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Preliminary Studies on Binding Potentials of Defatted Cake Derived From *Blighia Sapida* Seeds in Ascorbic Acid Tablets

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The physicochemical properties and binding potentials of defatted cake derived from *Blighia sapida* seeds (BSSC) were studied and compared with maize starch BP in ascorbic acid formulations. Milled seeds of *Blighia sapida* was macerated with n-hexane for 5 days to separate the oil, the resultant defatted cake was further extracted with a mixture of ethanol and water (4:10). The physicochemical properties of the BSSC were determined using standard procedures. Compatibility of BSSC powder with ascorbic acid was evaluated using Fourier Trans Infra-Red (FTIR) and Differential Scanning Calorimetry (DSC) techniques. Ascorbic acid tablets were formulated using varying concentrations of the BSSC as a binder at the same compression settings. The physical properties of formulated tablets were studied. BSSC had pH of 5.58 and a moisture content of 6.68 %. Its bulk and tapped density were 0.35 ± 0.3 g/mL and 0.45 ± 0.4 g/mL; the powder had fair flow with angle of repose 40 ± 1.5^0 and Hausner's ratio of 1.29. FITR technique showed that BSSC was compatible with ascorbic acid, however, the DSC thermogram showed that there was a well-defined interaction of the ascorbic acid and BSSC which were evidenced by the shift of the endothermic melting peak. The ascorbic acid tablets formulated using BSSC as binder had low friability; hard tablets with consistent disintegration rates and also similar binding properties to 2 %w/w maize starch BP were obtained. BSSC has similar binding properties compared to maize starch BP and can be a potential source of a low-cost binder.

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Introduction

The search for under-utilized, novel, and Renewable materials as sources of low cost excipients for the pharmaceutical industry has been a major focus for research in recent years [1, 2]. Development of excipients from natural sources such as fruits, seeds, agricultural wastes can help in the discovery of excipients with outstanding physicochemical and functional properties. A practical understanding of pharmaceutical excipients is essential to developing optimal, robust formulations and appropriate manufacturing processes [3]. Excipients influence drug delivery through increased or decreased solubility, modified dissolution rates, absorption enhancement, among others and ultimately leading to improved therapeutic activity [4]. Polymers offer a broad range of properties that can be reasonably well "built-in" by design and modified by altering polymer characteristics [5]. Studies have shown that exploring local sources for low-cost substitutes for the imported excipients which are mainly polymer-based will provide an alternative approach to reducing the import dependence of the pharmaceutical industry by developing countries [6, 7]. Other advantages of natural plant-based excipients include environmental friendliness, fairly free from side effects, bio-acceptability with renewable sources, local availability as well as better patient tolerance. Apart from being less expensive and freely available, they serve as basis for derivation of semi synthetic and synthetic excipients with desirable properties [8].

Different products derived from plants sources have numerous applications in dosage form preparations. They can be used as binders, disintegrants, diluents, vehicles, lubricants among others in formulation of different dosage forms [9]. They can be tailored for many applications based on the very large chains and functional groups which can be blended with other low- and high–molecular weight materials to achieve new materials with desirable physicochemical properties [10]. Good binders are assessed by their compressibility under pressure, have high plasticity, low elasticity and small particle size [11]. Starch is the most commonly used binder in the manufacture of tablets. Commercial starches are obtained from cereals (maize), tubers (yam) and roots (potato and cassava) and they dominate the world markets for starches in the food and pharmaceutical industries. These sources of commercial starches also serve as sources of food. The economic crisis in developing countries as well as food shortage call for utilisation of non-food based and low-cost sources for binder production.

Blighia sapida popularly known as ackee is a fruit tree which originates from the Guinean forests of West Africa [12]. It is noted particularly for its food, medicinal and aesthetic values [13]. The ripe and open fruit arils are consumed as fruits or roasted/fried to make a variety of meals, a good example being ackee and salt fish. The black shiny seeds revealed after ripening are usually thrown away in most places. Omobuwajo *et al*[14] had determined the physical properties of the seeds. It had been reported that the seed oil of *Blighia sapida* could be employed as a low-cost tablet lubricant [15]. A study showed that the defatted cake of *Blighia sapida* seed contains mainly starch 44.2 %w/w, proteins 22.4 %w/w and fibers 15.6 %w/w [16]. Detailed composition of *Blighia sapida* (Sapindaceae) defatted cake from Benin has been reported in a previous study [16].

Blighia sapida seeds are practically thrown away most times after consumption of the fruit aril and at present have no economic value. Efficient utilization of the seeds of *Blighia sapida* as pharmaceutical excipient would require adequate information on its characteristics, functional, physicochemical and thermal properties. To the best of our knowledge, despite the work done on the chemical composition of *Blighia sapida* defatted cake, there is no report available on the use of BSSC as an excipient.

