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Research Article Purified Cashew Gum as an Effective Natural Tablet Binding Agent

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ABSTRACT

Purpose: Cashew tree Anacardium occidentale is a spreading ever green perennial tree. The plant is naturalized and cultivated in the warmer parts of Sri Lanka. This study focused on evaluating purified cashew gum as an effective binding agent in tablet formulation using a range of binder solution strengths and different tablet formulations. A difficult to formulate "all starches filler tablet" was attempted as a challenge for the binding strength of the purified cashew gum. Method: Crude cashew gum was collected from the main trunk and purified by dialysis. The aqueous solution containing higher molecular mass fraction obtained from dialysis was then lyophilized. Placebo, pyridoxine hydrochloride 2 mg and carbamazepine 100 mg tablets were prepared using the high molecular mass fraction known as purified cashew gum. The physico-chemical properties of the purified gum were investigated. Physical properties of the tablets prepared with four binders, purified cashew gum, gum xanthan, hydroxypropyl methylcellulose and maize starch were studied and compared with respect to diameter, thickness, hardness, friability, weight variation and disintegration time. Results: The purified cashew gum was of a light amber color, glistening pieces and was odorless. It was found that the gum resembles the properties of gum acacia with parameters well within those of British Pharmacopeia specifications. A unique all starches filler tablets were a success. Tablets prepared with all four binders exhibited similar physical properties. **Conclusion:** It was possible to purify the gum to a specified quality similar to that of gum acacia. Tablets made with the cashew gum met the tested British Pharmacopeia specifications similar to the conventional binders indicating the potential for the use of purified cashew gum as a pharmaceutical binding agent.

Key words

Cashew gum; Branched hetero-polysaccharide; Dextrinized maize starch; All starches filler tablets



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INTRODUCTION

Excipients are the additives used to formulate pharmaceutical active ingredients into pharmaceutical dosage forms suitable for administration to the patients.(1) In many cases, an "active" substance may not easily be administered and absorbed by the human body. Excipients are also sometimes used to bulk up with potent formulations very active ingredients to allow convenient and accurate Pharmaceutical dosing. excipients play multiple roles in a pharmaceutical dosage forms. They modify important parameters such as solubility, stability and bioavailability of the active ingredients.(2)

Gums are hydrophilic polymers, useful as binders, gelling agents, emulsifiers, disintegrants, suspending agents and film forming agents.(3) Cohesive and adhesive properties of gums enhance their use in pharmaceutical preparations. The modern world prefers plant based natural products than the synthetic additives. Increased interest towards these natural products promotes researches based on new natural gums and mucilages to be used as pharmaceutical binders.(4)

Natural gums have greater benefits than synthetic gums, as they are biocompatible, cheap, chemically inert, nontoxic and easily available. Most natural gums consist of carbohydrates and few are proteins. Therefore, they are biocompatible and largely nontoxic. Natural gum production cost may be comparatively lower than the synthetic gum production. Natural gums are well tolerated by patients with less chance of side effects and adverse effects.(5) In the pharmaceutical industry, only a few accepted natural gums such as acacia, guar, sterculia. xanthan and tragacanth are available.(6) Identifying new natural gums and evaluating their physico-chemical and binding properties will support to maintain the consistency of the manufacturing process. A binder is added to a drug-filler mixture to ensure that granules and tablets can be formed with required mechanical strength in the wet granulation process.(7) Most of the binding agents require some moisture content to make them adhesive.

Cashew gum is the dried gummy exudate obtained from the stem bark of cashew tree, Anacardium occidentale Linn. family. Anacardiaceae.(8) Cashew tree is a spreading evergreen perennial tree. This plant is hardy and drought resistant. However, it is damaged by frost. The stem exudates a yellow or reddish colored gum. It occurs in a large stalactite piece and it is obnoxious to insects. The gum is found immediately under the bark of the tree, where it is sometimes collected in regular cavities. The gum is initially off white in color but changes to reddish brown or yellowish brown on exposure to air. The gum is a complex branched heteropolysaccharide comprising 61% galactose, 14% arabinose, 7% rhamnose, 8% glucose, 5% glucuronic acid and <2% other sugar residues.(9) Cashew plants were introduced from Brazil to Sri Lanka by the Portuguese in the 16th century. Now the plant is naturalized and cultivated in the warmer parts of Sri Lanka.

