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ASSESSMENT OF STARCH FREE *CISSUS POPULNEA* POLYMER AS SUSPENDING AGENT IN PARACETAMOL SUSPENSION

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ABSTRACT

The suspending properties of mucilage of starch free *Cissus populnea* (sfCPP) were evaluated comparatively with those of the native *Cissus populnea* (nCPP), and tragacanth in paracetamol suspension. The gums were used in concentrations of 0.5 to 3.0 % w/v. The sedimentation rates, sedimentation volume, ease of re-dispersibility and viscosity of the suspension were studied as assessment parameters. The rank order of the suspending ability of the suspending agents as evaluated by the sedimentation volume was sfCPP> nCPP> tragacanth. Paracetamol suspensions having sfCPP has significantly higher viscosity ($p<0.05$) when compared with those of nCPP, and tragacanth. The flow rate decreases with increase in the concentration of the suspending agent and viscosity. The viscosity of formulations containing sfCPP decreases with increased speed of agitation which confers good characteristic of suspension. On the basis of these findings, pharmaceutical suspension containing sfCPP as suspending agent having the highest performance when compared to nCPP and tragacanth may preferably be applied as liquid drug delivery system for paediatric patients.

Keywords: Paracetamol suspension, suspending agents, native polymer, starch free polymer, sedimentation volume, viscosity.

INTRODUCTION

Suspensions are an important pharmaceutical dosage form that are still widely in use. Owing to their versatility they are often used in situations where the patients are unable to swallow tablets or capsules (Marriot *et al*., 2010). Pharmaceutical suspensions are dispersions of an insoluble drug in an aqueous continuous phase and like other disperse systems they are thermodynamically unstable. Thus, it is necessary to include in the dosage form a stabilizer or a suspending agent. A well-formulated suspension should easily be re-suspended when moderately agitated and should allow uniform and accurate doses of the medicament to be withdrawn throughout the period of medication. Suspending agents are used in formulations to help the dispersed phase to remain suspended long enough when shaken and assist in easy re-dispersion of settled particles on standing (Ogaji, 2011). These have the benefit that consistent withdrawal of uniform doses is possible throughout the medication period. Natural gums from *Irvingia gabonesis, Albizia zygia Grewa* mollis and *Khaya grandifolia* have been reported to provide the needed platform for some of the quality attributes of a suspension due to their ability to swell when in contact with water and their viscous nature (Ndjouenkeu *et al*., 1996; Femi-Oyewo *et al*., 2004; Isimi *et al*.,2000; Ogaji, 2011; Nep and Conway, 2010). Natural gums are generally biodegradable, cheap, easily available, effective, and eco-friendly as compared to synthetic and semi-synthetic materials as

pharmaceutical excipients (Prasad *et al*., 1998; Rana *et al.*, 2011; Bakre and Abimbola, 2013). *Cissuspopulnea* is a plant found growing in the wild in the savannah region of tropical Nigeria. It is also said to be distributed from Senegambia through South Sudan to Uganda and Ethiopia (Olutayo *et al.,* 2005). It is a woody climber with small flowers and extends up to 15-20 M. The stems are pale up to 10M in diameter, which exude a clear sap when freshly cut (Ibrahim, 1990). In a study, Balami (1991) concluded that *cissus* mucilage might be used as a tablet binder, and as a suspending and emulsifying agent.

Several works have been done on the native *Cissuspopulnea* polymer; however, no work has been done on the starch free polymer. This has brought about the interest to assess the starch free polymer as a suspending agent in paracetamol suspension as compared to the relatively common natural agents like nCPP and tragacanth gum. Paracetamol was chosen as a model drug for this investigation (Femi-Oyewo *et al*., 2004; Mann et al., 2007) because it is a typical representative of practically insoluble drugs which would require a suspending agent to be prepared as a liquid dosage form.

MATERIALS AND METHODS

The materials used were paracetamol powder (Spectrum chemicals, USA), benzoic acid, tragacanth gum (Searl co., England). water was double distilled and every other chemical was of analytical grade including the extracted polymers (nCPP and sfCPP).