Materials and Methods

Materials

The dried seeds of *Blighia sapida* were obtained in August, 2015 from Ogbomosho, Osun state, Nigeria. The dried seeds were identified and

authenticated at the herbarium of the Department of Botany, University of Lagos, Nigeria and voucher specimen (LUH 6709) was deposited in the same herbarium for future reference. The seeds were stored at 25 ± 2°C.
Ascorbic acid powder, maize starch BP, sodium starch glycolate, talc were gifts from Ecomed Pharma Ltd, Nigeria. All the chemicals and solvents used were of analytical grade and were manufactured by BDH Poole England.

Methods

Processing of the ackee seeds

The seed bran was removed manually by peeling with knives to expose the endosperm. The seed was milled to powder using a 6N80-9FC21A rice mill/powder crusher/maize thresher. Two kilograms (2 kg) of the resulting powder was weighed out and macerated using n-hexane for 5 days. The oil was separated while the defatted cake was further extracted with 40 % ethanol in water for another 6 days to remove the water soluble protein hypoglycin A and B toxic components. The resulting cake was oven dried at 60°C and pulverized after drying and was passed through a 365 µm sieve. It was then stored for further use in a well-sealed air tight container at 25 ± 2°C.

Organoleptic and physiochemical properties of BSSC

Organoleptic properties

The following macroscopic and organoleptic properties of the BSSC were evaluated; appearance, colour, odour and flavour.

Solubility and pH determination

BSSC solubility in water was tested by dissolving 2 g of the sample in 100 mL of water and pH was determined using a Metler Toledo easy pH metre (Metler Toledo seven easy pH Meter, Schwerzenbach, Switzerland). After switching on the metre, the equipment was calibrated with a buffer solution, then the electrode was inserted inside the sample and the reading observed and documented (all experiments were carried out in triplicates)

Moisture content

The moisture content of the BSSC was carried out using a halogen moisture analyser (Metler Toledo HR83 Halogen moisture analyser, Greifenesee, Switzerland). The sample (2 g) was placed in the pan after tarring the equipment and the process of drying commenced when the start button was pressed; the moisture content was displayed once the material was completely dried.

Bulk and tapped densities

For determination of the bulk and tapped densities, the methods employed in a previous study [17] were adopted. The bulk density, D_{bulk}, and tapped density, D_{tap}, were determined using Eq. 1 and 2 respectively.

$$D_{bulk} = w/v_0 \quad (1)$$

$$D_{tap} = w/v_1 \quad (2)$$

Where *w,* is the weight of the powder, and v_0 and v_1 are the volumes of the bulk and tapped powders, respectively. The arithmetic mean of three replicate determinations was taken in each case.
e. *Hausner's ratio and Carr's compressibility index*
Carr's index [18] and Hausner ratio [19] for the BSSC were calculated from bulk and tapped densities using Eq. 3 and 4, respectively.

$$Carr's\ Index = \frac{D_{tap} - D_{bulk}}{D_{tap}} \times 100 \quad (3)$$

$$\text{Hausner Ratio} = \frac{D_{tap}}{D_{bulk}} \quad (4)$$

Angle of repose

This measurement was carried out using a fixed funnel apparatus (a manual powder flow tester

manufactured by electrolab mode EFT-01). The orifice was closed by pushing in the slider. The powder (130 g) was weighed out and poured into the cone. The orifice was opened by pressing the slider knob to allow the powder flow through to form a cone. The height, *h*, and radius, *r*, of the conical heap formed were measured, and then the angle of repose,θ, was calculated from Eq. 5. Determinations were done in triplicate, and the average was taken.

$$\theta = \tan^{-1}(h/r) \quad (5)$$

Average diameter and particle size distribution

Particle size analysis was determined using a sieve shaker, containing test sieves ranging from 75 to 250 µm aperture size arranged in a descending order. Twenty grams (20 g) of the powder was placed on the top sieve (250 µm) and the set-up shaken at amplitude 70 (revolutions) for 5 minutes. The weight of material retained on each sieve was determined. The average diameter was computed using Eq. 6.

$$\text{Average diameter} = [\Sigma\ (\%\ \text{retained}) \times (\text{mean aperture})]/100 \quad (6)$$

Compatibility studies

Compatibility of BSSC powder with ascorbic acid powder was evaluated using Fourier Trans Infra-Red (FTIR) spectrometer (Bruker, South Africa) and Differential Scanning Calorimeter (DSC) (Mettler Toledo, UK).For FTIR spectroscopy, approximately 5 mg BSSC powder and ascorbic acid powder were individually blended with solid KBr (≈ 50 mg) and compressed into discs. Also physical mixtures (1:1) of BSSC powder and ascorbic acid powder (≈ 5 mg) were blended with solid KBr (≈ 50 mg) and compressed into disc for compatibility study. The spectra were scanned from 500-4000 cm^{-1} in FTIR spectrometer under dry air at room temperature.

