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Effects of palm bunch potash, trona and their modified cashew gum-corn starch composite on the physicochemical properties of furosemide

[Efecto de la potasa de racimo de palma, la trona y el compuesto modificado de almidón de maíz-goma de anacardo sobre las propiedades fisicoquímicas de furosemida]

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Abstract

Context: In Nigeria, traditional cuisines are prepared using either palm bunch ash (PBA) or trona to impart emulsification, tenderizing and flavouring attributes to oils, proteins and polysaccharides in delicacies. Hypothesis is that they may improve the solubility and dissolution profiles of poorly soluble and permeable drug as furosemide.

Aims: To investigate the effects of palm bunch potash (PBP), trona and modified cashew gum-corn starch composite on the physicochemical properties of furosemide.

Methods: To generate PBP and purified trona, PBA or powdered trona was dispersed in water, filtered, centrifuged and supernatant evaporated to dryness. Cashew gum (CG) and cashew gum-corn starch composite (EC) were modified by mixing with PBP or trona at 5:1 and 10:1, wetted with water, stored in amber vials for 72 h. Furosemide was granulated with modified excipients at 1:1 ratio and characterized: FTIR, DSC, solubility and dissolution studies.

Results: Yield of PBP: 9.38 ± 1.24%, trona: 24.18 ± 0.93%. FTIR spectra of furosemide/granules were similar and retained key functional groups present in furosemide. Their DSC thermograms revealed complete amorphization of furosemide in granules. Mixing of PBP or trona and excipients at 5:1 ratio significantly ($p<0.05$) improved furosemide's solubility in comparison to 10:1. Excipient-trona was a significantly ($p<0.05$) better enhancer of furosemide's solubility than excipient-PBP. Modified excipients significantly ($p<0.05$) improved furosemide's dissolution profile, while unmodified cashew gum reduced it by 50%. Dissolution profile improvement by modified excipients ranked in the order: CG-Trona > CG-PBP > EC-Trona > EC-PBP.

Conclusions: Trona, PBP, modified excipients positively altered the physicopharmaceutical properties of furosemide.

Keywords: cashew gum-corn starch composite; furosemide; palm bunch potash; solubility and dissolution improvement; trona.

Resumen

Contexto: En Nigeria, las cocinas tradicionales se preparan utilizando ceniza de racimo de palma (PBA) o trona para hacer emulsión, ablandar y saborizar aceites, proteínas y polisacáridos comestibles. La hipótesis es que éstos puedan mejorar los perfiles de solubilidad y disolución de fármacos poco solubles y permeables como furosemida.

Objetivos: Investigar los efectos de la potasa de racimo de palma (PBP), trona y el compuesto modificado de la goma de anacardo-almidón de maíz sobre las propiedades físico-químicas de la furosemida.

Métodos: Para generar PBP y trona purificada, PBA o trona en polvo se dispersaron en agua, se filtraron, se centrifugaron y el sobrenadante se evaporó a sequedad. La goma de anacardo (CG) y el compuesto de anacardo-almidón de maíz (CE) fueron modificados mezclando con PBP o trona a 5: 1 y 10: 1, humedecido con agua y almacenada en viales ámbar por 72 h. La furosemida se granuló con excipientes modificados en relación 1: 1 y se realizaron estudios por FTIR, DSC, de solubilidad y estudios de disolución.

Resultados: El rendimiento fue de PBP: 9,38 ± 1,24%, trona: 24.18 ± 0.93%. Los espectros FTIR de furosemida/gránulos fueron similares y se retienen grupos funcionales clave presentes en la furosemida. Sus termogramas DSC revelaron amorfización completa de furosemida en gránulos. La mezcla de PBP o trona y excipientes en relación 5:1 de manera significativa ($p <0,05$) mejoró la solubilidad de furosemida en comparación con 10:1. Excipiente-trona fue significativamente ($p <0,05$) mejor potenciador de la solubilidad de furosemida que el excipiente-PBP. Excipientes modificados significativamente ($p <0,05$) mejoraron perfil de disolución de furosemida, mientras que la goma de anacardo sin modificar la redujo en un 50%. El perfil de disolución mejoró por los excipientes modificados en el orden: CG-Trona> CG-PBP> EC-Trona> EC-PBP.

Conclusiones: Trona, PBP y excipientes modificado alteran positivamente las propiedades fisicofarmaceuticas de furosemida.

Palabras Clave: compuesto almidón de maíz-goma de anacardo; furosemide; mejoramiento solubilidad y disolución; potasa de racimo de palma; trona.

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INTRODUCTION

Traditionally, potash derived from palm ash has been used as food additive, saponification ingredient, herbal medicine and agricultural input (Johnson, 2011). Empty palm fruit bunch is a by-product obtained from African oil palm, *Elaeis guineensis* Jacq (family Arecaceae or Palmae) (Iwu, 2014). It is an agricultural waste, which is mostly burnt because it does not easily decay and has capacity to occupy a lot of space. The ash derived from incinerating empty palm fruit bunch has been used for bioremediation of soil polluted by crude oil, preparation of traditional medicines and domestic purposes including preparation of delicacies (as an emulsifying agent, as well as a tenderizing agent in Igbo cuisine-Southeast Nigeria). Previous workers reported that palm bunch ash contains mainly potassium carbonate and potassium hydroxide, hence their effectiveness as saponification agents (Onuchukwu, 1989; Taiwo and Oshinowo, 2001).

Trona on the other hand is a solid mineral mined from underground deposits in many parts of the world. It occurs as sodium carbonate in the form of sodium sesquicarbonatedihydrate ($Na_2CO_3.NaHCO_3.2H_2O$). Sodium sesquicarbonate is used to manufacture sodium carbonate (soda ash). It is off-white to tan coloured crystalline solid with many applications: in a minimally purified state, trona is used as a rumen buffer (digestive aid) in cattle feed; used traditionally as salt of tobacco in combination with tobacco to produce tobacco snuffs; as tenderizer in cooking of food stuffs and to accelerate fermentation processes (Solvay, 2013). It has also been reported to be used as laundering agent, in wood scouring, as bath salts and in pharmaceuticals (Iro and Nagappa, 1998; Ameh et al., 2009). Interestingly, a very effective and popular formulation: NIPRISAN®, otherwise known as NICOSAN®, used for the management of sickle cell disease has been reported to contain trona as one of its ingredients (Obodozie et al., 2009). Trona is primarily made up of three chemicals, sodium bicarbonate (baking soda), sodium carbonate (soda ash) and water. Both sodium bicarbonate and sodium carbonate are food additives that are generally recognized as safe (GRAS) by the United States Food and Drug Administration (FDA). In addition, previous sanctions on trona's use in food have been waived by the Code of Federal Regulations of the United States of America (CFR, 1984; Solvay, 2013).