Cover of the cashew nut seed contains alkyl phenolic compounds such as cardanol, cardol, urushiol and anacardic acid which cause contact or systemic dermatitis.(10) These compounds are of low molecular weights and they can be easily removed by dialysis. Dialysis is the process that separate components in the mixture on the basis of their molecular weights. High molecular weight fraction remains in the dialysis tube while the low molecular weight fraction passing through the dialysis membrane. This method was used in the study to purify the crude cashew gum.

Physicochemical and binding properties of cashew gum was tested in a previous study by formulating metronidazole tablets. Cashew gum purified using a chemical method was used as a binder in tablet formulation in this study.(11) The cashew gum purified in this manner had showed low moisture content, low viscosity and low insoluble matter than the crude cashew gum. Metronidazole tablets prepared with cashew gum mucilage 4 - 8%w/w possessed the required hardness, friability, uniformity of weight, disintegration and dissolution.(11) Paracetamol tablets prepared using 2.5% w/w using cashew tree gum as a binding agent had showed greater mechanical strength and dissolution profile than the standard binders such as acacia and polyvinylpyrrolidone (PVP K-30).(12) Modified cashew gums were also useful in formulating sustained delivery theophylline and diclofenac sodium tablets.(13,14)

LD₅₀ (Lethal dose) of cashew gum and the comparative study of its functionality were evaluated in cotrimoxazole tablet formulations. Cotrimoxazole tablets had been prepared using cashew gum, gelatin, polyvinylpyrrolidone and corn starch as binders and their physical properties were compared. Granules prepared with cashew gum binder possessed good micromeritic properties at concentrations between 2-4% w/w than the standard binders.(15)

Aceclofenac gel prepared using cashew gum as a gelling agent did not produce any dermatological reactions and was well tolerated by guinea pigs.(16) Acute toxicity test was done on rats to identify the suitability of cashew gum to use as a coating material in the production of chocolate pebbles. In this study, the rats treated with cashew gum did not show any abnormal changes. Therefore, cashew gum is not toxic according to the World Health Organization Acute Hazard Ranking.(17)

The present study was undertaken to find out the binding strength of cashew gum with selected active ingredients, tablet in manufacture. This property was studied in comparison to popular binding agents. Particular interest was taken to find out the performance of purified cashew gum as a binding agent in a pioneering all starches filler tablet formulation devoid of lactose. Such a filler combination is not expected to perform well in granule and tablet formation. Purification of the brownish opaque crude gum translucent faintly amber colored into glistening flakes or granules is one of the main aspects of the study. The Purified Cashew Gum (PCG) was then subjected to combined analytical parameter requirements of the British Pharmacopoeia for other gums in the respective monographs. All starches filler tablets were also prepared with PCG binder. In this study dextrinized maize starch (DMS) maize starch (MS) filler combination was used without the excipient lactose.(18)

MATERIALS AND METHODS

Cashew gum was obtained from Nikaweratiya area, in the Kurunagala District, Sri Lanka. The cashew plant was authenticated at the National Herbarium, Peradeniya, Sri Lanka. The gum was collected from the main trunk during the months of November and December, 2016. Dialysis tube with 12 kDa molecular weight cutoff point was purchased from Thermo Fisher Scientific Company at Waltham, USA. Pharmacopoeial grade excipients and active ingredients were procured from Astron Pvt. Ltd, Galle Road, Ratmalana, Sri Lanka and from the State Pharmaceuticals Manufacturing Cooperation, Ratmalana, Sri Lanka. Granules were prepared in the Pharmacy Laboratory of Department of Pharmacy the and Pharmaceutical Sciences, University of Sri Javewardenepura. air-drving Hot oven Memmert UF160 (laboratory model – EF2W, Germany) was used for the dextrinization of maize starch. Manesty E2 tableting machine, England at the Pharmacy Department, and ten station tableting machine, model KMPC-10, Kambert Machinery Co Pvt Ltd, Ahmedabad, India was used to carry out tableting at Astron Pvt Ltd. Only the parameters applicable in the context of the present study were tested. Physical properties of PCG were compared with Gum Acacia. Tablets were then prepared using different active ingredients using a number of popular binding agents.