For DSC compatibility study, approximately 6 mg of the BSSC powder was weighed and placed in an aluminium pan. The pan was hermetically sealed and equilibrated at room temperature for 1 h, then heated at the rate of 10 °C/min from 30 - 300 °C with an empty sealed pan as reference. The same procedure was repeated for ascorbic acid powder and physical mixtures (1:1) of BSSC powder and ascorbic acid powder respectively.

Formulation of ascorbic acid granules and tablets

Five batches of granules (Table 1) containing ascorbic acid powder as the active ingredient were prepared using wet granulation method as described in an earlier study [17]; batch B1 which is the reference standard containing 2 %w/w starch as binder while batches B2 to B5 containing 2, 4, 5 and 8 %w/w of BSSC respectively as the test binder. The wet mass was dried in a tray drier at 60°C for one hour in an oven (RDTD-48, RidhiPharma, India) and then sieved through an American Standard Sieve No 16. The resulting granules were further dried for about 12 hours. The bulk and tap densities of the ascorbic acid granules were assessed using the same methods described for the defatted cake powder.

Table 1. Composition of Ascorbic acid granules and tablet formulations.

Batch	Ascorbic acid (%)	Maize starch paste (%)	BSSC paste (%)	Magnesium Stearate (%)	Sodium starch glycolate (%)	Talcum (%)	Maize starch to (%)
B1	5	2	0	2	4	4	100
B2	5	0	2	2	4	4	100
B3	5	0	4	2	4	4	100
B4	5	0	5	2	4	4	100
B5	5	0	8	2	4	4	100

For the formulation of the ascorbic acid tablets, 4 %w/w sodium starch glycolate (extra granular disintegrant) and 4 %w/w talcum (glidant) were added and mixed with the granules for 5 minutes before mixing with 2 %w/w magnesium stearate (lubricant) for 2 minutes. The different batches (Table 1) of the ascorbic granules were compacted using a Cadmach rotary press (Double rotary press, Cadmach Ahmebad-B India), punch size 9.5 mm, and weight 350 mg per tablet (batch size 1000 tablets) at the same compression settings.

Evaluation of ascorbic acid tablets

Uniformity of weight, hardness test, tablet thickness and disintegration test were carried out using procedures detailed in an earlier study[20]. The dissolution test was carried using the method described in the USP[21]. Dissolution tester (USP TDT 08L Dissolution tester, Electrolab, Mumbai, India) the paddle type was used. The dissolution medium used was 900 mL of distilled water at 50 rpm spindle speed.

Statistical analysis

The data obtained from the study was analyzed using OriginPro 2016 (64-bit) software (OriginLab Corporation Northampton, MA 01060 USA). Mean comparison with the standard was evaluated using one-way analysis of variance (ANOVA) at 95 % confidence level ($p < 0.05$). Significant differences of mean values were determined by Tukey test.

Results and Discussions

Organoleptic properties

The organoleptic properties of the defatted cake of BSSC revealed that the powder was light brown in colour with a characteristic pleasant smell and a desirable flavour.Excellent organoleptic properties are important in materials to be used as excipients in the pharmaceutical industry so as to ensure good appeal to the patient and to encourage compliance.

Physicochemical properties of the defatted cake of BSSC

The results of physicochemical properties of the defatted cake of BSSC are presented in Tables 2 and 3. The BSSC was insoluble in water but formed a thick paste with hot water; this can be attributed to its high starch content [16].

The pH of BSSC was 5.58; this is slightly acidic but it is within with the specified pH range for commercial maize starch. The British Pharmacopoeia recommends a pH range of 4.0 - 7.0 for starch [22].

Moisture content obtained was 6.68 %, the upper limit of residual moisture content for starch in BP is 15 %. High moisture content (> 15 %) could have adverse effects on starch quality as it promotes the growth ofmold and results in reduced shelf life. It may also affect starch quantity and market value as a result of high losses on drying. Optimal levels of moisture in starch and similar compounds (5 - 10 %) have been shown to be essential in producing compacts with high tensile strength and low friability [23].

The data from micromeritics properties (Table 2) of BSSC indicated that the powder had poor flow properties. The high indices of powder flowability observed, confirmed reports of native starches generally having poor flow properties [24]. They would therefore be ideal for wet granulations, where improved granule flow (as a result of the increased powder density) allows smooth tablet compression. The result of particle size and size distribution (Table 3) showed that BSSC had average mean diameter of 274.77µm.

Table 2. Physicochemical properties of the defatted cake of BSSC.

