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INVESTIGATION OF SALBUTAMOL TABLETS FORMULATION USING PURIFIED CASHEW (*ANACARDIUM OCCIDENTALE* L.) GUM AS BINDER

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ABSTRACT

The purpose of this study was to investigate purified cashew gum as a binder in salbutamol tablets preparation. Crude cashew gum was collected and purified by dialysis. The resulting higher mass fraction was subsequently freeze dried. The purified gum had a light amber color, sparkling pieces, and was odorless. Salbutamol tablets formulated using purified cashew gum were evaluated for weight variation, friability, hardness, disintegration time, in vitro dissolution studies, and assay tests. Tablets formulated with a low concentration of 2.75 % w/v purified gum as the binding agent showed excellent physical properties. The hardness of tablets was 10.80 kPa, and the friability < 1%. The disintegration time of the tablets was < 15 minutes and they disintegrated quickly in aqueous solutions, with > 80% dissolution in 30 minutes. This study shows that purified cashew gum has the potential to be used as a pharmaceutical binding agent in immediate release tablet formulations.

KEYWORDS: Purified cashew gum, binding agent, salbutamol tablet, natural gums.

INTRODUCTION

Binding agents are used in tablet formulations to increase mechanical strength and to improve the formulation's compressibility and flow properties. Wet granulation is the most common approach used to incorporate binder solution into a formulation.[1] Binding agents used in pharmaceutical industry are obtained from natural, semi synthetic and synthetic sources. Gum arabica, gum tragacanth, xanthan, gum acacia, and gum sterculia are natural binders collected as exudates or extractives from the bark of various plants' stems, branches, and roots.[2]

Increased interests in plant products encourage researches into natural gums and mucilage that could be employed as pharmaceutical excipients.[3] Gums are high molecular weight polymers that can be used as binding agents, gelling agents, emulsifiers, disintegrants, suspending agents, and film-forming agents.[4] Cohesive and adhesive properties of gums enhance their use in pharmaceutical preparations. Natural gums outperform synthetic gums in terms of biocompatibility, cost, chemical inertness, nontoxicity, and accessibility.[5] Only a few natural gums, such as acacia, guar, sterculia, xanthan, and tragacanth, are used in the pharmaceutical industry.[6] Finding new natural gums, analyzing their physicochemical and binding properties will help the manufacturing process due to wider choice.

Cashew gum is the dried gummy exudate obtained from the stem bark of cashew tree, *Anacardium occidentale* Linn, family, Anacardiaceae.[7] The stem exudates a yellow or reddish colored gum. The gum is initially off white in appearance, after exposing to the air, it turns reddish brown or yellowish brown. The gum is made of complex branched heteropolysaccharides. The main constituent of cashew gum is galactose and it comprises 61% of all total weight, and remaining constituents are 14% arabinose, 7% rhamnose, 8% glucose, 5% glucuronic acid and <2% other sugar residues.[8] The Portuguese introduced cashew plants from Brazil to Sri Lanka in the 16th century. The plant has now become naturalized and is growing in the warmer parts of Sri Lanka.

In a previous study, metronidazole tablets were prepared to investigate the physicochemical and binding properties of cashew gum. A chemical purification method of cashew gum was used in this study. Metronidazole tablets with 4–8% w/w cashew gum mucilage had the requisite hardness, friability, weight homogeneity, disintegration, and dissolution.[9] In another investigation, paracetamol tablets made with 2.5 % w/w cashew gum as a binding agent outperformed traditional binders like acacia and polyvinylpyrrolidone (PVP K-30) in terms of mechanical strength and dissolution profile.[10] Cashew gum used to prepare pyridoxine hydrochloride and carbamazepine tablets

showed excellent physical properties and met all the British Pharmacopeial specifications.[11] Modified cashew gums were also helpful in the formulation of a sustained delivery system.[12,13]

On the basis of a previously published work, cashew gum purification was carried out.[14] The aim of this study was to see how well purified cashew gum (PCG) performs in the production of conventional tablets with a specific active ingredient using wet granulation method.