Cashew gum and corn starch are excipients that have been researched by many workers. The former has been studied as binder in granules and tablets (Gowthamarajan et al., 2011; Abdulsamad et al., 2015), emulsifying agent and film coating agent (Ofori-Kwakye et al., 2012; Olorunsola et al., 2014); while the latter possesses diverse functionality characteristics (binder, disintegrant, lubricant, suspending agent) (Odeku, 2013). Cashew gum has been reported to retard drug release at concentrations >5% w/w as wet granulation binder; a property suggested to be by stabilization or hardening of drug crystals thereby decreasing solubility in aqueous environment, since cashew gum does not swell in water (Okoye et al., 2012; Okoye, 2014).

Biopharmaceutical classification system (BCS) is a system that differentiates drugs on the basis of their aqueous solubility and lipoid layer permeability. It serves as a guide in predicting intestinal drug absorption. The BCS system classifies drug compounds into four classes: Class I - high solubility and high permeability; Class II- low solubility and high permeability; Class III- high solubility and low permeability and Class IV- low solubility and low permeability (Benet, 2013). Revelation from recent reports that while the percentage of new chemical drug entities exhibiting poor aqueous solubilities, hence poor oral bioavailabilities is increasing, those with high aqueous solubilities and high permeability is dwindling (Griffin, 2012). Invariably, the implication is that most new chemical drug entities belong to Class IV of BCS. Furosemide is a BCS Class IV drug with the chemical name: 4-chloro-N-furfuryl-5-sulphamoyl- antranilic acid or 5-(aminosulfonyl)-4-chloro-2[(2-furanylmethyl) amino) benzoic acidand chemical structure shown in Fig. 1 (Lasix, 2011).

It is a loop diuretic used in the treatment of edematous states associated with cardiac, renal and hepatic failure. It is also used for the treatment of hypertension. It acts by inhibiting the reabsorption of sodium and chloride in the ascending limb of Henle's loop and also in the early distal tubules (Lasix, 2011).

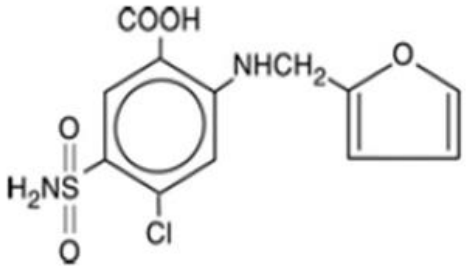

Figure 1. Chemical structure of furosemide.

The bioavailability of furosemide has been reported to be less than 50% (Oh and Han, 2015), so that the amount unavailable in plasma remains in the body performing no therapeutic activity, but however contributing to increased adverse effects of the drug. If therefore the solubility and permeability of furosemide could be improved, higher amount of the drug may become bioavailable, so that reduction in dose and adverse effects may be achieved. Some works in this direction involved the use solubilising agents in formulating furosemide solution or its nanoparticle dispersion. Both approaches involve the use of surfactants, which have been reported by various researchers to induce many adverse effects on humans and animals (Mercola, 2010; Kiss et al., 2013). Since the outcry against the use of surfactants in foods and pharmaceuticals is becoming loud, there is need to search for much safer excipients that may functionally replace surfactants. Bearing in mind that traditional African cuisines utilize palm bunch ash and trona (generally recognized as safe ingredients) as emulsifying and tenderizing agents, this study sought to investigate the possibility of improving the aqueous solubility and dissolution profile of furosemide (low solubility and low permeability drug) using excipient composite modified with them, in a process that had not been undertaken before.

MATERIAL AND METHODS

Chemicals

Crude cashew gum (dried exudates) from the stem bark of *Anacardium occidentale* Linn (family, Anarcardiaceae) was supplied by Mr Muazu, the plant collector in National Institute for Pharmaceutical Research and Development (NIPRD), Idu, Abuja; corn starch BP (Sigma-Aldrich, Germany); palm bunch (Fig. 2A) was collected from a local palm oil industry in Azigbo, Anambra state, Nigeria;trona (Fig. 2B) was purchased from Eke Awka Market in Anambra State; furosemide powder was a gift from Pauco Pharmaceutical Industry, Awka; 96% ethanol, Conc. HCl (JHD Chemicals, China), distilled water and other reagents were of analytical grade.

Preparation of palm bunch ash

The palm bunch was cut into small pieces using a cutlass, sun dried for one week and then incinerated inside a stainless steel bowl in the open. The resulting ash was collected and further processed to generate potash.

Purification of palm bunch ash potash and trona

One hundred grams (100 g) of palm bunch ash or trona powder was separately dispersed in about 200 mL of distilled water, stirred, made up to 500 mL with distilled water, shaken intermittently for 1 h and the filtered using Whatman number 1 filter paper. Each filtrate was centrifuged (80-3 Techmeland Techmel, Texas, USA) at 2000x g for 10 min and the supernatant carefully decanted into a stainless tray and dried in a hot air oven (Jiangsu, model DHG-9053A, China) at 60°C to a constant weight. The resulting powders were packed in air tight glass containers over silica gel.

Extraction and purification of cashew gum

This was conducted using a modification of method reported by Okoye et al (2012). Briefly, the dried exudates were handpicked, milled with a blender (Panasonic MX 337N, Japan) and sieved through aperture size of 150 µm. One hundred grams (100 g) of the resulting powder was then dispersed in 500 mL of distilled water at room temperature (32°C), stirred intermittently for 24 h. At the end of the 24 h, the dispersion was strained through a muslin bag and the resulting mucilage was precipitated by mixing it with thrice its volume of 96% ethanol. The precipitated gum was filtered using a filter cloth and air dried. Further purification of the gum was carried out by dissolving it in fresh dis-

tilled water to yield 1.0% w/v solution. This solution was filtered using a 100% cotton cloth overlaid with 0.05 m thick surgical cotton wool (Maimed GmbH, Germany) and the resulting filtrate mixed with thrice its volume of 96% ethanol to precipitate the gum. The precipitated gum was harvested and soaked in 96% ethanol for 18 h and finally air dried. In order to kill peroxidase enzymes present in the gum, it was further heated in a hot- air oven (Unitemp LTE Scientific Ltd Great Britain, Greenfield Oldham OL37EN) at 65°C for 1 h, at the end of which it was pulverized and stored in air tight containers over silica gel.