Extraction of Gum

The fresh inner bark from the stem of *Cissuspopulnea* was washed thoroughly with distilled water and then shredded. The shredded material was macerated under ambient conditions in 0.1 % w/v sodium metabisulphite for 24 h. The swollen gum was separated from the residue by filtration through a muslin bag. The filtrate was precipitated from solution using absolute ethanol. The precipitated polymer was washed repeatedly with more ethanol to remove all water content until the gum became brittle. It was then dried in a hot air oven at 60^0C for 1 h, the dried mass was blended to fine powder, passed through sieve number 250 (Fisher-brand test sieve UK) and stored in an air tight amber coloured bottle and labelled nCPP.

Starch Digestion

The starch content in nCPP was digested according to the method of Nep *et al*., (2016). Briefly, 3000 mL of 1 % w/v dispersion of nCPP were treated with termamyl 120 L (1 % v/v) (sigma Life Sciences) while stirring constantly at 70^0C for 4 h. The termamyl was pre-treated by heating at 70^0C for 30 min to deactivate any pectinoses and arabinoxylanases. Every 1 h an aliquot of the dispersion was removed and tested for the presence of starch. Starch digestion was complete in 3 h after which the sample did not test positive for starch. Subsequently, protein from the sample was precipitated by adjusting the PH to 4.5 with 2 M HCl and centrifuging at 4400 revolutions per minute (rpm) for 20 min. The recovered starch free nCPP was further washed with absolute ethanol to get a brittle polymer precipitate. The precipitate was oven dried for 1h at 60^0C. This sample was named sfCPP.

Formulation of Paracetamol Suspension

A 0.5 g quantity of tragacanth powder and 5 g of paracetamol were triturated together with 50 mL of water to form a smooth paste. The mixture was transferred into a 100 mL measuring cylinder and made up to volume with distilled water and then shaken vigorously for 2 min (thus making 0.5%w/v of the gum in the preparation). The procedure was repeated using 1, 1.5, 2 and 3 g of tragacanth powder. The aforementioned

procedure was repeated with starch free *Cissus populnea* and native *Cissus populnea* gums.

Evaluation of Suspensions

Sedimentation Volume and Rate

Each suspension (50 mL) was stored in a 50 mL measuring cylinder for 7 weeks at 35^0C. Observations were made at every hour for 7 h, every 24 h for 7 days and then every week for 7 weeks. The sedimentation volume, F (%), was then calculated using the following equation:

$F=100V_u/V_0$ [1]

Where V_u is the ultimate volume of the sediment and $V_0$is the original volume of the suspension.

Rheological Assessment using Brookfield Viscometer

Viscosities of the prepared suspensions were determined using a Brookfield synchro-electric viscometer, model LVF (Brookfield Laboratories, Massachusetts). Different concentrations of the prepared suspensions were put separately in a 600ml beaker, appropriate enough to immerse the spindle groove in the fluid. Viscosity values at rotational speeds of 10, 20, 50, and 100 rpm were determined at room temperature.

Determination of Flow Rate

The time required for each suspension sample to flow through a 10ml pipette was determined and the apparent viscosity (Ƞ) was calculated using the equation:

Flow rate Ƞ= volume of pipette (ml)/ flow time (s) [2]

Ease of Re-Dispersibility of Formulated Suspensions

Fifty millilitres quantity of the formulated suspensions were poured into bottles, stoppered and kept on a vibration free platform. After 7 days, the suspensions were shaken manually to find out how much of it was re-dispersed. The number of time required to re-disperse the suspensions were noted and recorded as re-dispersibility number. The presence of deposit if any after re-dispersion was also noted (Panda *et al*., 2007).

Statistical Methods

We used descriptive statistics of mean and standard deviation to describe the distribution of the variable after an initial exploratory analysis. The mean of the different parameters was compared within different measurements and between binder types using the one-way analysis of variance method (ANOVA). F-statistics and P-values were reported for the comparison of means. The mean of various parameters was visualized using appropriate charts. All the statistical analyses conducted on the data gathered from this research were performed using the IBM SPSS statistics for windows, version 20 (IBM corp, Armonk, New York, USA). The alpha (α) level was set at 0.05 and P-values <0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Effect of Various Suspending Agents on the Sedimentation Volume of Paracetamol Suspension