MATERIALS AND METHODS

Cashew exudate was collected from Nikaweratiya area, in the Kurunagala District, Sri Lanka. The gum was collected from the main trunk during the months of November and December. Dialysis tube with 12 kDa molecular weight cutoff point was purchased from Thermo Fisher Scientific Company (Waltham, USA).

Astron Pvt. Ltd, Galle Road, Ratmalana, Sri Lanka, and the State Pharmaceuticals Manufacturing Cooperation, Ratmalana, Sri Lanka, gifted pharmacopeial grade excipients and active ingredients. Granules were prepared in the Pharmacy Laboratory of the Department of Pharmacy and Pharmaceutical Sciences, University of Sri Jayewardenepura. Ten station tableting machine, model KMPC-10 (Ahmedabad, India) was used to carry out tableting at Astron Pvt Ltd. Precision balance AR1530 was used to weigh the API and raw materials. TBH 225 Hardness tester, ERWEKA ZT22X Disintegration tester and VT-02 Friabilator were used to determine the physical properties of the tablets.

Preparation of PCG

Crude Cashew Gum (CCG) was purified and freeze dried according to a previous study.[11] Powdered PCG was stores in an air tight container.

Microscopic identification of CCG and PCG

CCG and PCG powders were sprinkled in water, laid over with a coverslip and observed under the microscope at magnification x 400 (Fig. 1).

Evaluation of characteristics of PCG

Based on the BP 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 CCG and gum acacia for comparison (Table 2).

Preparation of Salbutamol tablets BP 2 mg

Salbutamol sulphate 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 850 micrometer sieve. PCG was weighed and dissolved in purified water at the room temperature. The above powder mix was transferred into separate container.

PCG binder solution was added portion by portion while kneading with a gloved hand. It was continued until no free powder was left and 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 %.

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 20-30 seconds each. The resulting powder mix was used for compression into tablets (Table 1). Ten station rotary tableting machine KMPC-10, with 8.0 mm flat beveled punches were used for compression with a tablet target weight of 200 mg.[11]

Table 1: Formulation of salbutamol tablets BP 2 mg with PCG solution (2.75% w/v) as binder.

Ingredients/ substances	Quantity	Pharmaceutical formulae per tablet	Function
Salbutamol Sulphate	3.010 g	2.408 mg	Active ingredient
Lactose	167.39 g	133.91 mg	Filler
Maize starch	57.50 g	46.00 mg	Filler
Purified Cashew Gum	1.38 g	1.104 mg	Binder
Purified talc	12.50 g	10.00 mg	Lubricant
Magnesium Stearate	1.25 g	1.00 mg	Lubricant
Colloidal Silicon Dioxide	0.43 g	0.34 mg	Glidant
Purified water	50.00 ml		To prepare binder
Final dry weight	250.00 g	200.00 mg	

Quality tests for Salbutamol Tablets BP 2 mg

Thickness and diameter of prepared tablets were determined using a caliper set and on a TBH 225 Hardness tester. The weight variation was determined by weighing twenty randomly selected tablets on a precision balance AR1530. Disintegration test was carried out in

distilled water with the ERWEKA ZT22X Disintegrating tester. The disintegration apparatus was filled with water up to the point of mesh of the tubes and the temperature was adjusted to 37 °C. The randomly selected six tablets were placed in the cylindrical glass tubes and the time taken for the tablets to disintegrate was recorded as disintegration time. Friability of tablets was determined with a VT-02 friabilator. Twenty tablets were randomly selected, de-dusted and weighed on analytical balance AR1530. The tablets were placed into the drum of the friabilator and set to rotate at 100 rpm. The tablets were de-dusted after the test, weighed and the difference in weights expressed as a percentage of the initial weight. Hardness was determined for ten randomly selected tablets, using TBH 225 hardness tester (Table 3).

Assay test for Salbutamol Tablets BP 2 mg

Assay test for salbutamol Tablets BP 2mg were carried out according to BP 2013 monograph, appendix III D (Table 3).

