International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Issue 2, 2011

Research Article

EVALUATION OF GREWIA POLYSACCHARIDE GUM AS A SUSPENDING AGENT

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Received: 27 Dec 2010, Revised and Accepted: 28 Jan 2011

ABSTRACT

Grewia polysaccharide gum was extracted from the inner stem bark of *Grewia mollis*, thereupon drying was achieved by air-drying (ADGG) or freeze-drying (FDGG). The suspending ability of grewia gum was compared to that of xanthan (XAN), sodium carboxymethylcellulose (SCMC) and acacia gum (ACA) in ibuprofen suspension. The physical stability of the ibuprofen suspension formulations, containing the suspending agents at a range of concentrations, was assessed by appearance and pourability, viscosity and rheology, sedimentation volume ratio, redispersibility, degree of flocculation, zeta potential and microbial load. The ADGG and FDGG-containing formulations exhibited pseudoplastic flow with a viscosity-imparting ability superior to ACA and SCMC-containing formulations, but not XAN, at all concentrations. ADGG-containing formulations (1.0 %w/v) remained fully suspended for over 42 days while all the other formulations sedimented within 24 hours except XAN-containing formulations. The FDGG and ADGG-containing formulations were more easily redispersed than SCMC-containing formulations and exhibited a higher degree of flocculation at 0.75 %w/v than ACA or SCMC-containing formulations. The zeta potential of XAN, ADGG or FDGG-containing suspension formulations were more negative than -30 mV and therefore more stable than SCMC or ACA-containing suspension formulations (zeta potentials of < -23 mV). All suspension formulations showed evidence of microbial growth on storage. ADGG or FDGG may provide a suitable alternative as suspending agent in pharmaceutical oral suspensions.

Keywords: Grewia polysaccharide gum, Ibuprofen, Oral suspension, Suspending agent.

INTRODUCTION

Pharmaceutical suspensions are solid dispersions of insoluble or sparingly-soluble drugs in an aqueous or oily vehicle. They are intended for oral administration, topical application or parenteral administration of drugs. Formulation of drugs as suspensions for oral administration is a convenient way to administer insoluble or sparingly soluble drugs to infants and the elderly that have difficulty swallowing tablets or capsules. They are also useful to mask taste, and to control the absorption rate of the drug.

A major challenge to formulation of oral suspensions is that of physical stability. The solid insoluble drug separates from the vehicle and settles to the bottom of the container. It is desirable that such a formulation re-suspend easily upon shaking. Settling and aggregation may result in the formation of cakes that are difficult to re-suspend. This is a common occurrence in deflocculated systems which do not easily settle but are difficult to re-disperse once set[1]. Redispersibility of insoluble drug substance is therefore a critical requirement in the evaluation of suspensions. It is also a critical requirement that the drug in suspension be homogeneously mixed and remain both physically and chemically stable during the shelf-life of the formulation. This is important because of the need to dispense a fairly uniform and accurate dose of the medicament per portion of the suspension.

In order to address these problems several ingredients perform different or synergistic roles in the formulation of oral suspensions. Hydrophilic colloids such as xanthan gum, acacia and the cellulose derivatives have been used as suspending agents and, like surfactants, can produce a deflocculated system when used in low concentrations. Acacia or gum Arabic is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent[2]. Sodium carboxymethylcellulose and xanthan gum are also used in pharmaceutical suspensions for their suspending effect. Grewia polysaccharide gum is a novel polysaccharide gum obtained by extraction from the inner stem bark of the shrub, *Grewia mollis* (Family, Tiliaceae). It is found abundantly growing wild or cultivated in the middle belt region of Nigeria where it is used as food ingredient in some delicacies. The gum has been isolated and reported to contain glucose, galactose, rhamnose, arabinose and xylose as the monosaccharide components[3]. Some physicochemical[4], binding[5], rheological[6], bioadhesive[7], and mechanical properties of aqueous based grewia gum films[8] have been evaluated. Such natural polymers are widely used in pharmaceutical dosage forms because of their biocompatibility, low cost and relatively free availability[9] and initial studies have indicated that grewia polysaccharide gum may be a useful pharmaceutical excipient in suspension formulations. If suitable, its relative abundance would have economical benefits to the area and the gum may have pharmaceutical benefits over costly and imported alternatives.