Preparation of PCG

The crude cashew gum was cleaned and the lumps of gum were crushed in a mortar and pestle into fine granules. Ten grams of granules was dissolved in 100 ml distilled water at 55 °C to form mucilage. Cashew gum mucilage (50 ml) was filled into 4 inch pieces of dialysis

tubes. Dialysis tube was then allowed to stand in a 500 ml beaker with 400 ml of distilled water. The beaker was kept in a magnetic stirrer at 4 rpm for 6 hours. Distilled water was replaced every 6 hours until the surrounding water becomes colorless. Cashew gum mucilage in the tube was collected into a suitable container and freeze dried at -44 °C. It was stored over phosphorus pentoxide in a desiccator overnight. The resulting PCG was stored in an airtight container.

Crude and PCG powders were sprinkled in water, laid over with a coverslip and observed under the microscope at magnification x 400.

Analysis of PCG

Based on the British Pharmacopoeia 2013 monographs for gums, the tests applicable for the PCG were performed. These included solubility, loss on drying, total ash, pH, swelling index, tannins, adulterants and protein content. Further, these tests were performed for gum acacia for comparison.

Formulation of placebo and pyridoxine hydrochloride tablets 2.0 mg with PCG and gum acacia solutions (2.75% w/v) as binders Conventional maize starch - lactose fillers were used in these tablets. Initially placebo tablets were prepared with PCG solution (2.75% w/v) as a reference formula for the Based on this successful trials trial formulation, pyridoxine hydrochloride was incorporated into the formula using the same binder with minor changes. This was to test the performance of PCG in formulating acceptable quality tablets using a low strength freely soluble active ingredient.

For the purpose of comparative binding property, a second batch of pyridoxine tablets was prepared with the same formula using gum acacia of the same strength as the binder (Table 1).

Ingredient	Placebo	Pyridoxine HCl Tablets (g)	
	tablets (g),	PCG binder	Gum acacia
	PCG binder		binder
Pyridoxine HCl		2.00	2.00
Lactose BP	144.432	139.422	139.422
Maize starch BP (Filler)	47.432*	51.121**	51.121**
PCG	1.104	1.104	
(Weight percent)	(0.55)	(0.55)	
Gum acacia BP			1.104
(Weight percent)			(0.55)
Purified talc	10.000	10.00	10.00
Magnesium stearate	1.000	1.00	1.00
Colloidal silicon dioxide	0.344		
Purified water	40.145 ml	40.145 ml	40.145 ml
Total dry weight	200.00	200.00	200.00

Table 1: Placebo and pyridoxine hydrochloride tablets 2 mg formulated with PurifiedCashew Gum (PCG) and gum acacia solutions (2.75% w/v) as binder

*Dry weight less 10% moisture is 43.120 g; **Dry weight less 10% moisture is 46.474 g; PCG, Purified Cashew Gum; BP, British Pharmacopoeia

For the placebo tablets, maize starch and lactose were mixed together and passed through an 18 mesh sieve. For the pyridoxine hydrochloride tablets, the drug was mixed with increasing portions of lactose and starch, thoroughly mixing before the addition of the next portions until the entire quantities were added. The resulting mix was passed through an 18 mesh sieve. PCG was dispersed in water and warmed to 50 °C to facilitate dissolution. The same procedure was repeated for gum acacia. The above powder mixes were transferred into three separate suitable containers and was separately processed further as follows.

Binder solution was added portion by portion while kneading with a gloved hand. It was continued until no free powder was left and a stiff dough had formed when it can be pressed into a lump. The dough was pressed through mesh number 12 to obtain wet granules. These were spread evenly on aluminium trays and loaded into an oven preheated to 55° C. After 2 hours granules were turned so that wet under surfaces were exposed and drying continued until the moisture content was between 1 - 2% w/w.

Dried granule aggregates were transferred into a mortar and reduced to smaller particles. The process was continued until all the granules were passed through a number 16 mesh sieve. The even sized granules were mixed with talc for one minute and then mixed with silicon dioxide and magnesium stearate as applicable for half a minute each. The resulting powder mix was used for compression into tablets. Single punch tableting machine Manyesty E2, England with 8.0 mm flat beveled punches were used for compression with a tablet target weight of 200 mg.