Modification of cashew gum and cashew gum-corn starch composite with PBP and trona

Cashew gum was mixed with each of the modifying agents at two ratios: 5:1 and 10:1 (i.e. cashew gum: modifying agent). Each powder mix was wetted with about 15% its weight of distilled water and kneaded using mortar and pestle. A control batch, which was not mixed with any of the modifying agents were similarly treated with distilled water and wet-massed using mortar and pestle. The different wet masses were packed in amber coloured glass bottles and stored at 35 ± 2°C for 72 h.

The cashew gum-corn starch composite was formulated by mixing the two excipients in a mortar using spatula at the ratios of 1:1, 2:1 and 1:2 (cashew gum: corn starch). Thereafter, the composites were mixed with each of the modifying agents at 5:1 and 10:1 (composite:modifying agent) (Table 1). Each powder mix was wetted with about 15% its weight of distilled water and kneaded using mortar and pestle. Three control batches for composite mixtures were made with no modifying agent added. They were similarly treated with distilled water and wet-massed using mortar and pestle. The different wet masses were packed in amber colored glass bottles and stored at 35 ± 2°C for 72 h. At the end of 72 h, the batches were dried in the oven at 60°C for 6 h and then screened through sieve of aperture size 600 µm and packed in glass bottles over silica gel.

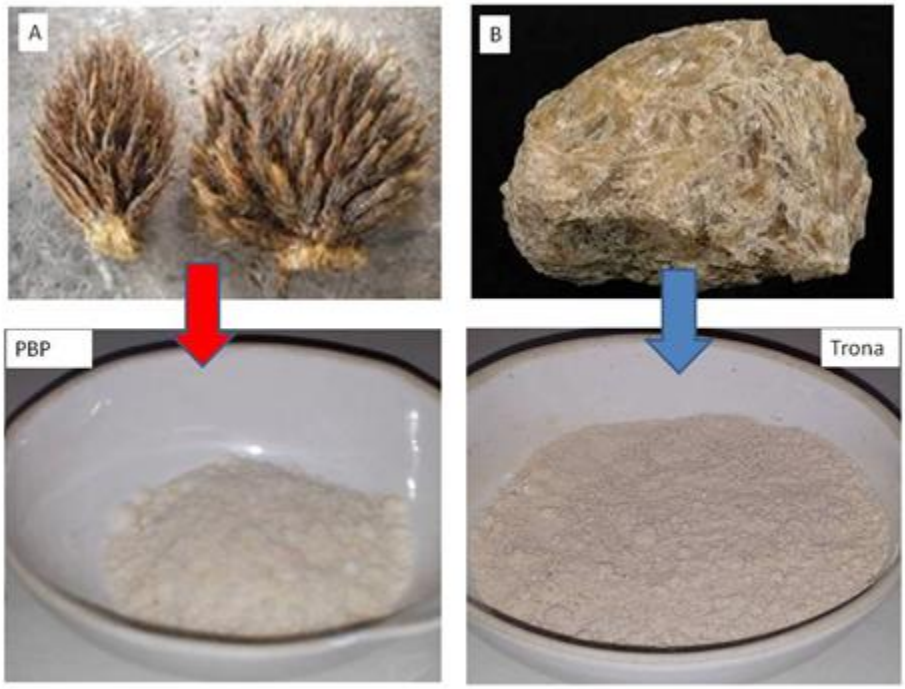

Figure 2. Palm bunch (A), unrefined trona (B), palm bunch potash (PBP) and refined trona (Trona).

Table 1. Excipients and furosemide combinations.

Primary excipient composite	Ratio	Code
Cashew gum: Corn starch	1:0	CG
Cashew gum: Corn starch	1:1	EC1:1
Cashew gum: Corn starch	2:1	EC2:1
Cashew gum: Corn starch	1:2	EC1:2
Modified excipient composite		
CG:PBP	5:1	CG-P5:1
CG:PBP	10:1	CG-P10:1
CG:Trona	5:1	CG-T5:1
CG-Trona	10:1	CG-T10:1
(EC1:1):PBP	5:1	EC1:1-P
(EC1:1):Trona	5:1	EC1:1-T
(EC2:1):PBP	5:1	EC2:1-P
(EC2:1):Trona	5:1	EC2:1-T
(EC1:2):PBP	5:1	EC1:2-P
(EC1:2):Trona	5:1	EC1:2-T
Furosemide: excipient combination		
Furosemide:excipient	1:0	Fur
Furosemide:CG	1:1	CG
Furosemide:CG-P5:1	1:1	CG-P5:1
Furosemide:CG-P10:1	1:1	CG-P10:1
Furosemide:CG-T5:1	1:1	CG-T5:1
Furosemide:CG-T10:1	1:1	CG-T10:1
Furosemide:EC1:1-P	1:1	EC1:1-P
Furosemide:EC1:1-T	1:1	EC1:1-T
Furosemide:EC2:1-P	1:1	EC2:1-P
Furosemide:EC2:1-T	1:1	EC2:1-T
Furosemide:EC1:2-P	1:1	EC1:2-P
Furosemide:EC1:2-T	1:1	EC1:2-T
Furosemide:EC1:1	1:1	EC1:1
Furosemide:EC2:1	1:1	EC2:1
Furosemide:EC1:2	1:1	EC1:2
Furosemide:PBP	1:1	Fur + PBP
Furosemide:Trona	1:1	Fur + Trona

Granulation of furosemide using the modified excipients and their controls

Each excipient was mixed with furosemide at 1:1 ratio (2 g of each) (Table 1), moistened with 1 mL of distilled water and kneaded to form a homogeneous wet mass. The wet mass was screened through the 600 µm sieve and granules dried at 60°C for 1 h. The generated granules were rescreened through 600 µm sieve, dried again at 60°C for 1 h and finally packed in glass bottles over silica gel. Furosemide powder was similarly treated with PBP and trona separately; and also without any excipient.