In this study, the suspending properties of the air-dried (ADGG) or freeze-dried (FDGG) grewia gum was compared with xanthan (XAN), sodium carboxymethylcellulose (SCMC) and acacia gum (ACA) as suspending agents for ibuprofen oral suspension at a concentration of 0.5 %, 0.75 % or 1.0 %w/w. The evaluation parameters were appearance and pourability, viscosity and rheology, sedimentation volume, redispersdibility, degree of flocculation, zeta potential and microbial load.

MATERIALS AND METHODS

The materials used for this study as procured from their manufacturers were: xanthan gum, sodium carboxymethylcellulose (MW 250,000), gum Arabic, Tween 20, glycerol, sodium saccharin, nutrient broth, nutrient agar and ibuprofen were purchased from Sigma. Grewia polysaccharide gum was extracted in our laboratory as detailed previously [3] and is therefore described briefly below.

Extraction and purification of grewia gum

The dried and pulverized inner stem bark of *Grewia mollis* was dispersed in 0.1 % w/v sodium metabisulphite and hydrated for 48 hours after which it was passed through muslin to remove extraneous materials. The filtrate was treated with 0.1N NaOH and centrifuged at 3,000 rpm. The supernatant treated with acidified ethanol was centrifuged again as described previously. The resultant supernatant was treated with absolute ethanol and the precipitate was wet-milled and then filtered through muslin to remove excess ethanol before air-drying the product or the precipitate was redispersed in water and thereupon freeze-dried. Freeze-drying was carried out using a Modulyo freeze drier (Thermo Fisher Scientific, UK) at – 40°C for 72 hours. The freeze-dried and air-dried product was dry milled and passed through a 1.0 mm sieve, weighed and stored in air-tight containers until use.

Formulation of ibuprofen suspension

Ibuprofen suspension was formulated using ibuprofen (2.0 g), glycerol (10.0 mL), sorbitol F 70 wt% (10.0 mL), Tween 20 (2.0 mL),

sodium saccharin (0.02 g) and suspending agent (0.5, 0.75 or 1.0 %w/v) in 100 mL of suspension. The suspending agents were incorporated at similar concentrations so the economical viability of the gums could be compared at similar concentrations. The stated amounts of saccharin, suspending agent and ibuprofen were accurately weighed and geometrically triturated with a mortar and pestle. Thereupon, sorbitol F 70 wt%, followed by glycerol was added while triturating continuously. Water was added to facilitate pouring and the content was poured into a 100 mL bottle and made up to 100 mL with rinses from the mortar. A total of 300 mL of formulation was made for each batch. Suspending agents evaluated were xanthan gum (XAN), acacia gum (ACA), sodium carboxymethylcellulose (SCMC) and air dried grewia gum (ADGG) or freeze dried grewia gum (FDGG).

pH, viscosity and rheology

The pH of the suspension formulations were measured using a pH meter. The viscosity of the preparations made with the different suspending agents was measured using a viscometer (DV-1+version 5, Brookfield Engineering Labs, Stoughton-USA) at 20°C using spindle number 2 and shear rates of 0.2, 0.4, 0.6, 1.0 and 2.0 reciprocal seconds.

Sedimentation volume

The suspension formulation (50 mL) was poured separately into 100 mL measuring cylinders and sedimentation volume was read after 1, 2, 3 and 7 days, and thereafter at weekly intervals for 12 weeks. Triplicate results were obtained for each formulation. Sedimentation volume was calculated according to the equation:

$$= / \qquad 1$$

Where, F = sedimentation volume, V_u = ultimate height of sediment and V_o = initial height of total suspension.

Degree of flocculation

Potassium dihydrogen phosphate (0.04 mL) was added as a flocculating agent. The degree of flocculation (β) was assessed by comparing the ultimate sedimentation volume (F_α) with control formulations in which no flocculating agent was added.

Degree of flocculation, $\beta = F / F_\alpha$ *equation* 2

Where, F is the ultimate flocculation height in the flocculated system and, F_α is the ultimate sedimentation height in deflocculated system

Redispersibility

The suspension formulations (35 mL) were transferred into capped cone tubes and evaluated for redispersibility at 7 day intervals, by turning them through a ninety degree cycle. Redispersibility was recorded as the number of vertical inversions required to completely re-suspend the formulation in the cone tube.