Parameter	*Blighia sapida* defatted cake
Solubility	Not soluble in cold water
Mucilage	Thin and cloudy
pH	5.58±0.54
Moisture content (%)	6.68±0.23
Bulk density (g/mL)	0.35±0.03
Tapped density (g/mL)	0.45±0.04
Hausner's ratio	1.29
Compressibility index (%)	22.22
Angle of repose (°)	40.0±1.50
Iodine test	Blue-black

Table 3. Particle size and size distribution of *Blighia sapida* seed defatted cake.

Sieve aperture (µm)	Weight of defatted cake retained (%)
>325	65.50
250-325	10.50
150-250	9.50
75-150	9.55
0-75	3.50

Compatibility studies

Figures 1, 2 and 3 show the FTIR spectra of BSSC, ascorbic acid powder and blend of BSSC and ascorbic acid powder respectively, highlighting some major bands and peaks. Some major characteristics peaks on the BSSC spectrum (Figure 1) were observed at ≈ 3246.5 cm^{-1} (-H-bonded O-H stretching), ≈ 2926.0 cm^{-1} (–C-H stretching), ≈ 1636.3 cm^{-1} (-C=CH_2) while the characteristics bands/peaks of ascorbic acid spectrum (Figure 2) were observed at 3526.1 cm^{-1}, 3406.8 cm^{-1}, 3309.9 cm^{-1}, 2990.8 cm^{-1}, 2698.0 cm^{-1}, 1751.8 cm^{-1} among others. A more detailed description of group frequency wavenumber (cm^{-1}) and their functional group/assignment of different substances can be found in the literature [25]. The FTIR spectrum of the physical mixture of ascorbic acid and BSSC (Figure 3) showed the presence of characteristics bands/peaks of ascorbic acid confirming that there was no change in the drug structure. Based on the FTIR results, it could be concluded that ascorbic acid is compatible with BSSC.