Fourier transform infrared (FTIR) spectroscopy of furosemide powder and granules

This was conducted using the apparatus FTIR-8400S spectrometer (Shimadzu, Japan). Two milligrams (2 mg) of each sample and 200 mg KBr were weighed using the analytical balance (Mettler Toledo AB54, Switzerland) and powdered with an agate mortar and pestle, and compressed into a pellet using the pellet press. The resulting tablet was mounted on the sample holder and the system was purged with nitrogen gas. Scanning was conducted in the range of 400 to 4000 cm^{-1} with a resolution of 1 cm^{-1}. Duplicate measurements were made and the spectrum with the clearer peaks was chosen.

Differential scanning calorimetry (DSC) of furosemide powder and granules

DSC characterization of each powder sample was conducted using the apparatus Netzsch DSC 204 F1 Phoenix (Nietzsche Germany). Four milligrams (4 mg) of each sample was carefully weighed using the analytical balance (Mettler Toledo AB54, Switzerland) and sealed in aluminium pan. Calibration of the calorimeter was done with indium and the purge gas was nitrogen. Heating of the sample was carried out at 10°C/min from 30°C to 400°Cunder nitrogen flow rate of 20 mL/min and cooling back to 30°C was at the same rate.

Encapsulation of furosemide granules

From each batch, an amount of granules equivalent to 20 mg of furosemide was weighed using the analytical weighing balance (Mettler Toledo AB54, Switzerland) and carefully transferred into a capsule shell (size 4). Furosemide powder was similarly treated. Twenty capsules were made for each batch of granules and furosemide powder.

Calibration curve (Beer - Lamberts plot) for furosemide

One hundred milligrams (100 mg) of furosemide was weighed, dissolved in 10 mL of methanol and the solution was diluted to 100 mL with a 1:1 methanol: water mixture in order to generate the stock solution. A serial dilution of the stock solution was made to obtain different concentrations (5, 10, 20, 30, 40, 50, 60 and 70 µg/mL) of furosemide using the methanol-water mixture. The absorbance of each concentration was determined at 273 nm using the methanol-water mixture as blank in a UV-Visible spectrophotometer (Yuefeng™ UV/visible spectrophotometer model 752, China). Triplicate determinations were made for each batch. The values obtained were subjected to regression analysis, which generated the calibration curve equation: $y = 0.056x + 0.108$; $r^2 = 0.9975$.

Solubility test on powder and granules of furosemide

An amount of furosemide granules equivalent to 20 mg furosemide was weighed using the analytical weighing balance and dispersed in 10 mL of distilled water contained in an amber bottle. The mixture was intermittently shaken at room temperature (35 ± 2°C) for 24 h. Thereafter, the mixture was filtered using Whatman number 1 filter paper, the resulting filtrate was diluted with distilled water and its absorbance was determined in the UV-Visible spectrophotometer at 273 nm using distilled water as blank. Triplicate determinations were made for each batch of granules and the amount of drug dissolved was evaluated using the calibration curve equation. Furosemide powder was similarly treated.

Dissolution test

Dissolution test was carried out on the capsules using the basket method (DBK Dissolution rate test apparatus England) rotated at 50rpm in 300mL of 0.1N HCl, maintained at 37 ± 0.5°C. Samples (5 mL)

were withdrawn and replaced with equal volume of fresh medium at five minutes interval over a period of 60 min. The absorbance of each withdrawn sample was determined using the UV-Visible spectrophotometer at 273 nm and 0.1 N HCl as blank. The amount of furosemide released was evaluated using the calibration curve equation and triplicate determinations were performed for each batch.

Statistical analysis

Graphing and regression analyses were performed with Graphpad Prism 5 (GraphPad Prism software Inc., 2012 San Diego, California, USA) while analysis of the results of various parameters tested was performed using one-way analysis of variance in Excel statistical package 2007. Significant differences were defined by $p<0.05$.

RESULTS

Organoleptic characteristics and yield of PBP and trona

The purified palm bunch potash realized was white in color, appeared crystalline (Fig. 2, PBP) and was sour/salty to taste. It was observed to be hygroscopic and hence needed good protection from moisture, which informed the choice of glass container for packaging it. Purified trona was light brown in color (Fig. 2, Trona) and sour to taste. It was less hygroscopic than purified palm bunch potash. The percentage yield of purified PBP was 9.38 ± 1.24% while that of trona was 24.18 ± 0.93%.

FTIR of furosemide powder and granules

The FTIR spectrum of furosemide is shown in Fig. 3A. It revealed peaks between 488 cm^{-1} and 1487 cm^{-1}, a region that belongs to the fingerprint section of the infrared spectrum. This region is mainly useful in authenticating samples of a compound whose spectrum is already established. This notwithstanding, the peaks between 729 cm^{-1} and 922 cm^{-1} may be due to aryl-chloro stretching vibration; while the ones at 1140 – 1248 cm^{-1} may be ascribed to amine C-N stretch. The peak at 1423 cm^{-1} may likely be due to methyl C-H asymmetric bend and that at 1574 cm^{-1} may be ascribed to asymmetric stretching vibration of carboxyl group, 1671 cm^{-1} to bending vibration of amino group or carbonyl C=O vibration and the weak peaks at 1822 cm^{-1} to 1937 cm^{-1} may be ascribed to a five membered ring furanyl group. The weak peaks between 2560 and 2630 cm^{-1}may be ascribed to C-H and HO-C=O stretching vibrations of carboxylic acid. The peak at 3284 cm^{-1} is likely due to the stretching vibration of sulfonylamino group (SO_2NH_2), while that at 3385 cm^{-1} may be ascribed to NH_2 stretching vibration of Ar-$NHCH_2$ (Patel et al., 2008). After the shoulder spectrum, the peaks between 3748 and 4012 cm^{-1} are characteristic of O-H stretching vibration from water or alcohol groups, which may be present as residual solvents (Coates, 2000). The spectra of the mixtures of furosemide and palm bunch potash (PBP) or trona are shown in Fig. 3A.From the spectra, it is obvious that the principal peaks were retained in both mixtures (furosemide + PBP/trona) except the peaks between 1423 and 1574 cm^{-1}, which did disappear. The spectra of the granules formulated with excipient/excipient composites modified with PBP or trona are shown in Fig. 3B (Fur + CG-PBP, Fur + CG-Trona, Fur + EC-PBP and Fur + EC-Trona). All the spectra are similar and retain the functional groups present in furosemide-potash and furosemide-trona.

