Formulation and Comparative *in vitro* Drug Release and Membrane Diffusion of Diclofenac Sodium Cream: *Vigna subterranea* Starch Based Pickering Versus Emulsifying Wax-Based.

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ABSTRACT

Pickering emulsion stabilized with starch is a promising alternative to conventional surfactant- based topical creams in support of green technology. Limited studies have been done on this research topic. This study compared the *in vitro* drug release kinetics and membrane diffusion characteristics of topical diclofenac sodium creams formulated as annealed *Vigna subterranea* starch-based Pickering emulsions and emulsifying wax-based creams. *Vigna subterranea* starch was extracted, modified to yield annealed starch. The morphology, crystallinity, swelling index, wettability, hydration, and emulsion capacities were evaluated. FTIR spectra of physical mixtures of diclofenac sodium and the excipients revealed no sign of incompatibility. Diclofenac sodium 1% topical oil -in- water creams, F1-F4 were prepared by fusion method, using varying concentrations of annealed starch (1.0, 2.5, 5.0, 7.5 % respectively) as the Pickering stabilizer. F9 and F11 with native *Vigna subterranea* starch and emulsifying wax respectively in the concentration of 7.5% were formulated for comparison. *In vitro* drug release was investigated using a cellulose membrane diffusion model in phosphate buffered saline, from where samples were collected at predetermined intervals and analyzed using UV- visible spectrophotometry. Release data was fitted into various kinetic models. Annealing modified the physicochemical properties of *Vigna subterranea* starch and improved its suitability as a Pickering stabilizer. F1-F11 showed satisfactory physicochemical characteristics. The release profiles showed differences ($P<0.05$) between the Pickering and conventional cream systems. This indicated the influence of the stabilizing matrix on drug transport. The optimized annealed starch cream F4 exhibited the highest release efficiency (87.94%) and area under release curve (527.5%) with the lowest mean dissolution time (0.67 hr) indicating rapid drug release whereas the emulsifying wax formulation (F11} showed a release efficiency of 77.54% and native starch formulation (F9) showed 52.24%. Higuchi was found to be the best fitting kinetic model, with the highest correlation coefficient (R^2 =0.989) while Korsmeyer -Peppas analysis showed Fickian diffusion ($n\leq 0.45$) as the release mechanism. These findings demonstrate that annealed *Vigna subterranea* starch is a promising, sustainable alternative to emulsifying wax for topical diclofenac sodium cream.

Keywords: Diclofenac sodium, annealed starch, Pickering, emulsifying wax, stabilizer, drug release, membrane diffusion.

INTRODUCTION

Topical creams are used in the management of localized inflammatory and musculoskeletal disorders. This is because of their ability to deliver therapeutic agents to the site of action while minimizing systemic exposure

and associated adverse effects. (Marto *et al*, 2015). They are used to administer non- steroidal anti-inflammatory drugs (NSAIDS), such as diclofenac sodium. Manian *et al*, 2022). They are easy to apply, acceptable to patients, and versatile in delivering both hydrophilic and lipophilic ingredients. The efficacy of topical diclofenac preparations depends not only on the pharmacological properties but also on the ability of the formulation to release the drug and facilitate its diffusion across membrane barriers (Jin et al, 2022). The choice of stabilizer is a critical determinant of emulsion's physical stability and the microstructure (Badruddoza *et al*, 2023). Surfactants such as emulsifying wax has been used over the years and the formulations exhibit acceptable physical stability but may be associated with skin irritation, and environmental concerns. The increase in enthusiasm in the choice of environmentally compliant and biocompatible excipients has led to adoption of the use of natural alternatives. (Marto *et al*, 2019) These days, starch stabilized emulsions have been found to be goods option when compared with surfactant-stabilized emulsions because of their inherent ability to reduce reliance on synthetic surfactants. It also has advantage of promoting stability of the formulation. Starch particles are considered good Pickering stabilizers due to their biocompatibility, biodegradability, low cost, and renewable nature (Mahfouzi et al, 2025). Nevertheless, native starches often exhibit limited functionality due to their poor hydration characteristics, variable swelling behavior, and restricted emulsifying capacity. Annealing, a form of heat treatment in moisture, has been demonstrated to improve starch functionality by causing internal rearrangement of the starch granular structure without affecting their integrity. (Fonseca *et al*, 2021) Several studies have looked into diclofenac sodium release from conventional topical formulations (Manian *et al*, 2022; Tabosa *et al*, 2022, and Iliopoulos *et al*, 2022). However, there is paucity of information on the effect of annealed *Vigna subterranea* starch-based Pickering emulsion on the *in vitro* drug release kinetics of diclofenac sodium creams. Addressing this knowledge gap is important for the development of sustainable, naturally stabilized topical formulations with improved performance. This study is aimed at comparatively evaluating the *in vitro* drug release and membrane diffusion characteristics of diclofenac sodium creams formulated as annealed starch-based Pickering emulsions and conventional emulsifying wax systems. The findings are expected to provide evidence of a potential application of annealed *Vigna subterranea* starch as natural and environmentally friendly stabilizer for topical pharmaceutical formulations

