ORIGINAL PAPER

Nig. J. Pharm. Res. 2017, 13 (1) pp 19-25
ISSN 0189-8434 **Available online at http://www.nigjpharmres.com**

The suspending properties of *Cissus rubiginosa* fruit mucilage in paracetamol suspension formulation

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A– research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Materials with suspending properties like mucilage have been obtained from natural sources and used to stabilize liquid formulations containing poorly dispersible solids.

Objective: The aim of this study was to evaluate the suspending properties of *Cissus rubiginosa* fruit mucilage (CRM) in paracetamol oral suspension.

Materials and Methods: Paracetamol suspensions containing 0.5, 1.0, 1.5 and 2.0 %w/v CRM were prepared and compared with suspensions formulated with same concentrations of compound tragacanth (CT). The sedimentation volume, ease of re-dispersibility, effect of shear rate on viscosity, flow rate and drug release pattern were studied as assessment parameters.

Results: Characterization studies of the suspensions revealed that there was a corresponding increase in the viscosity of the suspension with increase in the concentration of the gum. Paracetamol suspension having CRM had significantly higher viscosity ($p<0.05$) compared to those containing CT. The viscosities of all suspensions decreased with increase in shear rate. There was decrease in flow rate as the viscosity of the suspension increased. Paracetamol suspensions containing CRM were easily re-dispersible with minimum agitation at concentration less than 1.0 %. Drug release from the suspension containing 0.5 % CRM was rapid while release from suspension containing higher concentrations of CRM occurred at a later time, eliciting a delay in drug release.

Conclusion: This study has been able to elucidate the ability of *Cissus rubiginosa fruit* mucilage to act as a suspending agent in pharmaceutical suspensions.

Keywords: *Cissus rubiginosa* mucilage, compound tragacanth powder, Suspension, Suspending agents

INTRODUCTION

Suspensions are defined as heterogeneous systems consisting of two phases. The continuous or external phase is usually liquid or semisolid while the dispersed phase or internal phase is almost always an insoluble solid (Singh *et al*., 2013). A pharmaceutical suspension, like any other disperse system is thermodynamically unstable, thus making it necessary to include a stabilizer or suspending agent.

This reduces the rate of settling and permits easy re-dispersion of any settled particulate matter both by protective colloidal action and by increasing the consistency of the suspending medium (Femi-Oyewo *et al*., 2004; Kumar *et al*., 2009).

Suspensions can be administered via the oral route, topically or through the parenteral route. Formulation of drugs as suspension for oral administration is a convenient way to administer insoluble or poorly soluble drugs to infants and elderly that have difficulty swallowing tablets or capsules (Nep and Conway, 2011).

A number of plant gums and mucilages have been evaluated for use as suspending agents. Plant gums exert their activity as suspending agents by decreasing the sedimentation rate of drug particles in suspension; this is achieved by increasing the viscosity of the liquid vehicle thereby reducing settling in accordance with Stoke's law (Mahmud *et al*., 2010; Uhumwangho and Ileja, 2014). Natural gums from *Albizia zygia* (Femi-Oyewo *et al*., 2004), *Khaya senegalensis (*Mahmud *et al*., 2010) grewia (Nep and Conway, 2011), *Katira* (Singh *et al*., 2013), *Brachystegia eurycoma* (Uhumwangho and Ileja, 2014), *Chrysophyllum albidium and Albelmuscus esculentus* (Bakre and Ajakore, 2015) have been reported to be effective for use as suspending agent in pharmaceutical industry. Natural gums are biodegradable, cheap, readily available, effective and eco-friendly as compared to synthetic and semi-synthetic materials employed as pharmaceutical excipient (Bakre and Ajakore, 2015).

