Article published online: 2023-05-24

Formulation and Evaluation of Starch Phosphate-Based Cream Derived from *Manihot esculentus*

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Pharmaceut Fronts 2023;5:e109–e116.

Abstract

Starch is an important excipient employed in the pharmaceutical industry but irrespective of its source, the native starch is undesirable for many applications because of its inability to withstand processing conditions and hence needs its modification to achieve the desired properties. This study aimed to synthesize starch phosphate through the modification of starch obtained from *Manihot esculentus*, and then explore its potential in the preparation of cream formulations. In the present study, the starch was extracted from *M. esculentus* (cassava), then phosphorylated by reacting with varied concentrations of disodium hydrogen phosphate, anhydrous (Na_2HPO_4, 0.05, 0.1, and 0.2 mol/dm^3) under pH 6. A standard wet chemistry method was used for the determination of the degree of substitution by phosphate (DSp) of modified starch, and Fourier transform infrared (FTIR) spectra were used for structure identification. The starch phosphate obtained was employed to develop a cream formulation. The physicochemical properties of the formulation were further evaluated. Calamine cream BP was utilized as a control. Our result indicated that a higher concentration of Na_2HPO_4 favors a higher DSp (0.047). FTIR spectra of the modified starch suggested a new peak at 1,090 cm^{-1} (P-OR). The cream formulated with a high DSp of starch phosphate demonstrated good physicochemical properties with spreadability (7.84–8.65 gcm/s), pH (6.5–7.0), viscosity (267–296 cp), extrudability (2.05–2.62%) and physical stability, and were smooth, opaque, greasy, homogeneous, and easily removed on washing with water. Statistical analysis showed that there was no significant difference between the starch phosphate-based cream and the control, but a significant difference between the starch phosphate-based cream and a native starch-based cream. Given the above, starch phosphate with a high DSp can be prepared from *M. esculentus* starch and utilized as a promising emulsifying agent in cream formulation due to its being more widely available, more stable, and cost-effective.

Keywords

- *Manihot esculentus*
- starch phosphate
- cream
- disodium hydrogen phosphate

received
October 4, 2022
accepted
April 3, 2023

DOI https://doi.org/10.1055/s-0043-1768614.
ISSN 2628-5088.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Introduction

Topical preparations are designed to exert activity when applied to the skin. The preparations include creams, lotions, and ointments which are used in the treatment of burns, wounds, and bacterial and superficial fungal infections. Considering the concentration of the drug and degree of solubility, topical formulations are said to contain excipients that aid in providing the desired therapeutic effect.[1] Excipients play a great role in ensuring that the dosage form meets the required specifications of quality by modifying the release, absorption, distribution, and elimination profiles of the drug. This assures product efficacy, safety, patient compliance, and acceptance.[2] In recent years, the extraction, development, and use of starches in the formulation of dosage forms have attracted increasing attention from pharmaceutical scientists.[3] Starch is an edible polymer derived from a plant basis. It is the most commonly used excipient in the pharmaceutical industry, due to its availability and ease of chemical modification to other derivatives.[4] However, the use of native starch, irrespective of its source, is limited because of its inability to withstand processing conditions such as extreme temperature, diverse pH, high shear rate, and freeze–thaw variation. Thus, it is usually to modify the chemical structure of the native starch to enhance or repress its inherent property or to impact new properties to meet the requirements for specific applications. The modification alters the properties of starch including solubility, viscosity, and stability. Another purpose of starch modification is to stabilize starch granules during processing and make starch suitable for many food and industrial applications.[5]

Starch has been extensively modified through four basic types, namely, chemical, physical, enzymatic, and genetic. Starch phosphate is a representative product of the modified starch with manifold properties that are used as excipients in pharmaceutical industries and additives in food and nonfood industries.[6] Due to their swellable property, the highly substituted starch phosphates may be used as water-absorbing and water-storing materials for different applications in cosmetics and pharmacy.[7] The degree of substitution by phosphate (DSp) may be an important factor in affecting the properties of starch phosphates, including solubility, swelling properties, rheomechanical characteristics, stability of the dispersion, and transparency of solutions or dispersions which are desired for different applications.[8]