Formulation of carbamazepine tablets 100 mg with PCG and hydroxypropyl methylcellulose mucilages (15% w/v) as binders

The fillers used here were the conventional maize starch – lactose combination. Two batches of carbamazepine tablets were prepared with PCG and hydroxypropyl methylcellulose mucilages (15 % w/v). This was to test the performance of the binders at their near maximum concentration as binders. The binding ability of the PCG in the presence of a high percentage of insoluble active ingredient was tested. Furthermore, the binding property of PCG was compared with the popular binding agent hydroxypropyl methylcellulose. The same formula given in Table 1 was used except for the two different binding agents (Table 2).

Granules were prepared similar to the above procedure used for pyridoxine hydrochloride tablets. This was followed by compression into tablets in the same machine using the same punches as above.

Formulation of lactose free DMS - MS starch filler placebo tablets with maize starch paste (17.65% w/v) and PCG mucilage (10 % w/v) as binders The fillers used here were the DMS – MS combination, where DMS was used to replace the conventional tablet filler lactose. This experiment was carried out as an extension of the previous study, on lactose free all starches filler tablet project.(19)

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Table 2: Carbamazepine tablets 100 mg
formulated with Purified Cashew Gum
(PCG) and hydroxypropyl methylcellulose
mucilages (15% w/v) as binders

Amount (g)
100.00
28.956*
56.880
5.80
(2.9)
10.00
1.00
38.00 ml
200.00

*Dry weight less 10% moisture is 26.324 g; BP, British Pharmacopoeia; PCG, Purified Cashew Gum

It is interesting to note that DMS, maize starch and PCG chemically belong respectively to oligosaccharide, polysaccharide and to complex branched hetero-polysaccharide categories of starch. This all starches formulation is a new dimension in the application of starches in tablet manufacture.

These experiments were undertaken to test the performance of PCG mucilage as a binding agent in an all starches filler tablet formulation devoid of the popular filler lactose. Lactose was replaced with DMS (Table 3). The formula is basically similar in other aspects to placebo tablets made above (Table 1).

Table 3: Placebo tablets formulated with lactose free DMS - MS fillers using maize starch paste (17.65% w/v) and Purified Cashew Gum (PCG) mucilage (10% w/v) as binders

Ingredient	Placebo tablets (g)		
	Maize	PCG	
	starch	formula	
	binder		
	formula		
Dextrinized	127.392	140.488	
maize starch			
Maize starch BP	41.000*	45.945**	
PCG binder			
(Weight		6.400	
percent)		(3.2)	
Maize starch BP	24.00		
(binder)	(12.0)		
(Weight			
percent)			
Purified talc	10.00	10.00	
Magnesium	1.00	1.00	
stearate			
Colloidal	0.344	0.344	
silicon dioxide			
Purified water	135.997 ml	64.000 ml	
Total dry	200	200	
weight			

*Dry weight less 10% moisture is 37.264 g **Dry weight less 10% moisture is 41.768 g; BP, British Pharmacopoeia; PCG, Purified Cashew Gum

RESULTS

Analytical test results of excipients PCG and gum acacia

The dark amber to brown colored crude cashew gum was purified by dialysis and the light amber glistening final product was obtained with a yield of 61.50 % w/w. It was translucent, glistening, had an appearance of faint amber color and was free of any odor. PCG was soluble in water, insoluble in ethanol and diethyl ether. Many of the tested analytical parameters were quite similar to those of gum acacia (Table 4).

Table 4: Analytical test results of excipients
Purified Cashew Gum (PCG) and gum
agagia

Test	PCG	Gum
		acacia
Loss on drying	12.45 -	13.11 -
	14.0%	13.32%
Water soluble	81.02%	N/A
matter		
Water	7.93%	N/A
insoluble		
matter		
pН	6.0	6.0
Total ash	0.588 -	2.031 -
content	0.732%	3.201%
Tannins	Absent	Present
Starch and	Absent	Absent
dextrin		
Agar and	Absent	Absent
tragacanth		
Proteins	1.5%	N/A
Reducing	Absent	N/A
sugars		
Film forming	Thin film	Thin film
ability	formed	formed
Swelling index	Dissolves	N/A
	without	
	swelling	