Following equation was used to calculate for salbutamol assay percentage;

$$\frac{48.2}{100} \times \frac{99.85}{100} \times \frac{100}{\text{Weight of sample (g)}} \times \frac{\text{Weight of 1 tablet (g)}}{2} \times 0.8299 \times \frac{\text{Sample Peak Area (mAU)}}{\text{Standard Peak Area (mAU)}} \times 100$$

Area (mAU) - milli-Absorbance Units
48. 2 - Weight of standard salbutamol sulphate (mg)
99.85 - Strength of salbutamol sulphate
0.8299 - Factor of salbutamol sulphate

Dissolution test for Salbutamol Tablets BP 2 mg

Dissolution test was carried out with dissolution tester VK-7025. Distilled water 500 ml was used as a medium and the temperature was set at 37± 0.5 °C, and a paddle speed of 50 rpm. Samples was collected at 30 minutes and filtered, using 45 micrometer filter paper. Analysis was done in High Performance Liquid Chromatography, using a 0.048 % w/v salbutamol sulphate as standard. The amount of drug released was determined from the area under the curve obtained in chromatogram (Table 5). Same formula as above was used to determine the dissolution percentage of salbutamol tablets.

Real time stability test

The prepared salbutamol tablets were stored in room conditions (27-30 °C) for 18 months and real time stability test was performed for physical characteristics of the tablets. Weight variation, disintegration, friability, hardness, diameter and thickness were checked (Table 3).

RESULTS AND DISCUSSION

Microscopic identification of CCG and PCG

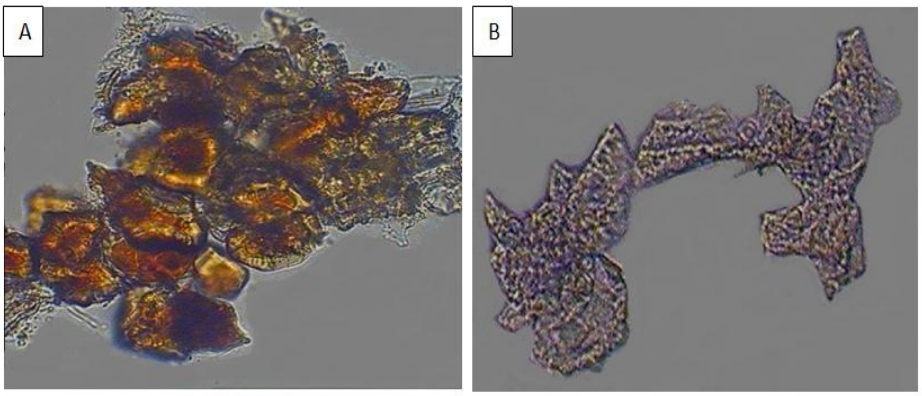

Fig. 1: (A) is microscopic picture of crude cashew gum at × 400 magnification; (B) is microscopic picture of purified cashew gum at × 400 magnification.

CCG showed an opaque brown color under the microscopic identification (Fig. 1). After purification PCG was translucent in appearance. This color change is possibly due to removal of phenolic substances.

Comparison of physical properties of CCG, PCG and Gum Acacia

It is necessary to manufacture a powder from CCG by removing all its impurities as much as possible before introducing it into the pharmaceutical industry. Initially, filtration and centrifugation methods were used to remove large visible particles from CCG. Later, dialysis was used to remove impurities with a smaller molecular weight (less than 12 kDa). Cashew gum solution retained inside the dialysis bag was freeze dried and, at last, PCG was obtained.

Table 2: Comparison of physical properties CCG, PCG with Gum Acacia.

Test	Observations		
	CCG	**PCG**	**Gum Acacia**
Solubility (28 °C) in water	Insoluble	Freely soluble	Soluble with froth formation
Solubility (100^0C) in water	Freely soluble	Freely soluble	Soluble
Solubility (95% Ethanol)	Insoluble	Insoluble	Insoluble
Loss on drying (%)	7	14	13.11
pH, 1% gum solution	3.5	7.53	6.12
Total ash (%)	0.610	0.588	3.201
Swelling Index	ND	ND	ND
Film forming ability	Thin, translucent film formed	Thin, translucent film formed	Thin, translucent film formed
Tannins	Precipitate was formed slightly	No precipitate was formed	Gelatinous precipitate was formed

CCG, Crude cashew gum, PCG, Purified cashew gum, ND, Not detectable

PCG has similar properties to gum acacia. CCG is acidic in nature which becomes slightly basic (pH = 7.53) after the purification process. Total ash and loss on drying both within the acceptance range. PCG has ability to form a thin translucent film but it does not have swelling property.