Creams are viscous semisolids intended for the external application of solutions or dispersions of medicaments to the skin or mucous membranes, e.g., the rectum and vagina, for therapeutic or prophylactic purposes where a highly occlusive effect is not necessary.[9] Given the above, modified starches may play a role in the development of creams and lotions because they provide viscosity and stability while maintaining an extremely cost-effective formulation, and they contribute a smooth skin feel and short texture to the formulation along with pH, shear, heat, and freeze/thaw stability. Modified starches have an excellent way of giving the final formulation a silky, nontacky skin feels. When used at higher levels, modified starches such as starch phosphate can present a powdery feel, i.e., the formula goes on like a lotion but feels like a powder.[6] In the present study, the potential application of starch phosphate as an agent in the formulation of cream was studied using native starches extracted from *Manihot esculentus*. The study enriched the use of modified starch in the pharmaceutical field.

Materials and Methods

Reagent

Disodium hydrogen phosphate anhydrous (Na_2HPO_4) and sodium metabisulphite were purchased from BDH Chemicals Ltd, Poole England. NH_4F, ammonium molybdate, and stannous chloride were obtained from Pub Chem, United Kingdom.

Native Starch Extraction

The *M. esculentus* was obtained from Kara market Sokoto State, Nigeria, and identified by the herbarium unit, Department of Pharmacognosy and Ethno Pharmacy, Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University, Sokoto, with Herbarium No PCG/UDUS/EUP/009.

Native starch was extracted from *M. esculentus* using the procedure described by Alves et al with some modifications.[10] Fresh tubers were thoroughly washed with water, peeled, and chopped into cubes. The cubes were soaked in sodium metabisulphite solution (0.075% w/v, 20 L) overnight. The mixture was milled using a grinding mill, stirred, and filtered using a calico cloth, and allowed to stand for some time for the starch to settle. Decant the water and add fresh water, and repeated it twice. The suspension was centrifuged at 4,000 rpm for 10 minutes. The pure starch was separated from water and non-water-soluble constituents and dried in an oven at 40°C for 24 hours. The pure starch was ground using mortar and pestle and sieved through a 100-micron sieve.

Proximate Analysis

The proximate analysis for moisture, crude protein, ash content, crude lipid, and fiber content of the starch was determined according to the method described by Association of Official Agricultural Chemists.[11]

Total Carbohydrate

The content of total carbohydrates was calculated by adding total lipid, moisture, nitrogen, crude protein, ash, and fiber content and then subtracting them from 100.

Synthesis of Starch Phosphate

Starch phosphate was prepared according to Chowdary et al's method.[12] Disodium hydrogen phosphate, anhydrous (Na_2HPO_4, 0.05, 0.1, and 0.2 mol/dm^3) was dissolved in distilled water (200 mL), and the pH value was adjusted to 6 by adding a few drops of 10 mol/L aqueous sodium hydroxide, then *M. esculentus* (cassava) starch (100 g) was added. The mixture was stirred for 20 minutes. The resulting slurry was allowed to equilibrate for 4 hours and decanted. The mixture was dried at 50°C for 24 hours and heated at 140°C in an oven to obtain starch phosphate with different degrees of substitutions. Unreacted sodium was extracted with a hot

aqueous ethanol solution. The collected starch was washed with distilled water and dried in an oven at 50°C. The product obtained was ground and sized.

Determination of Phosphorus Content and Calculation of Degree of Substitution

The phosphorus content of the starch was determined according to the method described by Wongsagonsup et al[13] with some modifications. Briefly, the starch phosphate (2 g) was ashed in a muffle furnace at 550°C. After cooling, the ash was dispersed in 40% HCl solution (5 mL), and then added water to make the total volume up to 50 mL. The suspension was filtered on a filter paper. To a 50 mL conical flask was added the filtrate (2 mL), followed by the addition of the 2 mL of phosphorus extraction solution (a mixture of 1.11 g of solid NH_4F solution dissolved in water + 4.16 mL of 6 N HCl), 2 mL of ammonium molybdate solution (4%), and 1 mL diluted stannous chloride solution (2%), respectively. After 5 minutes, the absorbance at 480 nm (A480) was determined. The phosphorus content was calculated using Equation (1):

$$\text{Phosphorus content} = \frac{\text{A480} \times 0.61 \times 25 \times 25}{\text{Atomic weight of phusphurus}} \quad (1)$$

where 0.61 is the conversion factor and 25 is the dilution factor.