Zeta potential

The zeta potential of the formulated suspensions was determined using a ZetaPlus (Brookhaven Instruments Corporation, USA). Approximately 1 mL of suspension was transferred into a plastic cuvette using a pipette and diluted with distilled water. The Brookhaven zeta potential software was used with measurement parameters set to a temperature of 25°C and refractive index (1.33). The zeta potential of the formulations was determined on day 0, 7, 14, 21 and day 28 post formulation.

Microbiological evaluation

The microbial loads of suspension formulations containing 1.0 %w/v of suspending agents were determined according to the BP 2010[10] method for assessing microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use. This was done on day 0 of formulation and on day 21 following storage under ambient conditions.

Statistical analysis

The data was subjected to ANOVA using the software Instat (GraphPad, San Diego, CA).

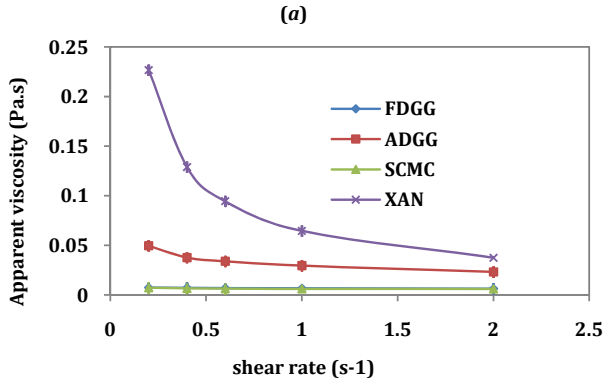
RESULTS AND DISCUSSION

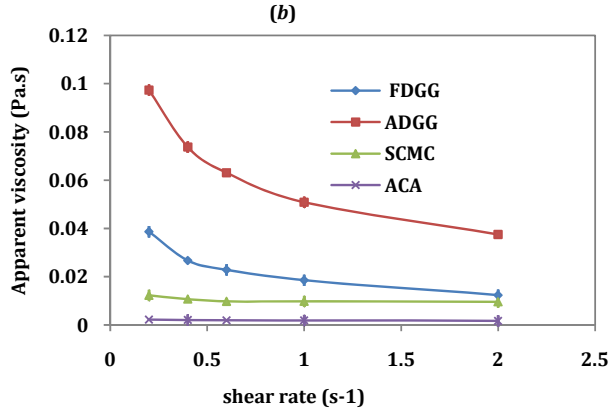
Appearance and pourability

All XAN-containing suspension formulations formed dispersed systems, with ACA and SCMC-containing formulations sedimenting after 2 hours. ADGG or FDGG-containing formulations did not sediment as quickly as the ACA or SCMC-containing formulations. This is attributable to the viscosity of the suspension formulations. Higher viscosity suspension formulations will sediment at a slower rate. Also the sedimentation volumes of ADGG or FDGG-containing formulations were larger. All the suspension formulations were pourable except those containing xanthan (1.0 %w/v) due to their high viscosity.

Viscosity, rheology and pH

A plot of apparent viscosity against shear rate (Figure 1*a*-*c*) showed that, at polymer concentrations of 0.5 %, 0.75 %, and 1.0 %w/v, all the formulated suspensions exhibited typical pseudoplastic flow behaviour. XAN-containing formulations had the highest viscosity at all concentrations and the flow characteristics could not be plotted at 0.75 % and 1.0 %w/v (fig.1*b* and *c*) because the suspension viscosity was beyond the experimentation range. This was also the case for ACA-containing suspension formulations at 0.5 %w/v (fig. 1*a*) but in this instance however, the ACA-containing formulations (at all concentrations) were of low viscosity and flow behaviour was Newtonian. Pseudoplastic flow behaviour is a desirable property in the formulation of suspensions[1] enhancing re-dispersion and pourability of the suspension prior to administration. At lower concentrations the SCMC and FDGG-containing formulations tended towards Newtonian flow.