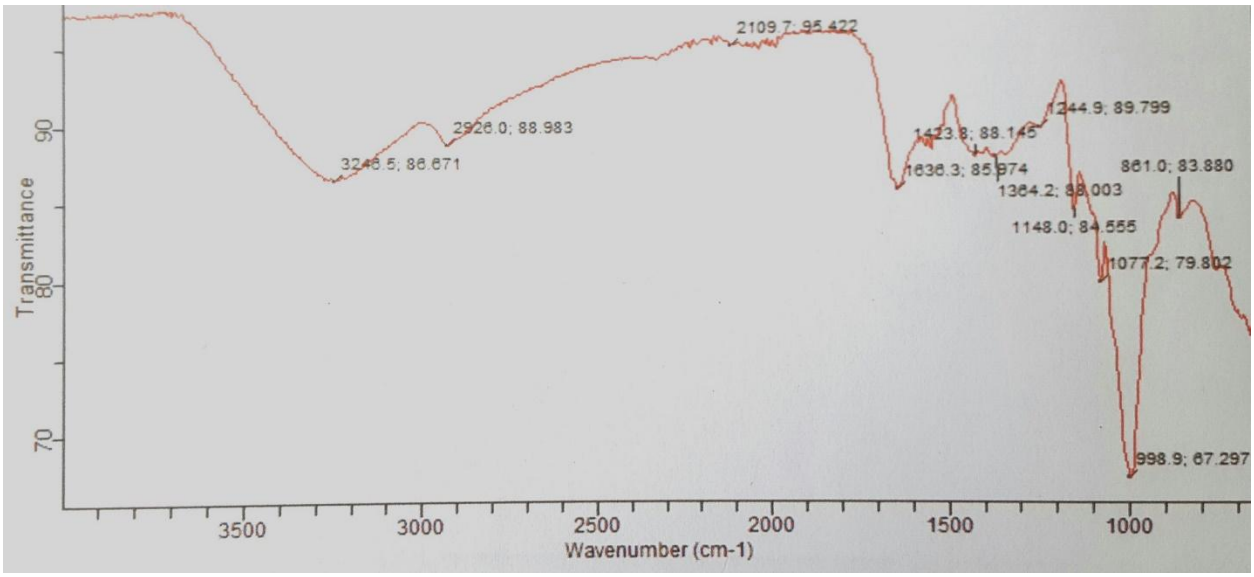

Fig. 1. FTIR spectrum of BSSC powder highlighting some major bands/peaks

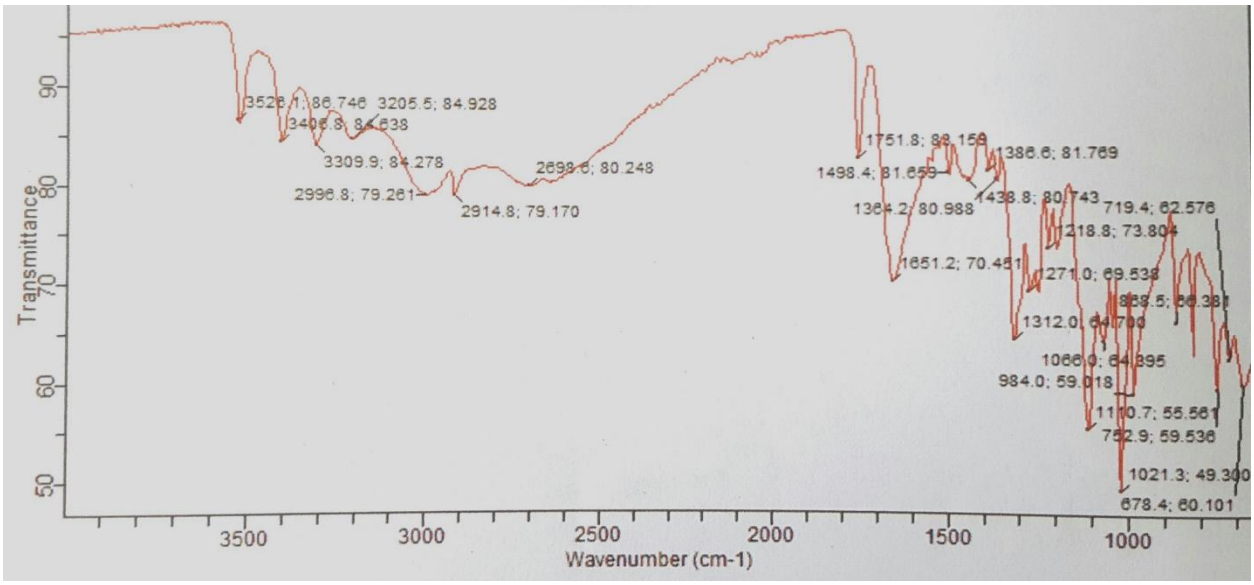

Fig. 2. FTIR spectrum of Ascorbic acid powder highlighting some major bands/peaks

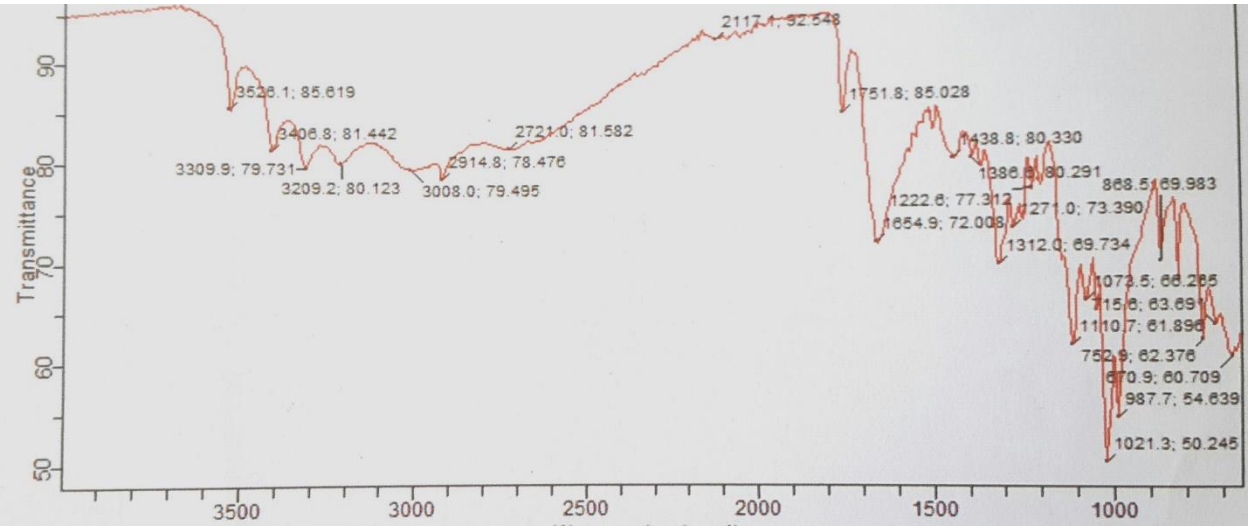

Fig. 3. FTIR spectrum the blend of ascorbic acid and BSSC powders highlighting some major bands/peaks