The DSp was calculated using Equation (2):

$$\text{DSp} = \frac{162 \times \text{P\%}}{3100 - 141.9 \times \text{P\%}} \quad (2)$$

where 162 is the molar mass of anhydrous glucose; *P*% is the percentage of phosphorus content, 3,100 is the atomic weight of phosphorus multiplied by 100; 141.9 is the molar mass of Na_2HPO_4.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FTIR) spectra were obtained to further determine the phosphorylation of starch phosphate. A 1 mg quantity of the starch powder was mixed with 49 mg of potassium bromide. The mixture (50 mg) was compressed to form a transparent pellet using a hydraulic press at 5 tons pressure and then scanned from 4,000 to 650 cm^{-1} (mid-infrared region) at a resolution of 4 cm^{-1} in an FTIR spectrophotometer (FT-IR, Nexus, United States). The IR spectrum of the physical mixture was compared with those of pure starch and matching was done to detect any appearance or disappearance of the peak.

Preparation of Cream Formulation

The code allotted to each batch of cream formulation and the corresponding types of emulsifiers are shown in ►**Table 1**, and the major emulsifying agents in the preparation of cream formulation were emulsifying wax, native starch, and starch phosphate, respectively. The formula in each batch was illustrated in ►**Table 2**.

Calamine Cream BP was prepared as the following: melt the emulsifying wax with the aid of gentle heat, add arachis oil, and warm the mixture. Add water (40 mL) at the same temperature and stirred until cold. Calamine and zinc oxide were triturated with the remainder of the water and incorporated into the cream. The cream was transferred into a container and labeled.

Starch phosphate-based cream was prepared as the following: to a beaker we added starch phosphate and water (40 mL), and the mixture was stirred in a water bath (set at 85°C) until the starch is fully gelatinized. Arachis oil was

Table 1 Batch code for each cream formulated

S/NO	Batch code	Type of cream formulated	Type of emulsifier used
1	Ms	Calamine cream BP	Emulsifying wax
2	Mn	Native starch-based cream	Native Starch
3	Mg	Starch phosphate-based cream	Starch phosphate (Conc. $Na_2HPO_4 = 0.05$ mol/dm^3)
4	Md	Starch phosphate-based cream	Starch phosphate (Conc. $Na_2HPO_4 = 0.10$ mol/dm^3)
5	Ma	Starch phosphate-based cream	Starch phosphate (Conc. $Na_2HPO_4 = 0.20$ mol/dm^3)

Table 2 Formula used in the preparation of creams

Ingredient	Ms	Mn	Mg	Md	Ma
Calamine (g)	4.00	4.00	4.00	4.00	4.00
Zinc oxide (g)	3.00	3.00	3.00	3.00	3.00
Emulsifying wax (g)	6.00	–	–	–	–
Starch (g)	–	12.00	12.00	12.00	12.00
Arachis oil (g)	30.00	30.00	30.00	30.00	30.00
Purified water freshly prepared and then cooled (g)	57.00	51.00	51.00	51.00	51.00

added and then continuously stirred until all of the oil is absorbed. Calamine and zinc oxide were triturated with the remainder of the water and incorporated into the cream. The cream was transferred into a container and labeled appropriately. The same method was used for the native starch-based cream.

Cream Evaluation

Selection of Volunteers

Ten volunteers aged 20 to 35 years (five male and female each) were selected to observe some physical characteristics of the creams formulated. Their observation was recorded, graded, scored, and analyzed.

Physical Examination

The color, odor, and physical state were observed by selected volunteers and their findings were noted and scored as follows: smooth (3 pts), watery (2 pts), and hard (1 pt).

Determination of pH

The cream (5 g) was dispersed in distilled water (45 mL), and the pH value was measured with a calibrated pH meter.

After Feel

The cream was applied by 10 selected volunteers to ascertain whether it was greasy or nongreasy. Their observations were recorded and scored as follows: greasy (3 pts), moderately greasy (2 pts), and nongreasy (1 pt).

Viscosity

A Brookfield viscometer was an instrument for the determination of the viscosity of the formulated creams. The sample was taken in a clean and dry 50 mL beaker. The text procedure was conducted using spindle no. 4 at speed of 60 rpm.