MATERIALS AND METHODS

Materials

Diclofenac sodium (RPS, France) was used as the model drug. Cellulose membrane was from Breda, the Netherlands, Native starch was isolated from the seeds of *Vigna subterranea*. Emulsifying wax, TEA, Methylparaben and other analytical-grade reagents were obtained from reputable commercial suppliers and used without further purification. Deionized water was used throughout the study.

Methods

Experimental design and replicates

All experiments were performed using a completely randomized experimental design. Unless otherwise stated, each determination was carried out in triplicate (n = 3) using independently prepared samples, and the mean ± standard deviation (SD) was reported. Cream formulations were prepared in three independent batches to evaluate batch-to-batch reproducibility. Physicochemical characterization was performed for each batch. Starch extraction and annealing were also conducted independently in triplicate to ensure reproducibility of the modified starch characteristics.

Optimization of Pickering cream formulations

A preliminary optimization study was conducted to identify the optimum concentration of annealed *Vigna subterranea* starch required to produce physically stable Pickering creams. Formulations containing 1.0, 2.5, 5.0, and 7.5% (w/w) annealed starch (F1–F4) were prepared and evaluated. The formulations were compared using the physical appearance and absence of phase separation; emulsion stability after centrifugation; viscosity, spreadability, globule size distribution, drug content uniformity and *in vitro* drug release

characteristics. The optimized formulation was selected based on the highest overall desirability, considering physical stability, drug content (95–105%), acceptable viscosity, ease of spreadability, and maximum drug release efficiency.

Validation of the membrane diffusion method

The membrane diffusion procedure was optimized and validated before the comparative drug release study. A regenerated cellulose membrane (molecular weight cut-off 6000–8000Da) was hydrated in phosphate-buffered saline (PBS, pH 7.4) for 24 h before use. The membrane was carefully inspected for defects before mounting between the donor and receptor compartments. The receptor compartment contained freshly prepared PBS maintained at 37.0 ± 0.5°C and stirred continuously at 100 rpm to maintain sink conditions throughout the experiment. Each membrane was visually examined before use and discarded if there were pinholes, tears, or leakages. The receptor medium volume was selected to ensure that the concentration of diclofenac sodium remained below 10% of its saturation solubility throughout the experiment. Drug release experiments were performed in triplicate using independently prepared cream samples. The relative standard deviation (RSD) for cumulative drug release at each sampling point was maintained below 10%.

Statistical analysis

Data were analyzed using GraphPad Prism version 10.6.1(892) (GraphPad Software Inc., San Diego, California, USA). Results were presented as mean ± standard deviation (SD) from three independent experiments. Normality of the data was assessed using the Shapiro–Wilk test. Comparisons among multiple formulations were performed using analysis of variance (ANOVA), followed by Tukey's multiple comparison post hoc test. When there were comparisons of two groups, an unpaired Student's *t*-test was used. Drug release profiles were compared using release efficiency (RE), mean dissolution time (MDT), and analysis of the release kinetic models. The goodness-of-fit of each kinetic model was assessed using the coefficient of determination (R^2), Differences were considered statistically significant at $p < 0.05$.