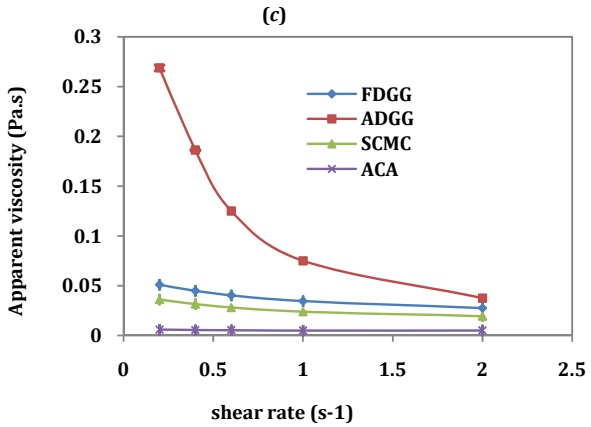


Fig. 1: Rheological profiles of ibuprofen suspension formulations containing *a*) 0.5%, *b*) 0.75% and *c*) 1.0% w/v suspending agent (n=3, mean ± s.d.).

The apparent viscosity (at 0.2 s^{-1}) of the suspensions containing 0.75 %w/v suspending agent was measured on day 1 and day 84 post formulation. Figure 2 shows that there is a reduction in the apparent viscosity of the suspension formulations on storage. Generally, natural polysaccharides may show a gradual loss or reduction in the viscosity of their dispersions or solutions with age due to bacterial or mould growth[1].

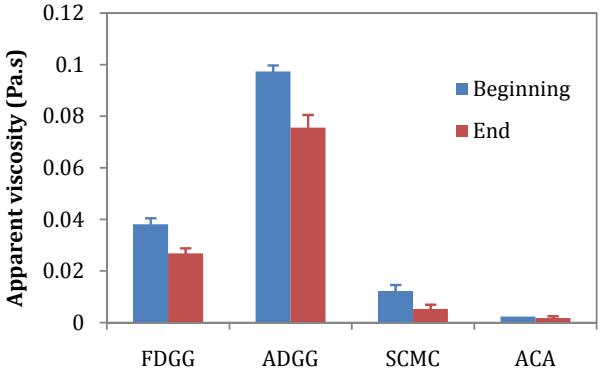


Fig. 2: Viscosity of ibuprofen suspension formulations at the beginning and at the end of the study (n=3, mean ± s.d.)

The pH of the suspension formulations (1.0 %w/v suspending agent) is shown in table 1. The results show that all the suspension formulations have an acidic pH which was stable over 28 days of observation.

Table 1:

Suspension formulation	Day 0	Day 28
XAN	4.7±0.02	4.7±0.10
ACA	4.7±0.10	4.8±0.10
SCMC	5.4±0.10	5.4±0.03
FDGG	5.0±0.10	5.0±0.04
ADGG	4.9±0.03	5.0±0.04

Sedimentation volume

The sedimentation volumes measured for the formulations at the different concentrations of suspending agent are shown in figure. 3*a-c*. All XAN-containing formulations remained completely suspended (sedimentation volume = 1.0) over the 84 days of the study. There was very rapid sedimentation of all the other formulations after 1 to 42 days of storage. At 0.5 %w/v, XAN-containing suspensions were superior to ACA, SCMC, FDGG and ADGG-containing formulations in their ability to suspend the insoluble drug particles. This was also valid at 0.75 % and 1.0 %w/v except that at these concentrations, the suspending capability of FDGG and ADGG-containing formulations was increased from 1 and 3 days respectively at 0.75 %, to 2 and >21 days respectively at 1.0 %w/v.