Cissus rubiginosa is a tropical plant belonging to the family *Vitaceae*. It is a woody herbaceous climber widespread found throughout tropical Africa, growing in rocky places. *Cissus rubiginosa* is commonly called rust stem vine and in Hausa language it is called Anaya. *Cissus rubiginosa* leaves has been implicated in the treatment of dysentery and as an antidiarrheal agent in Congo and known to possess antibacterial activity (Otshudi *et al*., 2000; Fernandes and Banu, 2012).The fruit is used in making soup in Northern Nigeria.

The present work is an attempt to investigate the suitability of *Cissus rubiginosa* fruit mucilage as a suspending agent in pharmaceutical formulations using paracetamol. Currently, there is little or no information on the use of *Cissus rubiginosa* fruit mucilage as a suspending agent in liquid formulations. Paracetamol was chosen for this investigation because it is a poorly soluble drug which would require a suspending agent to be prepared as a liquid dosage form. The choice of preparing paracetamol as suspension over syrup was based on the stability profile of the two dosage forms. Suspensions offer resistance to degradation of drugs due to hydrolysis, oxidation or microbial activity because it follows the zero-order kinetics. In addition, when compared to solution dosage forms, relatively higher concentration of drugs can be incorporated into suspension products.

MATERIALS AND METHODS

Materials

Materials

Paracetamol, compound tragacanth (BDH Chemicals, England), benzoic acid, concentrated strawberry syrup, chloroform water double strength, acetone were all of analytical grade. *Cissus rubiginosa* fruits were sourced from the tree growing on the rocky hills in Nok village, Kaduna state, Nigeria. The fruit was authenticated and given a voucher number 900330 in the herbarium, Department of Biological Sciences, Ahmadu Bello University, Zaria, Nigeria.

Methods

Extraction of the mucilage

The ripe fresh fruits of *Cissus rubiginosa were* cleaned, washed and sliced to remove the seed. The succulent part of the fruit was blended and then filtered using a muslin cloth. The mucilage was precipitated from the filtrate using twice its volume of acetone. The extracted mucilage was separated by filtration, washed with distilled water and then dried in a hot air oven at 40 °C for 4 h. The dried mucilage obtained was powdered and stored in an airtight bottle as CRM.

Preparation of paracetamol suspension

Paracetamol and CRM powders were geometrically triturated in the mortar according to the formula in Table 1. Chloroform water double strength (50 mL) was added to the contents of the mortar in aliquots to produce pourable slurry, followed by the preservative (benzoic acid) and sweetener (Strawberry syrup) incorporated into contents of the mortar and then transferred into the product bottle. The volume of suspension in the bottle was made up to 100 mL with distilled water, shaken for about 2 min and kept for further analysis.

Similar preparations were made at all concentrations using compound tragacanth (CT) as suspending agent (Table 1).

Table 1. Formula for preparing paracetamol suspensions containing CT and CRM as suspending agents

	Formulation code							
Ingredients	**CT1**	**CT2**	**CT3**	**CT4**	**CRM1**	**CRM2**	**CRM3**	**CRM4**
Paracetamol powder (g)	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
CT (g)	0.5	1	1.5	2	-	-	-	-
CRM (g)	-	-	-	-	0.5	1	1.5	2
Benzoic acid (mL)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Conc. strawberry syrup (mL)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Chloroform water D/S (mL)	50	50	50	50	50	50	50	50
Water q.s (mL)	100	100	100	100	100	100	100	100

Evaluation of suspension

Sedimentation volume determination

The sedimentation volume of the suspensions were determined by pouring 50 mL of each suspension in stoppered measuring cylinder and kept undisturbed on a flat surface at 25 ± 2 °C. The settling volume of each suspension was inspected and measured every 24 h for 7 days (Chaudhari *et al*., 2014). The sedimentation volume (*F*) was calculated using the equation below;

$$F = \frac{V_u}{V_o} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.1$$

Where *Vu*= Final volume of sediment

Vo = Initial volume of sediment

Rheological assessment

The rheological behaviour of the prepared suspensions were determined using Brookfield viscometer (LVDV-1 Prime, Brookfield Engineering Laboratories, USA). The viscosity was determined at shear rates of 10, 20, 50, and 100 rpm. All determinations were made in triplicates and the results expressed as mean values.