Homogeneity

The homogeneity of the cream was assessed by the visual appearance and touch of the selected volunteers, and scored as follows: homogenous (2 pts) and nonhomogenous (1 pt).

Ease of Removal

The ease of removal of the creams was examined by washing the applied part of the creams with tap water, and scored by the selected volunteers as the following: easy (3 pts), moderate (2 pts), and hard (1 pt).

Presence of Foreign Particles

A small amount of cream was taken and spread on a glass slide free from grease and observed against diffuse light to check for the presence of foreign particles.

Spreadability

The formulated cream (0.6 g) was applied in between two glass slides and compressed to uniform thickness by placing 200 g weight on it for 5 minutes. Thereafter, pull the top plate with the help of thread attached with 10 g weight. The time in which the upper glass slide moves the lower plate to cover a distance of 2 cm was noted. Spreadability was calculated using Equation (3):

$$\text{Spreadability} = \frac{\text{Weight applied} \times \text{Length moved}}{\text{Time}} \quad (3)$$

Stability Test

The cream was exposed to altered temperatures of 0, 30, and 45°C for 5 days. They were observed for any change in consistency and phase separation.

Extrudability

The formulation was filled into a standard caped collapsible tube and sealed. The tube was weighed and recorded. Place the tube between two glass slides and clamp tightly. Place 1 kg weight over the glass slide and open the cap of the tube. The amount of cream extruded was collected and weighed. The percent of cream extruded was calculated.

Statistical Analysis

A one-way ANOVA (analysis of variance) test was used to analyze the experimental data using SPSS software. The analysis was also done with descriptive statistics. The results were compared at a 95% confidence interval. The values of $p < 0.05$ were considered significant. Data were expressed as mean ± standard error of the mean.

Results and Discussions

Proximate Analysis

The contents of moisture, ash, lipid, fiber, nitrogen, crude protein, and carbohydrate of native starch derived from *M. esculentus* are shown in ►**Table 3**. Encouragingly, all the results were within the official limit as stipulated in the official compendia.[14] It is well known that the content of moisture influences the storage stability of starches. Moisture contents >12% encourage microbial contamination and induce degradative biochemical reactions leading to the spoilage of starches during storage.[15] The protein contents of cassava starch (0.196), lipid (trace amount), fiber (trace amount), and ash content (0.5%) were previously reported in the ranges of 1.3–1.8%, 0.1–0.8%, 1.5–3.5%, and 1.3–2.8%,

Table 3 Proximate analysis of native starch derived from *Manihot esculentus*

S/No	Property	Result (%)
1	Moisture	2.20
2	Ash	0.50
3	Lipid	Trace
4	Fiber	Trace
5	Nitrogen	0.196
6	Crude protein	1.23
7	Carbohydrate	96.07

Table 4 DSp of the starch phosphate determined by a spectrophotometric method

Code	Conc. of Na_2HPO_4 (mol/dm^3)	*DSp*[a]
Ma	0.20	0.047 ± 0.12
Md	0.10	0.031 ± 0.34
Mg	0.05	0.029 ± 0.22

Abbreviation: *DSp*, degree of substitution by phosphate.
[a]Data were represented as the mean ± standard deviation of three replications.

respectively.[16] The surface features of a starch granular such as surface pores including crevices can accumulate nonstarch components such as inorganic matter which can contribute to the variation of ash content.[17]

Degree of Substitution

As shown in ►**Table 4**, the degree of substitution of the starches was in the range of 0.029 to 0.047 when different amounts of Na_2HPO_4 were used. A higher concentration of Na_2HPO_4 favors a higher DSp.

►**Figs. 1** and **2** show the FT-IR spectra of native and modified starch phosphate, respectively. Our data showed that the two starches exhibited similar patterns except for the new peak observed in modified starch phosphate. The peak at 1,090 cm^{-1}, near 900 to 1,050 cm^{-1}, belongs to P–OR stretching vibration.