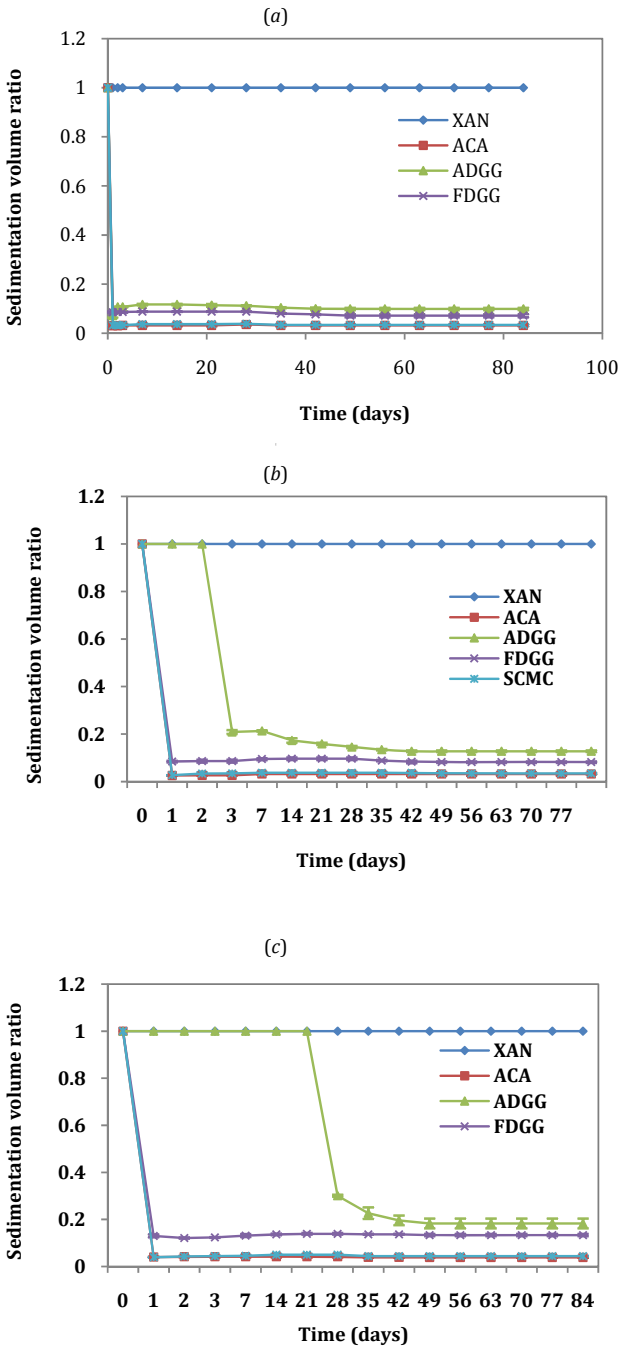


Fig. 3: Comparison of sedimentation volume among suspension formulations containing (*a*) 0.5%, (*b*) 0.75% and (*c*) 1.0% w/v suspending agent (n=3, mean ± s.d.)

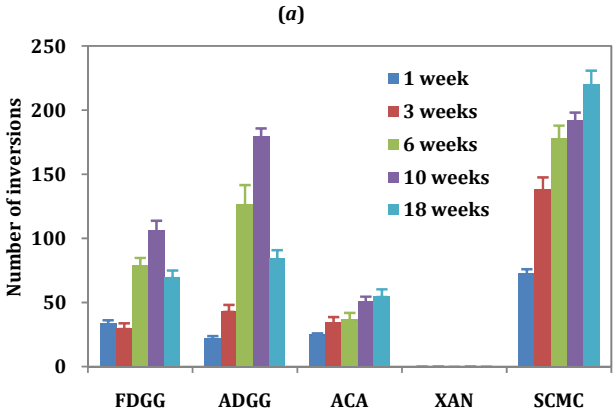
ADGG was a better suspending agent than FDGG at all concentrations, and both were superior to ACA and SCMC. The ability to suspend particles varies according to the ability of the

polymer to impart viscosity. The sedimentation volume has been used as a measure of flocculation[11] and highly flocculated systems sediment to give large sedimentation volumes.

Redispersibility

The number of vertical inversions required to completely redisperse the suspension formulations are presented in figure 4*a*-*c*.As XAN-containing formulations did not sediment throughout the 18 weeks of storage, they did not require redispersion. The ACA-containing formulations required the least number of inversions to achieve complete redispersion at all concentrations for the entire duration of the study. At all concentrations SCMC-containing formulations required the highest number of inversions to achieve re-dispersion of the suspension. This implies that the SCMC-containing formulations are more likely to cake on storage compared with the other formulations. The FDGG-containing formulations were more easily redispersed compared to the ADGG-containing formulations at 0.5% and 0.75 %w/v with FDGG formulations being more re-dispersible and maintaining a consistent measure of redispersibility at 0.75 %w/v irrespective of shelf-life. The same trend was noticeable for ADGG-containing formulations at 1.0 %w/v.