Ease of re-dispersibility of formulated suspension

The suspensions (50 mL) were poured into bottles, stoppered and kept on a vibration free platform. After 7 days, the suspensions were shaken manually using tumbling type motion 3 times to determine the ease of re-dispersibility (Mahmud *et al*., 2010).

Flow rate

The flow rate was calculated as the time taken for 10 mL of the suspension to flow through a 10 mL pipette (Sankar *et al*., 2010).

$$\text{Flow rate} = \frac{Pipette\ volume(ml)}{Flow\ time\ (sec)} \ldots\ldots\ldots\ldots\ldots\ldots Eq.2$$

Release test

The paddle method was used to determine the release of drug from the formulated suspensions. Dissolution profile of each suspension was determined at 37 ^{0}C in 500 mL simulated gastric fluid without pepsin (pH 1.2) at a paddle rotation speed of 25 rpm. Ten (10 mL) of suspension was introduced into the bottom of the flask with a syringe and aliquots were withdrawn after every 5 min for 30 min. An equivalent volume of withdrawn medium was replaced with fresh medium to maintain sink conditions. The withdrawn

samples were filtered and analysed for drug content using the UV spectrophotometer at 234 nm (Mahmud *et al*., 2010).

Statistical analysis

Statistical significance for viscosity and drug release was compared using one way ANOVA (Minitab Software Ver. 16). The test was considered to be statistically significant, if $p < 0.05$

RESULTS AND DISCUSSION

Sedimentation Volume

The sedimentation volumes of the prepared suspensions are presented in Figure 1. Sedimentation volume was found to increase with increase in concentration of suspending agent with the suspensions containing CRM exhibiting more consistency than compound tragacanth suspensions in terms of sedimentation volume ratio. There was rapid sedimentation of all the formulations after 3 days of storage. High sedimentation volume is an indication that internal phase particles have settled but the inter particle attraction and bonding were loose and not strong enough to form hard cake during the study period. The sedimentation volume has been used as a measure of flocculation and highly flocculated systems sediment to give large sedimentation volume. This shows that suspensions with CRM exhibited characteristics of flocculated systems. Highly flocculated systems tend to settle faster because the dispersed solid particles have formed aggregates or flocs thereby affecting the stability of the suspension. However, the sediment that is formed can be easily redispersed upon minimal shaking because the aggregates formed are loosely bound. Flocculated systems have also been associated with a decrease in bioavailability of the dispersed drug due primarily to small specific area as a result of increase in particle size of the dispersed solid (Nutan *et al*., 2007).

Rheological studies

Rheological consideration is of great importance in the study of the stability of pharmaceutical suspensions because viscosity, as discussed under Stokes' law can modify the sedimentation rate. (Uhumwangho and Ileja, 2014). Maintaining the proper viscosity of suspensions is also important to ensure the accuracy of dosing and ease of application. The optimum concentration of the suspending agent that ensures thickening of the suspension has to be identified such that the stability is maintained alongside the dispersibility of the suspension (Singh *et al*., 2013). The viscosity of different concentrations of the test gums are as shown in Table 2. It was observed that there was a corresponding increase in the viscosity of the suspension with increase in the concentration of the gum. The suspensions containing CRM had significantly higher viscosity ($p<0.05$) than those containing compound tragacanth. The viscosity of formulations decreased as the speed of shearing increased from 10 – 100 rpm (Figure 2).

This implies that with minimum agitation the suspension will be easily re-dispersed and a stable dose can be withdrawn. An ideal suspension should have a high viscosity at negligible shear and low viscosity at high shearing rate in order to aid flow during agitation to facilitate easy pouring (Ayorinde and Odeniyi, 2012).