Formulated Creams' Evaluation

The physicochemical properties of different batches of cream are shown in ►**Table 5**. All formulated creams were light pink

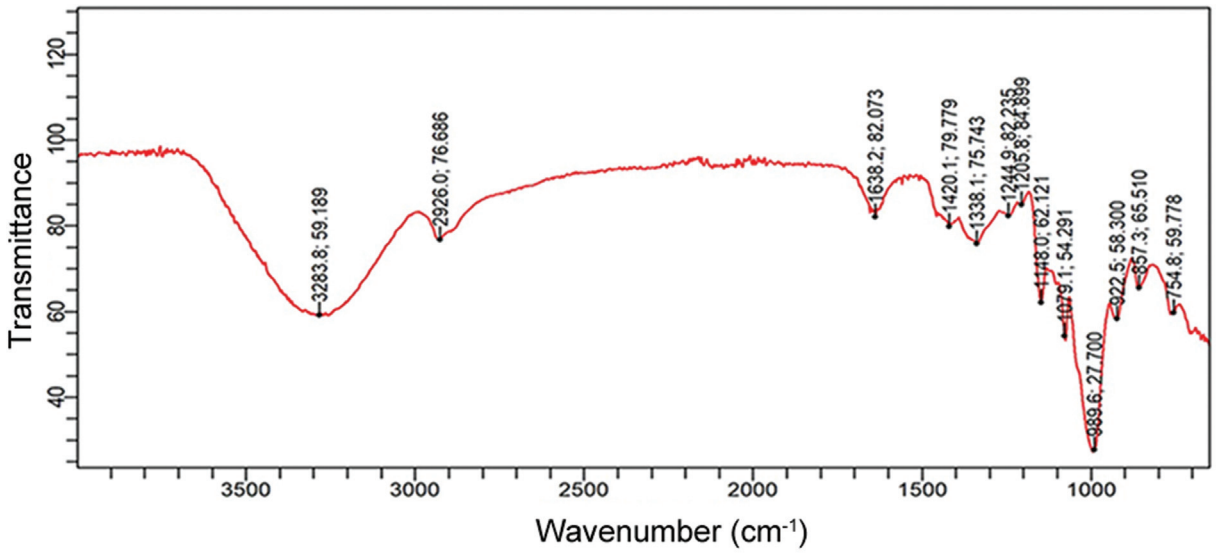

Fig. 1 Fourier transform-infrared spectrum of native starch.

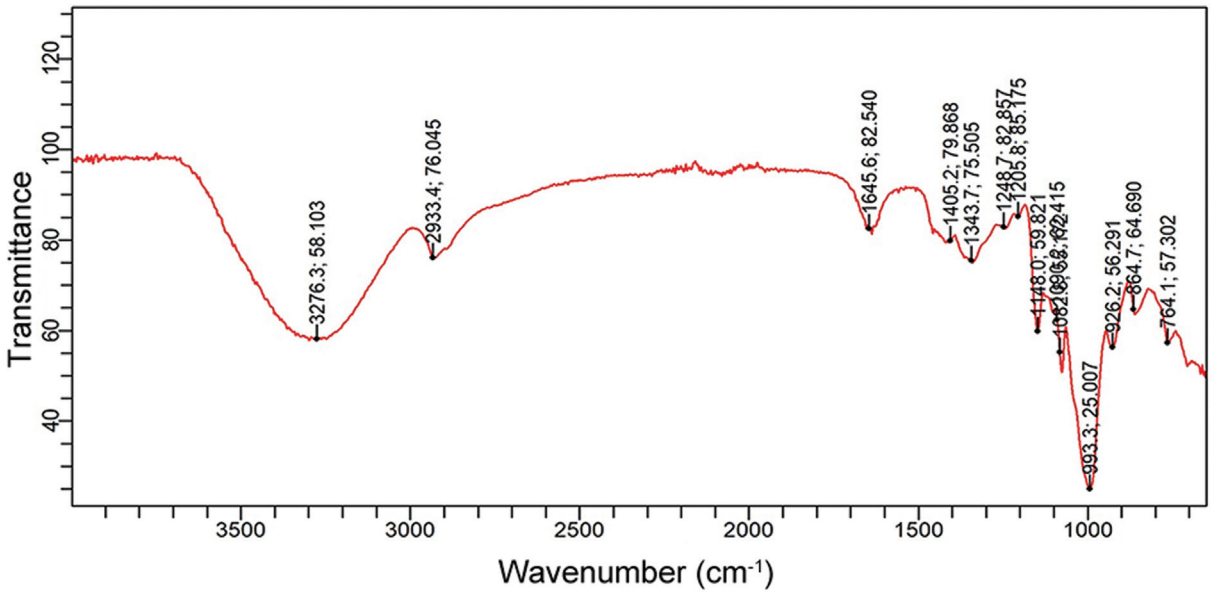

Fig. 2 Fourier transform-infrared spectrum of starch phosphate.