N/A: Not available; BP, British Pharmacopoeia; PCG, Purified Cashew Gum

Results of physical test parameters of placebo and pyridoxine tablets 2 mg made with PCG and gum acacia solutions (2.75% w/v) as binders All three tablet formulations were designed for a 200 mg tablet. Placebo tablet formula was a success and therefore adopted for the processing of two pyridoxine tablets. However, the two pyridoxine tablets had to be compressed at 175 mg. This is possibly due to the unusually low tapped densities of the granules, 0.55 and 0.5 for PCG and gum acacia respectively for the two pyridoxine tablet formulations (Table 5). Due to unusual lower tapped density, the final weight of the individual tablets was reduced than the expected reference formula weight. There appeared to be insufficient fineness, 9.4% and 6.8% in the blends resulting in a comparatively high degree of voids and low tapped density. Despite the revised target tablets weight it was possible to get an idea about the comparative binding properties of PCG and gum acacia. Most parameters of the two pyridoxine tablet formulations made with PCG and gum acacia binders does not warrant adverse comments as these were found to be very similar within British Pharmacopeia limits (Table 5).

Results of physical test parameters of carbamazepine tablets 100 mg made with PCG and hydroxypropyl methylcellulose mucilages (15% w/v) as binders

The tested parameters showed a striking similarity between the tablet batches made with the two binders PCG and hydroxypropyl methylcellulose at the same strength of 15% w/v. The results of the analysis are indicated in Table 6. The results show that the PCG binding power is as strong as that of the established binder hydroxypropyl methylcellulose.

Results of physical test parameters of lactose free all starches filler DMS - MS tablets made with starch paste (17.65% w/v) and PCG solution (10% w/v) as binders The results of these two tablet formulations prove the strong binding properties of PCG. The composition of the formula wass kept as even as possible to other formulations except for the adjustment of filler quantities.

Stage of analysis	Test item	Placebo tablets (PCG)	Pyridoxine tablets (PCG)	Pyridoxine tablets (GA)
Granule	Fines < 80 mesh	N/A	9.4%	6.8%
analysis	Granule density,	N/A	0.526/0.555 g/ml	0.435/0.500 g/ml
-	Pouring/Tapped		_	_
Tablet	Av. thickness (mm)	2.950	2.760	2.800
analysis	Friability %	0.430	0.006	0.049
	DT (Min. Sec).	0.160	2.37	3.00
	*Weight variation(g), Min/Max	196.1/202.5	170.8/185.2	171.4/180.5

Table 5. Physical test results of placebo and pyridoxine tablets 2 mg formulated with Purified Cashew Gum (PCG) and gum acacia solutions (2.75%w/v) as binders

PCG: Purified cashew gum binder, GA: Gum acacia binder, N/A: Not available. *Target weights of placebo tablets 200.0 mg and for both pyridoxine tablets 175 mg.

Table 6: Physical test results of
carbamazepine tablets 100 mg formulated
with PCG and hydoxypropyl
methylcellulose mucilages (15% w/v) as
binders

Test item Tablets Tablets made with made with purified hydoxypro cashew gum pyl mucilage methylcellu lose mucilage 28 Thickness (mm) 2.8 Friability% 0.055 0.232 Weight variation. 200.7/209.0 202.9/208.7 Min/Max (mg) Disintegration 5.36 2.0 time (Min. sec.)

However, the filler ratio 1: 3 of DMS – MS was kept constant. The most obvious weakness was in the friability test in which all the tablets made with starch paste completely crumbled during the test. The hardness was poor at 2.27 kPa. This means that the all starches DMS – MS filler tablet formulation made even with a very high strength starch paste, which was 12% w/w on dry basis still failed to make acceptable quality tablets. However, PCG mucilage of 10% w/v strength produced tablets of acceptable physical qualities (Table 7). On a dry weight basis, the amount of PCG used was less than $1/3^{rd}$ the amount of starch (Table 3). This shows that lactose free all starches DMS - MS filler tablets could be successfully prepared with PCG binder, an indication of the strong binding property of the gum.

Table 7: Physical test results of lactose free placebo tablets formulated with DMS- MS fillers using starch paste (17.65% w/v) and Purified Cashew Gum (PCG) (10% w/v) as binders

Test	Placebo tablets	Placebo tablets	
	starch paste	PCG	
	binder	binder	
Thickness (mm)	3.95	3.90	
Hardness (kPa)	2.27	4.57	
Friability%	*	0.16	
Weight variation,			
Min/Max (mg)	197.1/202.7	195.7/205.5	
Disintegration	1.67	1.40	
time (Min. sec.)			