DSC of furosemide and furosemide granules

The DSC thermograms of furosemide and its granules are shown in Fig.4. The thermogram of furosemide (Fur) showed the occurrence of desolvation, a relatively broad endothermic peak at 56°C. There was evidence of crystal disruption at about 220°C, followed immediately by an exothermic event: restructuring/recrystallization at 223°C, before eventually melting at 271 °C and finally decomposed at 348°C.The thermograms of granules of furosemide and PBP or trona are shown in Fig. 4 (Fur + PBP and Fur + Trona). The first endothermic event on both thermograms was desolvation, which was followed by broad melting peaks that might be from the agents, thus indicating that they are amorphous in nature. Fig. 4 (Fur, Fur + PBP and Fur + Trona) reveals that the visible components of furosemide thermogram, an exothermic event at about 240°C might be ascribed to recrystallization (which was broad and incomplete) and decomposition at 258°C (which is much less than 348°C for pure drug). The thermograms of furosemide gran-

ules formulated with PBP or trona modified excipient or excipient composites (Fig. 4, Fur + CG-PBP, Fur + CG-Trona, Fur + EC-PBP and Fur + EC-Trona) reveal that the granulation of furosemide powder with PBP or trona modified cashew gum or cashew gum-corn starch composite resulted to complete amorphization of the drug.

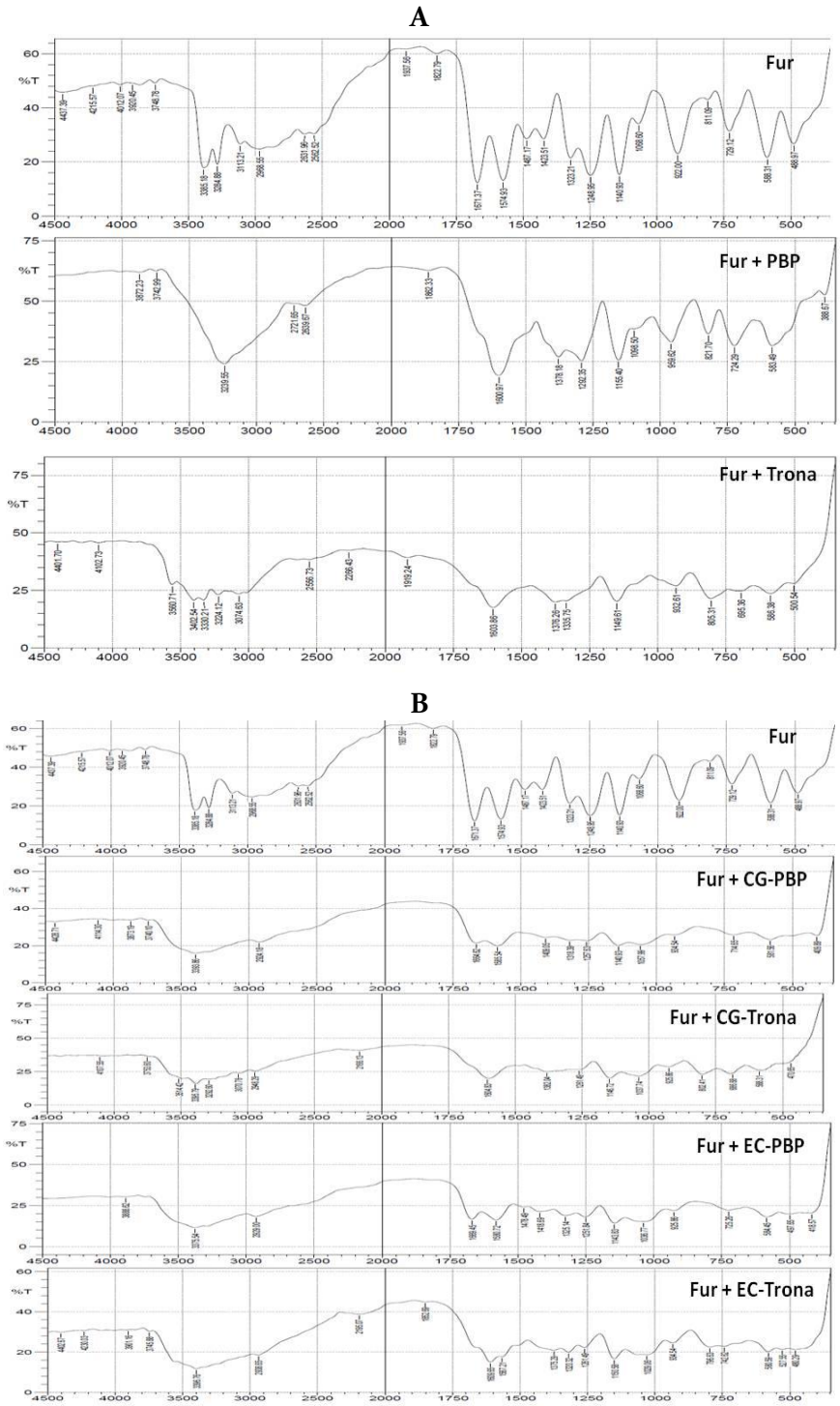

Figure 3. A. FTIR of furosemide (FUR), granules of furosemide and palm bunch potash (FUR+PBP), granules of furosemide and trona (FUR + Trona). **B.** FTIR of furosemide (FUR), granules of furosemide and cashew gum modified with: PBP (FUR + CG-PBP),

trona (FUR + CG-Trona), granules of furosemide and excipient composite modified with: PBP (FUR + EC-PBP), trona (FUR + EC-Trona).