The high redispersibility of ACA-containing formulations may be attributable to the low viscosity of the dispersing medium which would have magnified the effects of the agitation applied during the redispersibility experiments. The poor redispersibility of SCMC-containing formulations, irrespective of their low viscosity, may be attributable to the deflocculated nature of the system. The presence of carboxylic groups on the SCMC may result in absence of adsorption and consequent deflocculating of the system[12]. Only SCMC-containing formulations demonstrated a correlation between concentration and redispersibility in which redispersibility decreased with an increase in the polymer concentration.



Degree of flocculation

Two mechanisms of flocculation have been identified[13]: first, double layer repulsion between charged particles may be reduced by polyelectrolytes or by adsorbed non-ionic polymers. Flocculation occurs because of attractive Van der Waals forces. There is a second mechanism in which neither electrical properties nor adsorption are involved rather, free energy changes which result when particles approach each other so closely that the space between the particles is too small for polymer molecules in solution to fit in.

The flocculation behaviour of the ibuprofen suspension formulations was studied at 0.5% and 0.75 %w/v suspending agent. At both concentrations, XAN-containing formulations did not sediment but remained highly flocculated throughout the study. The flocculation behaviour of the formulations containing FDGG, ADGG, SCMC and ACA is shown in figure 5*a* and *b*. At a concentration of 0.5 %w/v suspending agent, there was no variation in the degree of flocculation between the formulations (P>0.05). However, at 0.75 %w/v suspending agent, ADGG and FDGG-containing formulations showed the same degree of flocculation and were significantly more flocculated than the SCMC or ACA-containing formulations(P<0.05).

Flocculated suspensions produce bulky sediments which redisperse easily with mild agitation while deflocculated suspensions settle to form very compact sediment which does not redisperse easily, a condition known as caking[13]. The degree of flocculation exhibited by SCMC-containing formulations, coupled with their low sedimentation volume and relative difficulty of redispersibility, is indicative of a highly deflocculated system. The degree of control exhibited by the grewia gum-containing formulations has significant advantages over the ACA and SCMC-containing formulations.

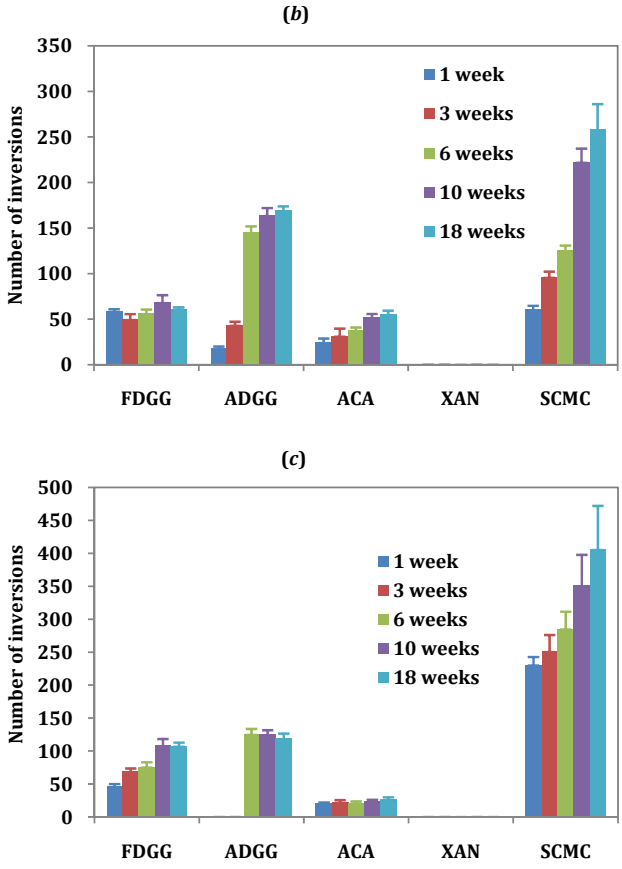
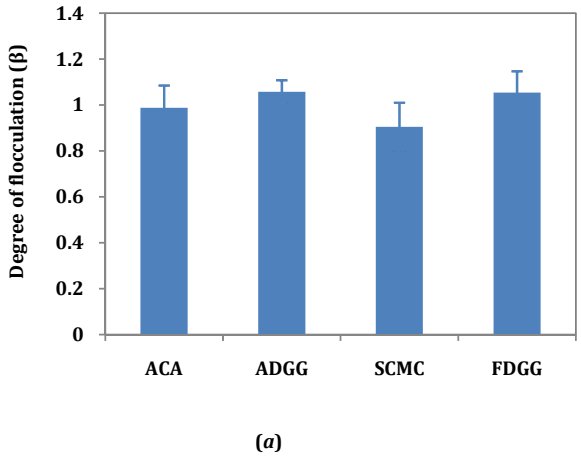
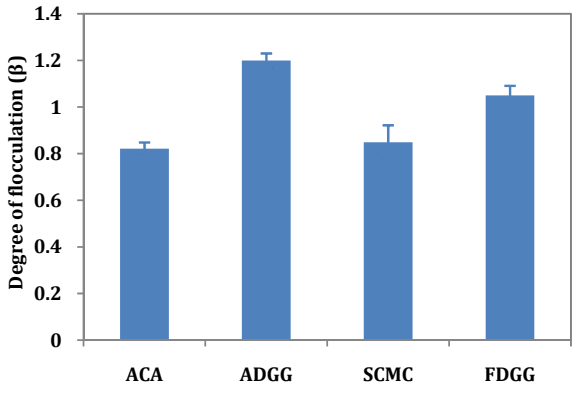