Table 1 shows the sedimentation volume of the paracetamol suspensions at 0 to 3.0 % w/v suspending agents for 7 weeks. The internal phase settled rapidly within the first 1 h of preparation for suspensions containing tragacanth and settled constantly over the next 7 weeks. Paracetamol suspension formulated with sfCPP exhibited the highest sedimentation volume while suspensions containing tragacanth had the lowest sedimentation volume. High sedimentation volume is an indication that although the internal phase particles have settled as would be expected with suspensions, the inter

particle attraction and bonding were loose and not strong enough to form hard cakes during the study period. The result suggested that differences in the sedimentation profiles was probably due more to the suspending agent used than the properties of the internal phase. The rank order of the suspending ability of the suspendants as evaluated by the sedimentation volume was sfCPP>nCPP>tragacath.

Most pharmaceutically useful polymers contain polar functional groups that are separated by a hydrocarbon backbone. This structure provides the polymer molecule with many active centres that permit interaction with a particle surface. At very low concentration of polymer, a large number of sites on the surface of the dispersed solids are available for adsorption of the polymer. The simultaneous adsorption of the polymer molecules on to the surfaces of different particles creates a bridge. At a high concentration of polymer, there is complete coverage of the particles by the polymer and insufficient binding sites remain on the particles to form interparticulate bridges. This consequently leads to deflocculation due to formation of adsorbed layers of polymer on different particles (Gennero, 2000). Generally, at higher gum concentration of 2.0 and 3.0%w/v, it was observed that the suspensions showed low sedimentation volume.

Effect of Type of Suspending Agents and Concentrations on the Viscosity, Flow Rate and Re-Dispersibility of Paracetamol Suspension

The viscosity of suspensions is a factor of great importance to stability and pourability of suspensions. Suspensions are the least stable dosage form due to sedimentation and cake formation. The viscosity of different concentrations of the test gums are shown in Table 2.

Suspensions containing sfCPP have significantly higher viscosity ($p<0.05$) than those containing nCPP, and tragacanth. This suggests that paracetamol suspensions formulated with sfCPP have a low terminal settling velocity, thus, the dispersed phase settles at a slower rate and remains dispersed for a longer time yielding higher stability to the formulated suspension. As the concentration of the gum increases, the viscosity of the paracetamol suspension increases. This suggests that paracetamol suspension with higher gum concentration is expected to give a suspension that settles slowly. The flow rate (Table 2) decreases with increase in the concentration of the suspending agent and viscosity.

Effect of Speed of Rotation on the Viscosity of Gums

Figure 1 shows the effect of speed of rotation on the viscosity of paracetamol suspension formulated with 1 % w/v concentrations of test gums.

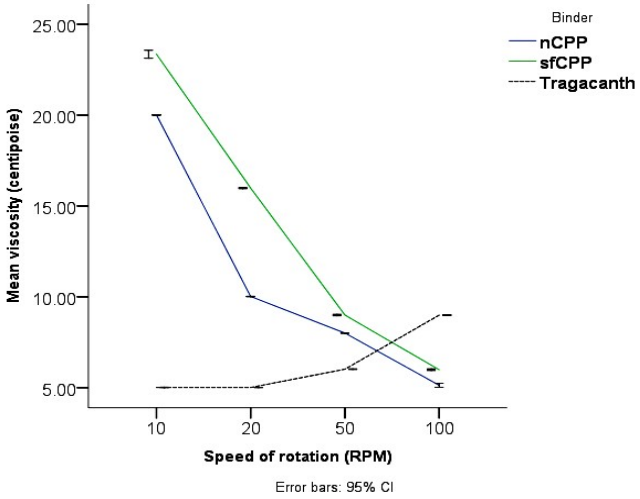

Figure 1: Effect of speed of rotation on viscosity of paracetamol suspension formulated with 1%w/v concentration of test gum

The decreased viscosity values observed with increasing speed of rotation for formulations containing sfCPP and nCPP could be attributed to the nature of the mixture which may likely be pseudoplastic. This implies that

with minimal agitation the suspension will be easily re-dispersed and a stable dose can be withdrawn. At higher shear speed, viscosity decreased due to increase in shear force caused by high speed of the spindle which reduces internal friction leading to thinning i.e. increase in fluidity of the material. This is an indication that sfCPP and nCPP would undergo a pseudoplastic behaviour (figure 1), during storage (at low shear speed), it will have a high viscosity and during shaking or pouring (at high shear speed), it will have low viscosity. However, the viscosity of tragacanth was proportional to the speed of agitation. The performance of sfCPP is as well observed to be superior to that of nCPP, since less agitation is required to disperse the suspension with sfCPP.