The purified cashew gum was light amber colored indicating that the phenolic compounds and other unwanted substances had been removed. Since gum acacia is the most extensively used plant gum in pharmaceutical and other industries, PCG was compared to its qualities and most of the BP analytical parameters were very similar to those of gum acacia. (Table 2). According to solubility studies, PCG is soluble in water at room temperature. Therefore, as per the definition of gums, PCG is hydrophilic. The pH of the solution prepared with CCG was 3.5. It is an acidic pH, and it may be due to the presence of phenolic compounds. The pH of the solution prepared with PCG was 7.35, a basic pH. This indicates that the dialysis procedure has removed the small molecular weight phenolic compounds. Tannins were absent in PCG, whereas it was positive for gum acacia (Table 2).

Quality test results of Salbutamol tablets

White, flat, circular tablets with a break line on one side, 8 mm in diameter, and 3.6 mm in thickness were formulated.

Table 3: Physical test results of salbutamol tablets BP 2 mg.

Tests	**Results**	**Results after real time stability studies**
Diameter (mm) ± SD	7.97 ± 0.03	7.97 ± 0.03
Thickness (mm) ± SD	3.67 ± 0.06	3.67 ± 0.06
Disintegration (Minutes) ± SD	0.39 ± 0.08	0.45 ± 0.32
Hardness (kPa) ± SD	10.80 ± 0.81	10.40 ± 0.93
Friability % w/w ± SD	0.44 ± 0.01	0.41 ± 0.01
Weight variation (mg) ± SD	199.6 ± 1.51	200.2 ± 1.01

SD, standard deviation, Real time stability studies were performed after 18 months

Table 4: Results of assay for Salbutamol Tablets BP 2 mg.

Test solution	**No of injection**	**Area under the curve**	**Average area under the curve**	**% of assay**	**Mean % of assay**
Standard 1	1	1640.84	1646.24	-	-
	2	1638.38			
Standard 2	1	1654.11			
	2	1651.60			
Sample 1	1	765.64	767.14	93.64	93.58
	2	768.64			
Sample 2	1	766.54	766.09	93.51	
	2	765.64			

The test result of assay was 93.52%, where the BP standard range is 92.5%-107.5%. The tests were duplicated and mean assay percentage was calculated.

Table 5: Results of Dissolution for Salbutamol tablets BP 2 mg.

Test solution	No of injections	Area under the curve	Average area under the curve	% of dissolution	Mean % of dissolution
Standard 1	1	164.08	164.79	-	-
	2	171.51			
Standard 2	1	161.99			
	2	161.55			
Sample 1	1	70.85	70.51	85.87	87.67
	2	70.17			
Sample 2	1	73.25	73.25	88.77	
	2	73.25			
Sample 3	1	72.89	72.92	88.37	
	2	72.95			

In the dissolution test, 87.67% of the salbutamol had been released in 30 minutes. According to BP standards, salbutamol dissolution should be at least 80% in 30 minutes. The tests were triplicated and mean dissolution rate was calculated.

Gum exudates of *Anacardium occidentale* have good water soluble properties, and this is a very important characteristic that can be used in drug formulations. The granules formed by PCG are white in color, and therefore, they do not impart any discoloration to the formulation. The mean friability value (0.44%) reflects well on this property. Salbutamol tablets prepared were within an acceptable range of diameter, thickness, hardness, friability, weight variation, and disintegration. In a dissolution test, 87.67% of the drug had been released in 30 minutes (Table 4). The assay was 93.52%, where the BP standard range is 92.5%-107.5% (Table 5). According to BP 2013 standards, salbutamol dissolution should be at least 80% in 30 minutes. According to the results, salbutamol tablets comply with BP 2013 standards. Real time stability studies have further proven that the prepared salbutamol tablets remained within their physical characteristics and complied with BP 2013 standards till their shelf life.

CONCLUSION

Formulated salbutamol tablets possessed good physical properties with acceptable assay and dissolution range. 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 towards meeting the requirements, particularly given the minimum amounts of gum required for effective binding.

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