The thermal behaviour of BSSC, ascorbic acid and physical mixture of BSSC and ascorbic acid is presented in the DSC thermograms shown in figures 4, 5 and 6. The DSC scan for ascorbic acid (Figure 5) showed two sharp endothermic peaks at about 106.12and 270.69^{o}C with a linear onset temperature of 98.29and 255.31^{o}C respectively. The DSC scan of the physical mixtures of BSSC/ascorbic acid powders (Figure 6) showed a shift in the two corresponding peaks observed in the DSC scan of ascorbic acid. The corresponding endothermic peaks of the physical mixtures were observed at about 91.07 and 229.78^{o}C with a linear onset temperature of 85.78and 224.53^{o}C respectively. The first endothermic peak might be attributed to loss of water from the samples while the second peak suggests that the melting process of the samples [26]. From the ascorbic/BSSC themogram, it can be concluded that there was a well-defined interaction of the ascorbic acid and BSSC which were evidenced by the shift of the endothermic melting peak. Thus, it can be said that BSSC (excipient) increased the thermal degradation of ascorbic acid (active substance). This observation is not in agreement with the findings from FTIR analysis which showed no noticeable interactions between ascorbic acid and BSSC. The differences between the findings from FTIR and DSC analyses may be attributed to the different temperatures used for the analysis by the two different methods [27]. Moreover, it has been reported that although, it is accepted that any changes in DSC thermogram may be as a result of interaction, such changes are not always due to incompatibilities between the samples [27].

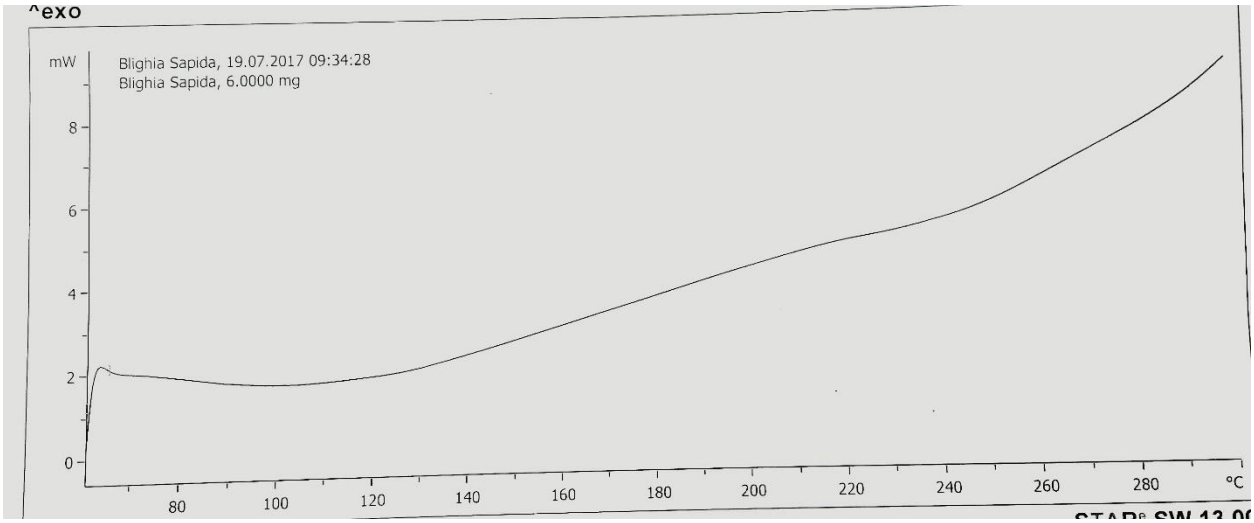

Fig. 4. DSC thermogram of BSSC powder.