Table 5 Physicochemical characters of cream formulated

Parameter	Ms	Mn	Mg	Md	Ma
Physical appearance	**Light pink color and smooth on application**	**Light pink color and watery on application**	**Light pink color and smooth on application**	**Light pink color and smooth on application**	**Light pink color and smooth on application**
Creaming	−	+	−	−	−
Cracking	−	−	+	−	−
Odor	Characteristic arachis odor	Characteristic arachis odor	Characteristic arachis odor	Characteristic arachis odor	Characteristic arachis odor
pH	6.8	6.9	6.7	6.8	6.6
Presence of foreign particles	Absent	Absent	Absent	Absent	Absent
Extrudability[a] (%)	2.62 ± 0.22	4.13 ± 0.18	1.1 ± 0.28	2.23 ± 0.36	2.05 ± 0.12
Spreadability[a] (gcm/s)	7.84 ± 0.16	266.6 ± 0.32	1.1 ± 0.18	8.65 ± 0.24	7.84 ± 0.22

Abbreviations: +, cracked/creamed; −, not cracked/creamed.
[a]Data were represented as mean ± standard deviation of three replications.

in appearance which was mainly due to the presence of calamine powder used as an active ingredient. Cracking was observed in batch Mg, and this may be a result of its low degree of substitution. This finding is in line with the fact that only highly substituted starch phosphates are swellable enough to be used as water-absorbing and water-storing materials.[7,18] The pH of the creams formulated was in the range of 6.6 to 6.9, which is suitable for topical application as the pH of the skin is considered normal at a slightly acidic pH <7.[19]

The spreadability is used to denote the extent of the area to which the cream is readily spread when applied to the skin on an affected part. The spreading value is usually associated with the therapeutic and bioavailability of the formulation.[20] Our data showed that Ma and Md have very good spreadability as they all spread over glass slides in less than 1 minute with a spreading ability of 7.84 to 8.69, while Mg formulation was very less spreadable with a spreading ability of 1.1. Extrudability is a useful empirical test to measure the force required to extrude the material from a tube, percentages of cream extruded in Ma and Md formulations were 2.05 and 2.2% respectively, while Mg showed the least extrudability due to its high viscosity. Given the above, the formulations of Ma and Md gave satisfactory results in terms of spreadability and extrudability.

The after-feel rating by selected volunteers demonstrated significant greasiness in the formulations of Ma and Md, and less greasiness in the formulation of Mg (►**Fig. 3A**). This is particularly important because less-greasy creams are easier to wash off, while greasy creams are more difficult to handle but will release hydrophobic drugs faster than less-greasy creams, therefore the cream can stay long enough to release medicaments before being washed off.[21] Our data showed that Mg had poor texture in nature and was nonhomogeneous, suggesting a bad consistency of the formulation; moreover, Mg was easily removed (►**Fig. 3B–D**). However, Ma and Md were greasy, smooth, homogenized, and easily removed on washing with tap water. Besides, the viscosities of Ma and Md were 271.5 and 267.5 cp, respectively, while for