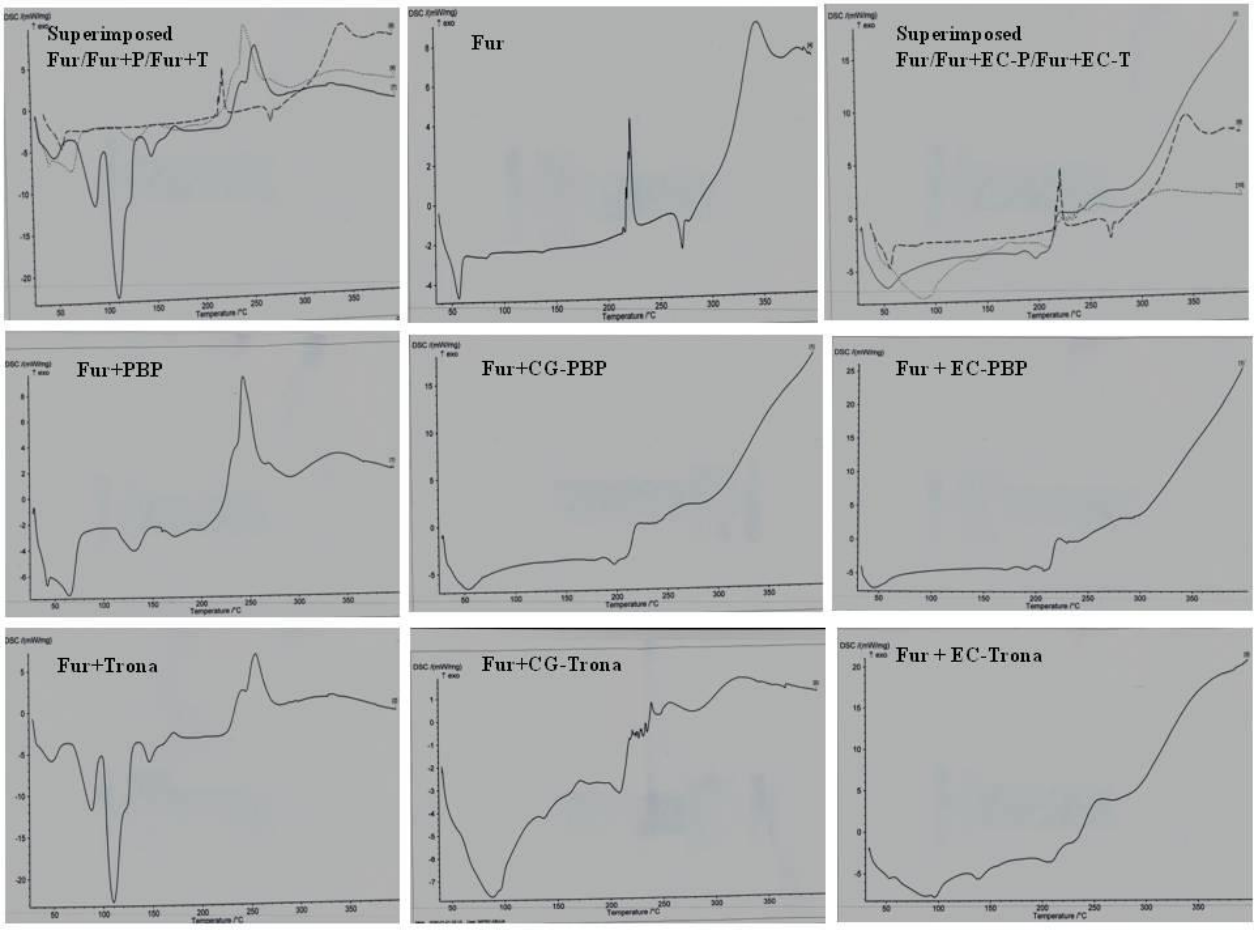

Figure 4. DSC thermograms of furosemide (FUR), granules of: furosemide+PBP (FUR + PBP), furosemide+trona (FUR + Trona), granules of furosemide and cashew gum modified with: PBP (FUR + CG-PBP), trona (FUR + CG-Trona), granules of furosemide and excipient composite modified with: PBP (FUR + EC-PBP), trona (FUR + EC-Trona), superimposed products thermograms.

Solubility profile of furosemide from drug powder and granules

The results of solubility studies are shown in Fig. 5. About 10% of drug dissolved from pure furosemide powder, implying an approximate solubility of 0.20 mg/mL. Upon granulation with cashew gum alone, the amount of furosemide dissolved from the granules was about 7%, which translates to solubility of 0.14 mg/mL. Furthermore, mixing of PBP or trona and cashew gum at 5:1 (cashew gum:PBP or trona) ratio significantly ($p<0.05$) improved solubility of furosemide in comparison to 10:1 ratio (1.32 mg/mL and 0.86 mg/mL), i.e. approximately 66 and 43% respectively (Fig. 5A). In addition, cashew gum-trona (CG-Trona) was a significantly ($p<0.05$) better enhancer of furosemide solubility than cashew gum-PBP (CG-PBP) mixture. The lower solubility of furosemide from granules formulated with cashew gum only (CG) (Fig. 5A) was not significant in comparison to pure drug, however deserves to be mentioned. The addition of corn starch to form the excipient composite led to further reduction of furosemide solubility (Fig. 5B), with higher proportion of starch resulting to lower amount of dissolved drug (see EC 1:1, EC 2:1 and EC 1:2) (Fig. 5B).

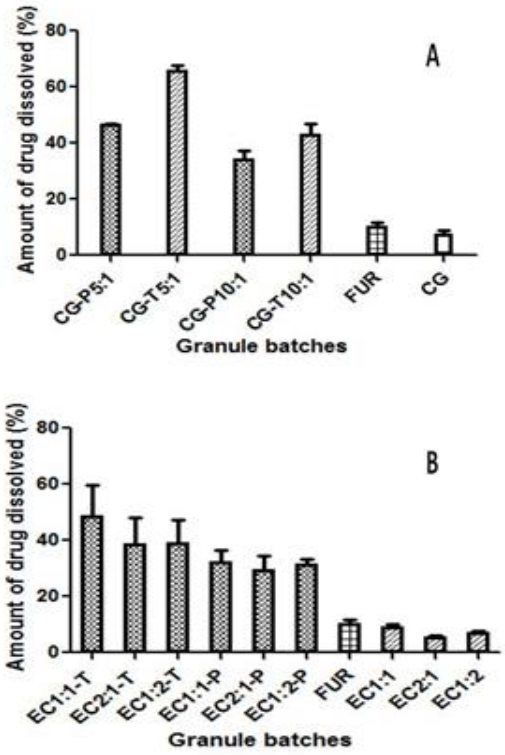

Figure 5. A-Solubilities of furosemide (FUR), granules of furosemide and:cashew gum (CG), cashew gum:PBPat 5:1 and 10:1 (CG-P 5:1; CG-P 10:1), cashew gum:trona at 5:1 and 10:1 (CG-T 5:1; CG-T 10:1). **B**- Solubilities of granules of furosemide and cashew gum:corn starch- 1:1, 2:1, 1:2 modified with: PBP (EC1:1-P, EC2:1-P, EC1:2-P), trona (EC1:1-T, EC2:1-T, EC1:2-T), unmodified (EC1:1, EC2:1, EC1:2). Data are expressed as percentage drug dissolved (mean±SD) n=3. Significant differences ($p<0.05$) were found in amounts dissolve (One way ANOVA and *post hoc* t-test).