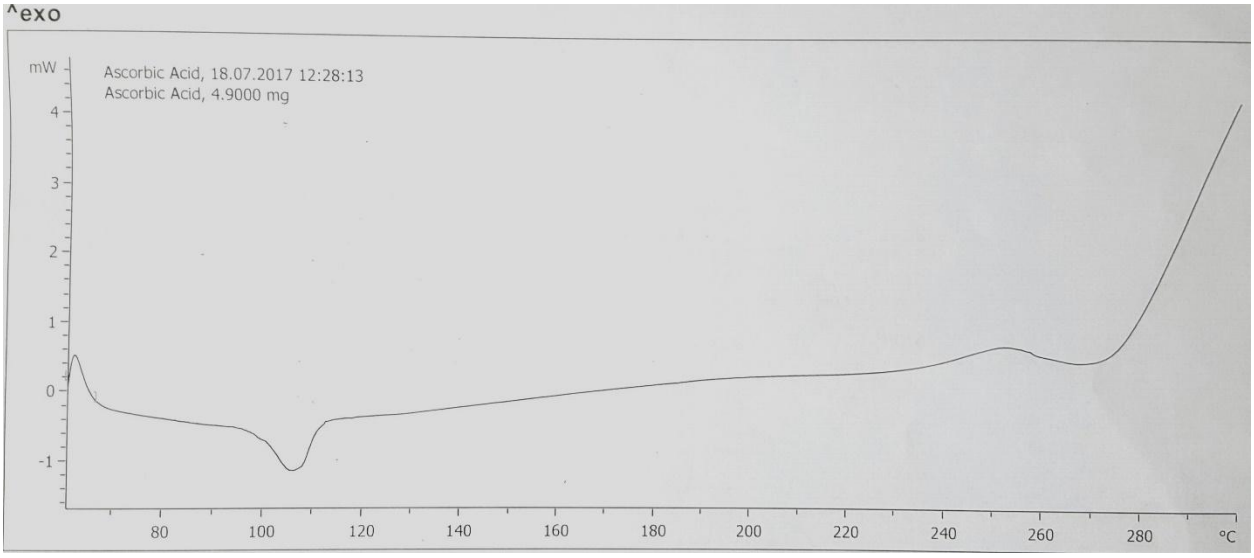

Fig. 5. DSC thermogram of the of ascorbic acid powder.

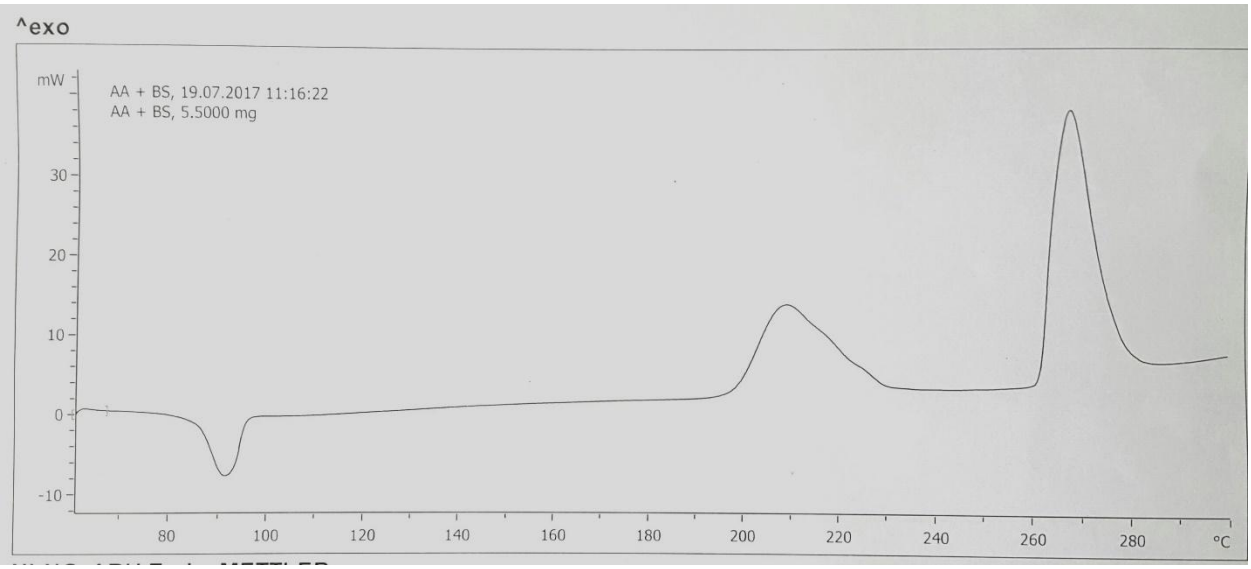

Fig. 6. DSC thermogram of the blend of ascorbic acid and BSSC powders.

Properties of compressed granules

Ascorbic acid granules formed using the defatted cake as binder gave good flow properties (Table 4), Hausner's ratio ranged from 1.033 -1.039 among the various binder concentrations compared to maize starch which gave Hausner's ratio (HR) of 1.039; HR of < 1.1 is considered excellent [19]. The compressibility index (CI) also ranged from 3.17-3.73; Carr's CI<10 is considered excellent flow [18], therefore the granules could be said to have excellent flow properties. There was no significant difference in the bulk and tap densities of granules containing 2 %w/w starch BP, 2 %w/w BSSC and 4 %w/w BSSC. The bulk and tapped densities reduced with increasing binder concentrations of BSSC showing a decrease in porosity and increased agglomeration.

Table 4. Physical properties of ascorbic acid granules.

Batch	Tapped density(g/mL)	Bulk density(g/mL)	Bausner's ratio	Compressibility index (%)
B1	0.670±0.052	0.645±0. 076	1.039	3.73
B2	0.670±0.061	0.645±0.032	1.039	3.73
B3	0.655±0.006	0.632±0.065	1.037	3.51
B4	0.641±0.071	0.620±0.086	1.033	3.23
B5	0.630±0.052	0.610±0.023	1.033	3.17

Mean ± standard deviation where applicable. Binder concentration of the granules: B1; Starch 2%, B2; BSSC 2%, B3; BSSC 4%, B4; BSSC 5% and B5; BSSC 8%.