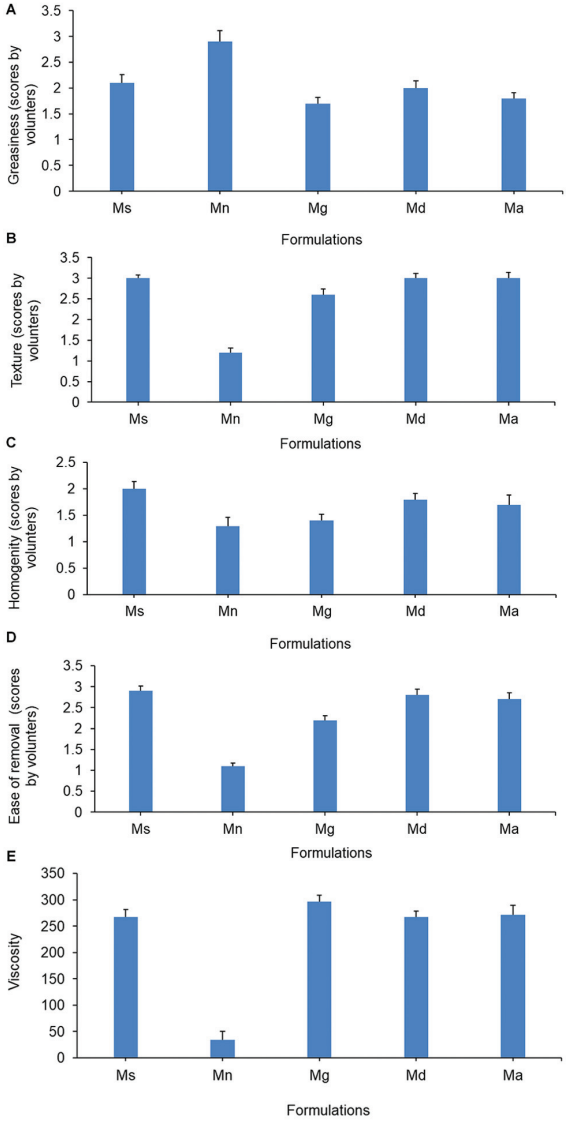

Fig. 3 Evaluation of the formulated creams. Evaluation of (**A**) greasiness, (**B**) texture, (**C**) homogeneity, (**D**) ease of removal, and (**E**) viscosity of the modified starch phosphate-based cream in comparison to calamine cream BP and native starch-based cream.

Table 6 Stability profile of the formulated creams at different temperatures

Type of cream	45°C	30°C	0°C
Ms	Smooth, opaque, homogenous, physically stable, and greasy on application	Smooth, opaque, homogenous, physically stable, and greasy on application	Hard, opaque. nonhomogenous, physically frozen into a solid mass, and nongreasy on application
Mn	Watery, cloudy, nonhomogenous, physically separated (phase separation), and greasy on application	Watery, cloudy, nonhomogenous, physically separated (phase separation), and greasy on application	Hard, cloudy, nonhomogenous, physically frozen, and nongreasy on application
Mg	Hard, nonhomogenous, physically cracked, and moderately greasy on application	Hard, nonhomogenous, physically cracked, and moderately greasy on application	Hard, nonhomogenous, physically cracked, and nongreasy on application
Md	Smooth, opaque, homogenous, physically stable, and greasy on application	Smooth, opaque, homogenous, physically stable, and greasy on application	Smooth, opaque, homogenous, physically stable, and greasy on application
Ma	Smooth, opaque, homogenous, physically stable, and greasy on application	Smooth, opaque, homogenous, physically stable, and greasy on application	Smooth, opaque, homogenous, physically stable, and greasy on application

Mg was 296.9 cp (►**Fig. 3E**), which is considered too viscous in comparison with the standard, this may be a result of its cracked nature.

The effect of temperatures on the cream was also assessed. Our data showed that the formulations of Md and Ma were smooth, opaque, homogenous, physically stable, and greasy when stored at 45, 30, and 0°C. However, Mg was found to be hard, nonhomogenous, and physically cracked at all study temperatures (►**Table 6**), indicating the storage of Md and Ma is stable at the text temperatures. This is particularly important because starch phosphate can be used as an emulsifying agent in creams used in tropical and temperate regions of the world.

In addition, our statistical analysis shows no significant (p-value > 0.05) difference in starch phosphate-based cream when compared with calamine cream BP, but a significant difference (p-value < 0.05) when compared with native starch-based cream, suggesting a great potential of starch phosphate in exploring novel cream formulations in the future.

Conclusion

Starch phosphate with a high degree of substitution can be prepared by reacting cassava starch with Na_2HPO_4 under weakly acidic conditions and then can be applied to formulate cream. The formulated cream demonstrated good physicochemical properties when compared with a native starch-based cream. Such starch phosphate was found to have promising use in the cream formulation and can be efficiently used as its more widely available, more stable, and cost-effective.

Conflict of Interest

The authors declare no conflict of interest.

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