Dissolution profile

The dissolution profiles of pure furosemide powder and furosemide granules from capsule dosage form are depicted in Fig. 6. Maximum amount of drug released in 60 min from pure furosemide powder was approximately 1.4%. On the other hand, excipients modified with potash or trona significantly ($p< 0.05$) improved the dissolution profile of furosemide (Fig. 6 A, B, D). It is obvious from Fig.6D that the presence of unmodified cashew gum reduced the amount of furosemide released by about 50%. Improvement in dissolution profile of furosemide by excipients modified with potash or trona can be ranked in the order: CG-Trona> CG-PBP> EC-Trona> EC-PBP.

DISCUSSION

The organoleptic properties of PBP and trona point to the fact that they are alkaline, for example the sour/salty tests. The low yield of PBP was not unexpected bearing in mind that major component of the material was ash from which the PBP was extracted. No previous report on the extraction and purification of the material is available, so the current result could not be compared.

Disappearance of some functional groups in furosemide upon treatment with excipients modified with PBP or trona may be accounted for by the likely interaction between the $-OH^-$ group of the potash or $-HCO_3^-$ of trona and the –COOH of furosemide to form potassium and sodium salts respectively of the drug. The formation of the salt depleted the electron density at the C=C bond of the benzene ring and shifted the electrons to the metallic species (K^+ and Na^+) participating in the bonding activities. The formation of –COOK or –COONa salt actually cannot be interpreted as destructive chemical interaction because upon introduction into water, the salt will dissolve to release the anionic specie of the drug, which will then be absorbed. All spectra of granules of furosemide and excipients are similar and retain the functional groups present in furosemide-potash and furosemide-trona.

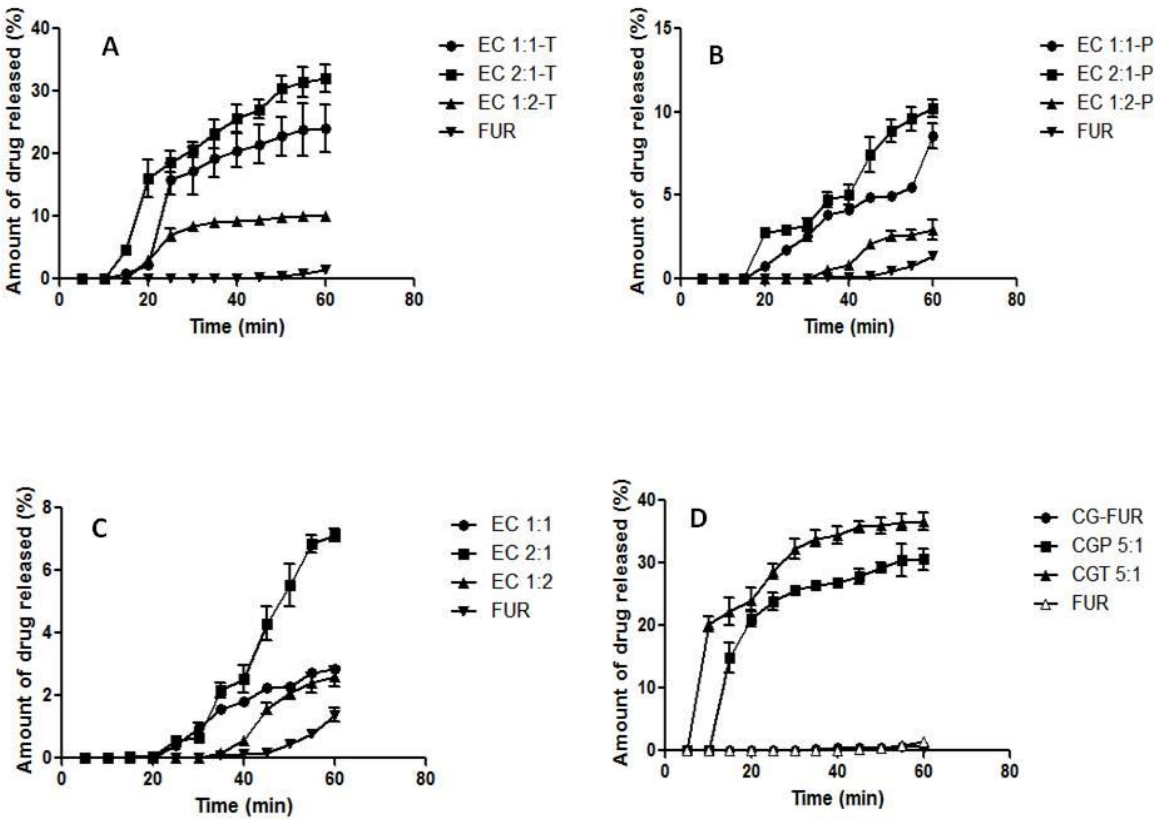

Figure 6. Dissolution profiles- **A.** Furosemide (FUR), granules of furosemide and excipient composite modified with trona (EC1:1-T, EC2:1-T, EC1:2-T). **B.** Furosemide (FUR), granules of furosemide and excipient composite modified with PBP (EC1:1-P, EC2:1-P, EC1:2-P). **C.** Furosemide (FUR), granules of furosemide and unmodified excipient composite (EC1:1, EC2:1, EC1:2). **D.** Furosemide (FUR), granules of furosemide and cashew gum (CG-FUR), granules of furosemide and cashew gum modified with PBP (CGP 5:1), granules of furosemide and cashew gum modified with trona (CGT5:1). Data are expressed as percentage drug released (mean ± SD) n=3. Significant differences ($p<0.05$) were found in amounts released (One way ANOVA and *post hoc* t-test).

The implication is that the presence of cashew gum or cashew-corn starch composite did not lead to any other chemical interaction between the drug and the excipients. This however may not rule out the occurrence of physical interaction between the excipients and the drug, a possibility that was explored using differential scanning calorimetry.