Table 5. Properties of ascorbic acid tablets formulated using different concentrations of the defatted cake (BCCS) and 2% Starch B.P as binder.

Parameter	B1	B2	B3	B4	B5
Mean Weight (mg)	354±3.50	354±4.36	356±3.30	351±4.09	362±5.98
Tablet Thickness (mm)	4.0±0.12	4.0±0.06	4.0±0.16	4.0±0.17	4.0±0.16
Crushing Strength (kgf)	3.1±0.5	3.4±0.4	3.4±0.3	3.5±0.5	4.0±0.7
Friability (%)	>1.00	0.50	0.49	0.40	0.37
Disintegration Time (min)	2.50±0.13	3.13±0.43	3.48±0.15	3.52±0.56	3.65±0.76
% Dissolved at 45 min	85	85	85	85	85

Mean ± standard deviation where applicable. Binder concentration of the formulations: B1; Starch 2%, B2; BSSC 2%, B3; BSSC 4%, B4; BSSC 5% and B5; BSSC 8%.

Evaluation of ascorbic acid tablets

The post compression evaluation of the tablets showed that the tablets of BSSC binder concentrations 2 to 5 %w/w showed uniform thickness (Table 5). The compendia specification for uniformity of weight states that for tablets weighing more than 250 mg, weights for not more than two tablets should deviate from the average weight by more than 5 % [22]. All the tablets containing 2 to 5 %w/w BSSC as binder did not deviate by more than ± 5 % from the 350 mg target weight for the ascorbic acid tablets. The highest concentration of the binder however did not pass the weight uniformity test, a few tablets had higher weight; from the BP specification, not more than 2 tablets should have the upper limit of the tablet weight which is 370 mg. The weight variation could have resulted from demixing of the granules just before compression since the mixing was done manually.

The mean crushing strength for the control (2 %w/w maize starch as binder) was 3.1 kgf and it differed significantly from formulations containing different concentrations of defatted cake as binder: 2 -8 %w/w (3.4 - 4.0 kgf) (Table 5). Tablet hardness should generally not be less than 1 kgf. A tablet which is 'soft' and just handleable would give a reading of 1 to 2 kgf on a Monsanto tester; for highly compacted tablets up to 6 kgf or more [28]. The formulation containing 8 %w/w of BSSC as binder had the highest crushing strength of 4.0 kgf. The binder helps to hold the particles together resulting in formation of harder tablets.

Friability measures the ability of tablets to withstand stress; the B.P specifies a friability limit of not more than 1 %. The control batch (maize starch 2 %w/w as binder) did not pass the test for friability, (Table 5) the tablets practically crumbled. This could be due to the fact that maize starch provides optimum binding in concentrations of 5-10 %w/w, however batches B2-B5 (defatted cake as binder 2 – 8 %w/w) all passed the friability test with friability ranging from 0.37 - 0.50 % therefore the defatted cake can be said to have better binding effects in terms of friability. The friability did not differ significantly among the varying binder concentrations.

Disintegration is a crucial step in release of drugs from immediate release dosage forms. The rate of disintegration is directly proportional to the rate of dissolution. The rate of disintegration is influenced by the rate of influx of water into the tablets which is also dependent on the porosity of the tablets. When the porosity is high, disintegration is hardly influenced by tablet formulation; otherwise, disintegration will be affected by the excipients [29]. The BP [22] specification for disintegration of ascorbic acid is that the tablets should disintegrate completely in 15 minutes. All the batches passed the disintegration test as they all disintegrated within a time range of 3.03-3.52 minutes. The disintegration time was significantly higher than that of maize starch BP which was 2.5 minutes

($p<0.05$). The disintegration time showed elevations with increasing binder concentrations until the binder concentration of 5 %w/w after which no increase was observed, rather a non-significant decrease at 8 %w/w.

The rate of dissolution determines the rate and extent of absorption and subsequent therapeutic outcome of a drug. The factors that affect dissolution include type and concentration of binder, hardness, surface area, distance of diffusion, solubility of the drug, manufacturing process (wet granulation, dry granulation or direct compression) and diluents [30]. Ascorbic acid is classified under the biopharmaceutical classification system (BCS class III) high solubility and low permeability. The USP [21] specifies that after 45 minutes, not less than 75 mg of the drug must have been released. All batches released 85 % of ascorbic acid in 45 minutes, implying rapid dissolution and similar dissolution profile with maize starch.

Conclusion

BSSC at 2 %w/w concentration, demonstrated good binding properties compared to a commercial brand maize starch B.P in ascorbic acid tablet formulations hence it could serve as potential source of low-cost binder for pharmaceutical industry.

Conflict of Interests

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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