Table 1. Sedimentation Volume of Pcm Suspension

Evaluation of Suspensions.																							
Conc g/ml	**Time hr**								**Time in days**							**Time in weeks**						
	0	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
sfCPP																							
0.5	100	40	40	40	39	38	38	38	37	36	36	35	35	34	34	34	34	32	32	31	31	30
1	100	63	63	62	62	61	61	61	60	59	58	58	58	57	57	57	56	56	55	54	54	53
1.5	100	95	95	95	95	95	95	95	95	94	94	94	94	94	93	93	93	92	92	92	91	90
2	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	99	99	99	99	99	99	98
3	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	99	99	98
nCPP																							
0.5	100	50	50	50	49	49	48	48	48	47	47	46	46	45	45	45	44	44	43	43	43	42
1	100	70	70	69	69	68	68	68	67	66	66	65	65	64	64	63	62	61	61	61	60	60
1.5	100	93	93	92	92	91	90	90	89	89	89	88	88	87	87	86	86	86	86	86	86	85
2	100	100	100	100	100	100	100	100	100	100	100	100	100	99	97	96	95	92	90	89	96	95
3	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	99	99	99	98	98	98	97
Traga canth																							
0.5	100	22	22	21	20	20	20	20	20	19	19	19	18	17	17	17	16	16	15	15	15	14
1	100	32	32	32	30	30	30	30	28	24	24	24	23	23	23	23	23	23	22	22	21	21
1.5	100	34	34	32	32	30	30	30	30	28	28	27	27	26	26	26	26	25	25	24	24	23
2	100	40	40	32	32	30	30	30	29	29	28	28	28	28	27	27	27	27	26	26	25	25
3	100	48	47	36	34	34	34	34	33	33	33	32	32	31	31	31	31	30	30	29	29	29

Table 2: Effects of the type and concentration of suspending agents on the flow rate (mL/s), viscosity at 50 rpm (centipoise) and re-dispersibility of paracetamol suspension

Conc. (%)	Binder	N	Mean Viscosity(Centipoise)	Mean Flow Rate (ml/s)	Mean Re-dispersibility
	sfCPP	10	6.720 (± 0.02)	0.717 (± 0.001)	12.0 (± 0.67)
0.5	nCPP	10	6.514 (± 0.01)	0.775 (± 0.01)	10.2 (± 0.63)
	Tragacanth	10	6.017 (± 0.01)	1.170 (± 0.14)	13.6 (± 0.52)
1	sfCPP	10	8.37 (± 0.02)	0.1163 (± 0.17)	9.6 (± 0.70)
	nCPP	10	7.68 (± 0.01)	0.6340 (± 0.01)	9.9 (± 0.57)
	Tragacanth	10	6.01 (± 0.01)	1.0900 (± 0.01)	8.3 (± 0.48)
1.5	sfCPP	10	20.033 (± 0.02)	***	***
	nCPP	10	18.114 (± 0.01)	0.529 (± 0.01)	5.4 (± 0.52)
	Tragacanth	10	8.016 (± 0.02)	0.832 (± 0.01)	5.4 (± 0.52)
2	sfCPP	10	***	***	***
	nCPP	10	***	***	***
	Tragacanth	10	8.008 (± 0.07)	0.831 (± 0.01)	2.3 (± 0.48)
3	sfCPP	10	***	***	***
	nCPP	10	***	***	***
	Tragacanth	10	0.008 (± 0.08)	0.773 (± 0.01)	2.1 (± 0.32)

*** Not pourable.

CONCLUSION

The present study indicates that starch free *Cissus populnea* appear to exhibit good suspendabilty for paracetamol suspension compared to the native *Cissus populnea,* and tragacanth. In view of these properties, it can be concluded that polymer of starch free *Cissus populnea* has a higher potential compared to nCPP and tragacanth and could possibly be preferred as a suspending agent, stabilizer and thickener for various pharmaceutical suspension.

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