Fig. 4: Number of inversions required to completely resuspend to homogeneity of ibuprofen suspension formulations containing different suspending agents at *a*) 0.5%, *b*) 0.75%, *c*) 1.0% w/v (n=3, mean ± s.d.)



(*a*)



(*b*)

Fig. 5: Comparison of the degree of flocculation for ibuprofen suspension formulations containing *a*) 0.5% and *b*) 0.75% w/v suspending agent (n=3, mean ± s.d.)

Zeta potential of the suspension formulations

Without polymer, the particles of ibuprofen in suspension exhibited a slightly negative zeta potential (-5.2 ± 0.8 mV), due to the carboxylic acid groups. Inclusion of XAN, ADGG, FDGG, ACA or SCMC in the system drastically increased the magnitude of the zeta potential (fig. 6*a*). This is attributable to adsorption of polymer onto the ibuprofen particles with a consequent increase in the distance between the particle surface and the shear plane[14, 15]. However, ACA or SCMC in the suspension formulation systems only slightly modified the zeta potential of the ibuprofen particles in suspension. The anionic nature of these colloids resulted in reduced adsorption. A similar effect was observed by[12] and was attributed to the absence of adsorption or the presence of carboxylic groups on the SCMC similar in charge to the carboxylic group present in the drug particles. The absence of adsorption may account for the slight modification of zeta potential by ACA. ACA has some proteinaceous material that can influence adsorption[16].

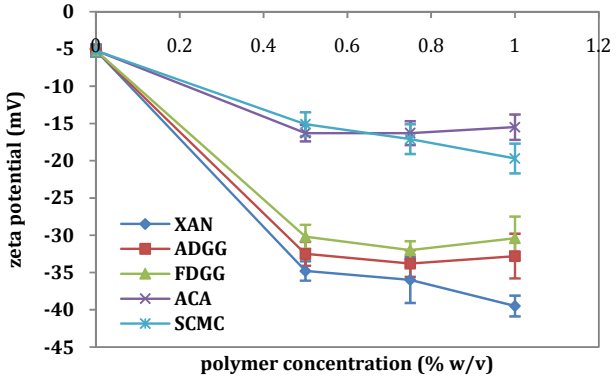
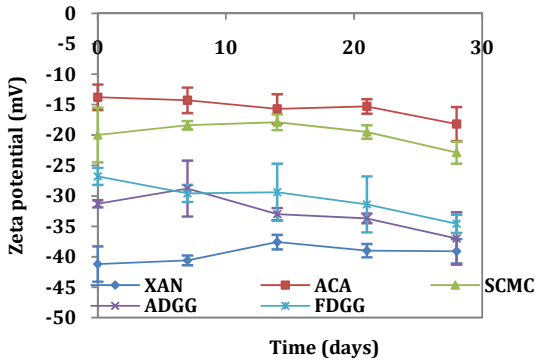


Fig. 6a: Effect of polymer type and concentration on the surface electrical property of suspended ibuprofen particles (n=3, mean ± s.d.)

