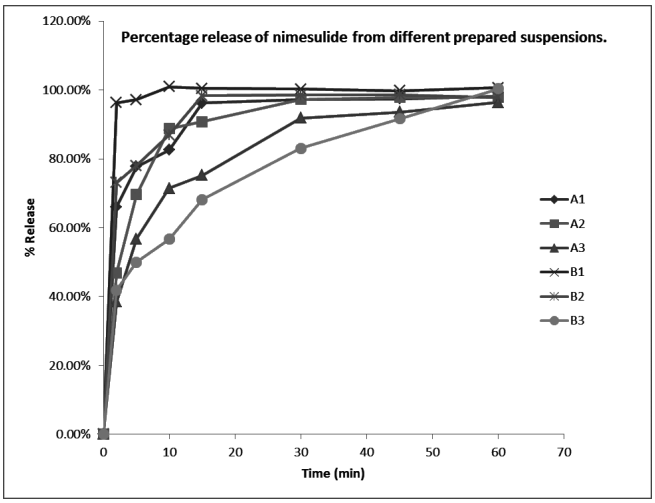

Figure 5. Drug release profile of formulated suspensions

4. CONCLUSION

Katira gum could be used as suspending agent in the formulation of suspensions. Moreover, the parametric tests of suspensions prove katira gum to be a better suspending agent compared with acacia gum. Hence katira gum can be employed as stabilizer and thickener of choice when high viscosity is desired especially in cosmetic, pharmaceutical and food industries.

5. ACKNOWLEDGEMENT

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