The rheological studies of the suspension with both gums shows that the suspensions are pseudoplastic in nature. Pseudoplastic flow behaviour is a desirable property in suspensions because it enhances redispersion and pourability of the suspension prior to administration (Nutan *et al*., 2007; Nep and Conway, 2011).

3.3. Re-dispersibility and flow rate

Since suspensions produce sediment on storage, it must be easily re- dispersible for an accurate dose to be withdrawn at any given time. Table 2 shows that particles suspended with CRM re-dispersed easily on agitation when the concentration was not more than 1%.

All the suspensions of CRM were seen to flow well through the pipette (Table 3). The flow rate decreased with increasing concentration of suspending agent and viscosity of the suspension. A good suspension is one that easily flows through a container allowing uniform dose withdrawal (Bamiro *et al*., 2014).

Table 2. Properties of paracetamol suspensions formulated using CT and CRM as suspending agents

Suspending Agent	Formulation Code	Concentration (%w/v)	Viscosity (m.pas at 10 rpm)	Flow rate (mL/s)	Re-dispersibility
CT	CT1	0.5	18.2 ± 0.23	1.60	+++
	CT2	1.0	49.6 ± 0.14	1.25	+++
	CT3	1.5	63.5 ± 0.11	1.10	+++
	CT4	2.0	73.6 ± 0.26	1.00	+++
CRM	CRM1	0.5	52.3 ± 0.15	1.40	+++
	CRM2	1.0	106.8 ± 0.21	0.90	+++
	CRM3	1.5	347.9 ± 0.32	0.80	++
	CRM4	2.0	656.1 ± 0.19	0.50	++

+: Not re-dispersible with cake formation
++: Re-dispersible with vigorous agitation
+++: Easily re-dispersible with minimum agitation

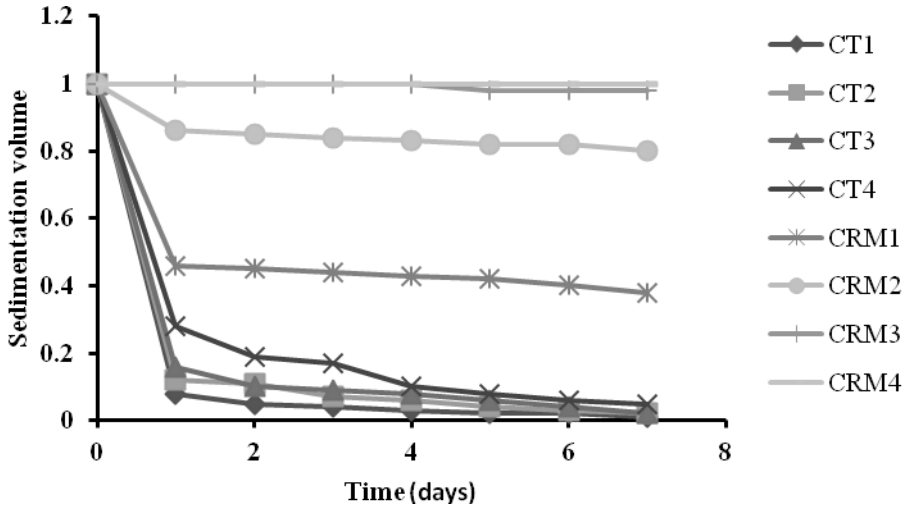

Figure 1: Sedimentation volume of paracetamol suspension formulated with different concentrations of CT and CRM