*Tablets completely crumbled; PCG, Purified Cashew Gum

DISCUSSION AND CONCLUSION

We did not find any historical uses of cashew gum in the traditional system of medicine in Sri Lanka. The reason may be that the cashew tree was introduced to this part of the world in the 16th century by the Portuguese and never made in to the indigenous medicinal compositions.

Among many trials performed, only those formulations that were successful for the purpose of interpretation of the performance of PCG as a binder were listed in the tables. Two fundamentally different formulations were used in tablet formulation, the traditional starch – lactose filler tablets (Tables 1 and 2) and the radically different all starches filler tablets with DMS-MS fillers (Table 3). The second type posed a greater challenge as this combination was attempted for the first time as a formulation strategy and there is no guarantee that tablets may form at all. The binder strengths in all instances were given in both w/v percentages of the binder and also on a dry basis of w/w percentage of the binder with respect to the total formula.

The placebo tablets made with PCG solution 2.75% (0.55% w/w of the formula on dry basis) was a success. The percentages of excipients used in this formulation were applied to all other trials as far as possible (Table 1). Physical test parameter results of placebo tablets were most favorable (Table 5). However inevitable changes to the formulations had to be made due to varying amounts of active ingredients and binding agents used in different trials.

Pyridoxine tablets made on this basis showed nearly similar results for PCG and gum acacia binders. Friability and disintegration times were more favorable on tablets made with PCG. The soluble nature of the active ingredient had no influence on the physical quality of tablets. Tablets with higher strength using highly soluble active ingredient must be formulated with necessary changes to PCG binder strength in order to check the performance in formulating tablets with highly soluble ingredients.

Carbamazepine tablets 100 mg amounting to 50% of tablet weight were made with PCG and hydroxypropyl methylcellulose mucilage of

15% w/v strength. The dry PCG binder to total formula weight was 2.9% w/w. This is over 5 times that of the amount used in Table 1. All physical test parameters met the British Pharmacopeia requirements. Despite this increase in binder, the disintegration time had increased only up to 5.36 minutes. The concentration of PCG appears to have no adverse impact on disintegration test since in all other instances the maximum disintegration time was only 2.37 minutes.

The preparation of all starches filler tablet formulation consisting of DMS – MS was first attempted using regular strengths of maize starch binder. Many formulations failed to form even the dough and the powder mix remained partly dry. Finally, unusually high amounts of the paste yielded tablets which were of poor physical quality. Near maximum concentration of 17.65% w/v of the starch paste had to be used as against 10 % w/v for the PCG (Tables 3 and 7). It must also be noted that the total weight of starch paste was 160 g in a 200 g experimental batch. In the case of PCG, the total weight of the binder is 70 g, less than half the amount of starch paste required. The unusually large amounts were due to the fact that regular amounts of paste were insufficient to wet the powder mix possibly due to the presence of DMS.

The purification process of the gum described here could be considered a success. The purified product was light amber colored indicating that the phenolic compounds urushiol, cardol, anacardic acid and other unwanted substances had been removed from the gum during the dialysis process. Further, the British Pharmacopeial analytical parameters were very similar to those of gum acacia. Tannins were absent in PCG whereas it was positive for gum acacia (Table 4). The presence of any traces of unwanted chemical substances could not possibly have any untoward effect since as little as few milligrams of the gum were sufficient to make the tablets (Tables 1, 2 and 3).

The strong binding properties of PCG was established during the trials undertaken here. Low friability values ranging from 0.006% -0.16% are a reflection of this property. The ability of PCG binder to form tablets with all starches DMS – MS fillers is further proof in this regard. In future, PCG may be added to the limited list of gums available to the pharmaceutical industry. All starches filler tablets were successfully prepared using about $1/4^{\text{th}}$ PCG compared to starch paste (Table 3). There are good prospects of producing the gum in Sri Lanka unlike other imported gums. However thorough toxicity studies need to be carried out before it is accepted for regular use. The outcome of the study brings PCG closer to official acceptance of the gum as a pharmaceutical binder. The focus of the present study was about potential binding properties. Future work should involve more elaborate dissolution and stability studies with fine-tuned formulations. The worldwide extent of cashew plantations could be a source of the gum that may go a long way in meeting the requirements, particularly given the minimum amounts of the gum required for effective binding.

Author's Declaration

The authors declare that all persons listed as authors have read and given approval for the submission of this manuscript.

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Competing Interests

The authors declare that they have no competing interests to disclose.

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