The effects of shelf-life on the surface electrical charge of the suspension formulations containing 1.0 %w/w suspending agents were also characterized by determining the zeta potential (Fig. 6*b*). The results show that over a 28 day period, the zeta potential of the suspension formulations was fairly stable. The zeta potential of dispersed systems has been used as an indication of stability of the systems[1]. The general dividing line between stable and unstable suspensions is generally taken at either +30 mV or -30 mV. Dispersed systems with zeta potentials more negative than -30 or more positive than +30 mV are considered to be stable systems. The implication for this study is that, XAN, ADGG or FDGG-containing formulations were stable (their electro kinetic property being more electronegative than SCMC or ACA) while SCMC or ACA-containing formulations had zeta potentials less negative than -30 mV indicating that both dispersed systems would be less stable, and sedimentation was seen to occur very rapidly after formulation.



(b)

Fig. 6b: Zeta potential profile of suspension formulations containing 1.0% w/v suspending agent (n=3, mean ± s.d.)

Microbiological evaluation

The ability of natural polysaccharide gums to increase solution viscosity accounts for their use as suspending agents in oral pharmaceutical suspensions. However, natural polysaccharides can show a gradual reduction in the viscosity of their dispersions or solutions with age due to bacterial or mould growth[1]. The microbial load and/or growth in suspension formulations containing 1.0 %w/v of suspending agent was evaluated on day 0 and on day 21 of storage and the results are presented in tables 2 and 3 respectively. Microbial growth evident by colony forming units or cloudiness and darkening of the nutrient agar is indicative of positive result while a clear and transparent nutrient agar is indicative of a negative result.

Table 2

Formulation	Results for each quantity of suspension formulation			Probable number of bacteria per ml of formulation
	0.1 ml	0.01 ml	0.001 ml	
ADGG	+	-	-	$< 10^2$ and > 10
FDGG	+	+	-	$< 10^3$ and $> 10^2$
SCMC	+	-	-	$< 10^2$ and > 10
ACA	+	-	-	$< 10^2$ and > 10
XAN	+	-	-	$< 10^2$ and > 10

Table 3

Formulation	Results for each quantity of suspension formulation			Probable number of bacteria per ml of formulation
	0.1 ml	0.01 ml	0.001 ml	
ADGG	+	+	+	$>10^3$
FDGG	+	+	+	$>10^3$
SCMC	+	+	+	$>10^3$
ACA	+	+	+	$>10^3$
XAN	+	+	+	$>10^3$

The results show that all the suspension formulations contain some degree of microbial contamination from day 0 of formulation. After 21 days the probable number of bacteria per ml of formulation increased for each suspension formulation indicating microbial growth and multiplication. Figure 7 shows typical microbial growth on the suspension formulations. This result provides an explanation

for reduction in viscosity of the suspension formulations after storage for 84 days. Consequently in the formulation of oral pharmaceutical suspensions containing grewia gum, preservatives will need to be employed to inhibit microbial growth and to preserve the formulation, similar to the requirements of the other agents tested.

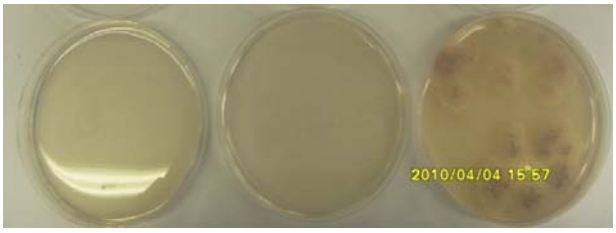


Fig. 7: Typical microbial growth pattern of the suspension formulations on nutrient agar on day 0.

CONCLUSION

Grewia-containing formulations showed consistent superiority over ACA or SCMC-containing formulations in terms of sedimentation volume ratio and degree of flocculation at the same w/w ratio. ADGG or FDGG-containing suspension formulations are more easily redispersed when compared with SCMC-containing formulations. They form more stable suspension formulations with zeta potentials below -30 mV. Grewia polysaccharide gum (freeze-dried or air-dried) may provide a suitable alternative to SCMC or ACA as suspending agent in pharmaceutical oral suspensions, providing a more readily available and affordable option in the countries where it is found growing abundantly, wild or cultivated.

ACKNOWLEDGEMENT

The authors wish to acknowledge financial support for this work from the British Commonwealth and Aston University.

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