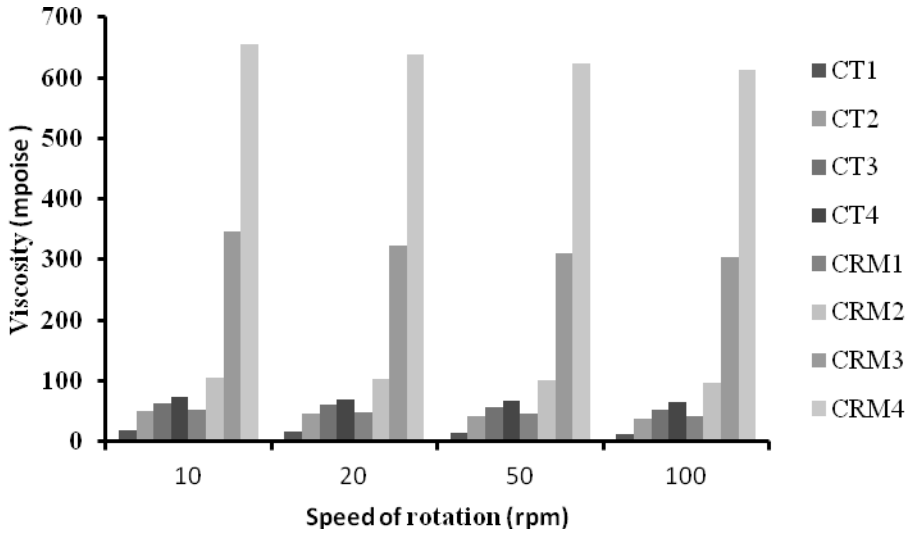

Figure 2: Effect of speed of rotation on the viscosity of paracetamol suspension formulated with different concentrations of CT and CRM

Drug release study

The suspending agent used in suspensions can interfere with the dissolution of the drug from the dosage form (Manish *et al*., 2009).The time taken for 50 % of drug release (t_{50}) of formulation CRM1 and CRM2 were 13 mins and 25 mins respectively. CRM3 and CRM4 formulations could not attain 50% release within the study period. By increasing the concentration of the CRM, the release rate was decreased. This may be due to entrapment of the drug in the polymer chain or adsorption of the polymer on the drug particle (Azam and Haider, 2008). Suspension containing 0.5 % mucilage (CRM1) released over 70 % of the drug in less than 30 min which meets the BP 2002 specification (Figure 3). The difference in drug released by CT and CRM suspensions compared at the same concentration was not statistically significant at $p < 0.05$ except for suspensions containing 2 % of CT and CRM (CT4 and CRM4).

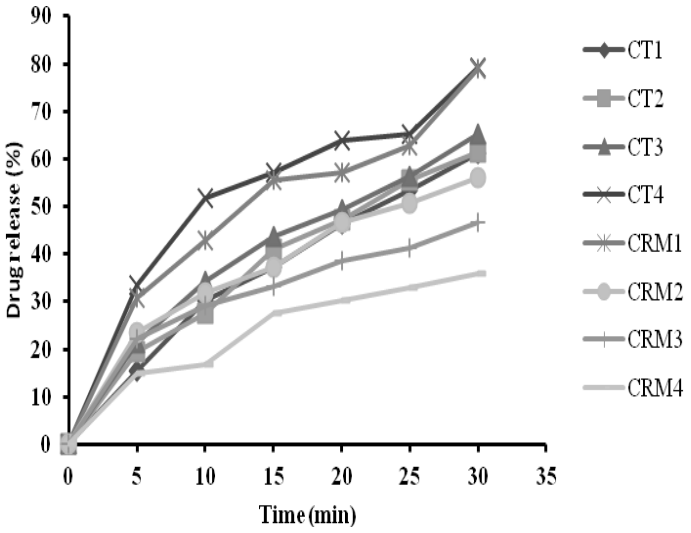

Figure 3: Drug release profile of paracetamol suspension formulated with different concentrations of CT and CRM

CONCLUSION

The study has shown that *Cissus rubiginosa* fruit mucilage has the ability to form suspensions. Hence, the incorporation of *Cissus rubiginosa* fruit mucilage at 0.5 % concentration can be exploited as an alternative suspending agent in formulation of pharmaceutical oral suspensions containing insoluble solids.

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Conflict of Interest: None declared

Received: 8 February, 2017

Accepted: 10 May, 2017