In the DSC, the endothermic event at 56°C may be ascribed to evaporation of adsorbed moisture from the particles of the drug, while the exothermic event: restructuring/recrystallization at 223°C may be linked to the mesomorphic structure of furosemide whereby it tried to reorganize to a more stable phase before eventually melting at 271°C and finally decomposed at 348°C. Fig. 4 (Fur, Fur + PBP and Fur + Trona) reveals that the visible components of furosemide thermogram, an exothermic event at about 240°C might be ascribed to recrystallization (which was broad and incomplete) and decomposition at 258°C (which is much less than 348°C for pure drug). These events suggest that both PBP and trona individually disrupted the crystal structure of furosemide and prevented complete recrystallization from taking place. This otherwise minor physical change may influence the solubility and dissolution characteristics of the drug eventually. The thermograms of furosemide granules formulated with PBP or trona modified excipient or excip-

ient composites (Fig.4, Fur + CG-PBP, Fur + CG-Trona, Fur + EC-PBP and Fur + EC-Trona) reveal that the granulation of furosemide powder with PBP or trona modified cashew gum or cashew gum-corn starch composite resulted to complete amorphization of the drug. The observed events in the thermograms cannot be interpreted as incorporation of the drug into the matrices of the excipients or formation of inclusion complexes because the excipient:drugration was maintained at 1:1 all through; and none of the excipients exhibits the attributes of forming inclusion complexes. This complete amorphization of the drug is expected to really improve the solubility and dissolution profile of the drug (Kulkarni and Nagarsenker, 2008; Liua et al., 2010; Jensen et al., 2014; Penkina et al., 2015).

The results of solubility studies are shown in Fig. 5. Cashew gum reduced the solubility of furosemide, however the introduction of potash or trona significantly ($p< 0.05$) improved the solubility of furosemide. Furthermore, mixing of potash or trona and cashew gum at 5:1 (cashew gum:potash or trona) ratio significantly ($p< 0.05$) improved solubility of furosemide in comparison to 10:1 ratio. In addition, cashew gum-trona (CG-T) was a significantly ($p<0.05$) better enhancer of furosemide solubility than cashew gum-potash (CG-P) mixture. The lower solubility of furosemide from granules formulated with cashew gum only (CG) (Fig. 5A) was not significant in comparison to pure drug, but deserves to be mentioned. Solubility reduction in this instance may be attributed to the ability of cashew gum to bind furosemide particles to form granules, which must disintegrate before the drug particles dissolve. Cashew gum is a water-soluble gum and reduces surface tension of water as it dissolves hence it has been reported to be a good emulsifying agent (Olorunsola et al., 2014). It was therefore expected to improve the solubility of furosemide, but in the contrary furosemide's solubility was reduced by it. The explanation of this observation is not empirically evident in the present study, but previous report on similar observation with metronidazole suggested that it might be because of physical interaction between the molecules of the drug and cashew gum to form a complex with higher bonding strength (Okoye, 2014). The increase in solubility on incorporation of PBP or trona may be linked to the ability of the agents to form salts with the drug or disrupt the formation of the complex between drug molecules and cashew gum. The latter is evident from the DSC thermograms of drug and modified cashew gum (Fur + CG-PBP; Fur + CG-Trona, Fig. 4). The addition of corn starch to form the excipient composite led to further reduction of furosemide solubility (Fig. 5B), with higher proportion of starch resulting to lower amount of dissolved drug (see EC 1:1, EC 2:1 and EC 1:2) (Fig. 5B). This observation may not be unconnected with the ability of starch to form more swellable granules in the presence of gums (Mandala and Bayas, 2004; Zámostný et al., 2012). The swollen granules thus reduced the exit of dissolved drug molecules from granules interior to surrounding fluid, thereby reducing solubility. In addition, the presence of starch increased viscosity of dispersion medium thereby decreasing the available free solvent molecules that otherwise would have interacted with drug molecules and probably increase solubility. Modification of excipient composites with PBP or trona gave rise to improvement in solubility of furosemide from granules. Some of the processes that might have contributed to this may include: formation of salt form of drug on interaction with potash or trona; disruption of the crystal lattice of drug/drug-excipient composite complex; decrease in viscosity of dispersion medium and further decrease of surface tension between the dispersion medium and granules/drug particles.

Dissolution profiles show that the maximum amount of drug released in 60 min from pure furosemide powder was approximately 1.4%. On the other hand, excipients modified with potash or trona significantly ($p< 0.05$) improved the dissolution profile of furosemide (Fig.6 A, B, D). It is obvious from Fig. 6D that the presence of unmodified cashew gum reduced the amount of furosemide released by about 50%. The mechanism for this may still be tied to that afore discussed in solubility section. The important role of PBP or trona in enhancing dissolution of furosemide is better appreciated in their absence as depicted in Fig. 6C. In the absence of potash or trona, excipient composites improved drug release by just 7% maximum in comparison to about 36% when modified with trona. Improvement in drug release from unmodified composites against unmodified cashew gum may be linked to the abil-

ity of starch to reduce surface tension (Prochaska et al., 2007) and prevent cashew gum-furosemide physical interaction to form a less soluble complex from taking place. Having done this, the combined ability of starch and cashew gum to reduce surface tension enhanced drug release from granules. It is pertinent to note that the volume of dissolution fluid used was 30 times the volume of fluid used in solubility experiment, and this explains the seeming contrast between the solubility results of granules formulated with unmodified excipients and their dissolution profiles. In larger volume of dispersion medium, the granules are surrounded by greater number of solvent molecules and such interaction will lead to improved solubility and drug release from granules. This is also evident from modified Noyes-Whitney's expression, which reveals that larger volume of dissolution medium enhances the rate of drug release from solid particles (Fischbach, 1995; Aulton, 2013).

CONCLUSIONS

This study has revealed that fine potash could be extracted from palm bunch ash at approximately 10% w/w yield. Both PBP and trona successfully modified cashew gum-corn starch composite and furosemide. Modification of furosemide was achieved probably by salt formation between the drug and PBP or trona. In the presence of the modified excipients, complete amorphization of the drug was achieved and this impacted positively on the solubility and dissolution profiles of furosemide, which were improved by approximately 65% and 35% respectively. This finding gives insight into the possible use of herbal sourced raw materials as adjuncts in improving physicochemical and pharmaceutical properties of BCS class IV drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Concepts or Ideas	X		
Design	X		
Definition of intellectual content	X		
Literature search		X	X
Experimental studies		X	X
Data acquisition		X	X
Data analysis	X		
Statistical analysis	X		
Manuscript preparation	X	X	
Manuscript editing	X		
Manuscript review	X		

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