Quality control

Before each experiment, all glassware was calibrated; the UV-visible spectrophotometer was wavelength calibrated; buffer pH was verified using a calibrated pH meter; temperature was monitored throughout the diffusion study. Receptor medium was degassed before use to eliminate air bubbles beneath the membrane Acceptance criteria were established before experimentation. Experiments showing membrane leakage, air bubbles beneath the membrane, phase separation of formulations, or drug recovery outside the acceptable range (95–105%) were excluded and repeated.

Extraction and annealing of starch from seeds of *Vigna subterranea (*Bambara groundnuts*)*

Bambara starch was extracted using a slightly modified method reported by Nwaogazie *et a.l*(2024). The extracted and dried starch was milled, sieved and packaged in an air tight container and stored at room temperature until use. The annealing process followed a previously described method by Anida *et al* (2015) with slight modification. Eighty (80) gram quantity of starch sample was mixed with distilled water and the volume adjusted to 400 ml and incubated at 55 ºC in a hot air oven for 24 hours. The treated starch was centrifuged, purified with distilled water, dried at 45°C for 14 hours. The dried product was stored in air tight plastic containers for further analysis.

Physicochemical characterization of native and annealed starches

The native and annealed starches were characterized for their physicochemical and functional properties.

Determination of hydrogen ion concentration (pH)

The pH of *Vigna subterranea* starch was determined thrice using a digital pH meter (Hanna Instruments, USA) according to Compart *et al*, (2023) and the average pH taken.

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Wettability and water absorption capacity

‘’One thousand milligrams of *Vigna subterranea* starch was weighed and introduced into a calibrated 10 ml capacity centrifuge cell and 4 ml of water added and made to disperse by stirring with a glass rod (Leach *et al*, 1959). The volume was made up to 10 ml by the addition of distilled water. The mixture was sonicated for 5 min and thereafter centrifuged at 100 revolutions per min (rpm) for 0.25 hour. The volume of the settled solid phase and the supernatant water layer were visually determined from the cylinder. The wetting properties of the starch, W*p,* was determined by the equation (Compart *et al*, 2023)’’;

$$Wp = \frac{Sf}{St} X\ 100 \quad \text{---------- (1)}$$

where Wp = Wettability

Sf= final volume of sediment

St= Initial volume of sediment

Water absorption and retention capacity were determined using a gravimetric method as described by Oladele, & Aina, (2007). The hydrated starch was separated by centrifugation, and weighed. Determinations were performed in triplicates and the hydration/ water absorption and retention capacity (H) calculated using the relation;

$$H = \frac{W2}{W1} \text{ ..... (2)}$$

Where W_2 Weight of sediments

W_1 weight of dry sample

Swelling index

A standard method described by Ordu , & Onyemelukwe, 2018 was adopted and modified. A 3.0 g quantity of *Vigna subterranea* starch was transferred into a scrupulously dry 50 ml graduated cylinder and was gently leveled by tapping for about 20 times. The volume was recorded followed by the introduction of 30 ml of distilled water. The cylinder and its content were gently swirled manually at 180°C and left undisturbed for 1 hour. The new volume was noted and recorded. The swelling indices determined by the relation;

$$SI = \frac{Vf}{Vi} \text{ ..... (3)}$$

V_f is the final measured volume of sample in the graduated cylinder

$V_{i\ is}$ Initial measured volume of sample in the graduated cylinder

Determination of starch particle size, shape and size distribution

Shape, surface features, mean diameter and size distribution of *Vigna subterranea* starch granules were examined, and measured using a light microscope (AMScope 5.0, USA). A quantity of 0.05 gram of test starch sample was placed on a glass slide and viewed under the light microscope with a magnification or x100 to check the particle configuration and their diameter (Adebowale, & Lawal, 2003). The analysis of particle size was done with microscopy and the application of its software. The mean particle size was calculated from randomly selected starch granules

Thermal behavior evaluations

‘’Thermal characteristics of starch sample were studied by using differential scanning calorimeter (PerkinElmer, USA) equipped with a thermal analysis station (Krueger *et al*, 1987)The onset T_O, Peak (T_p), conclusion (T_c) temperatures and enthalpies of gelatinization (ΔH) were obtained from the thermograms.

Evaluation of starch crystallinity

Powder X-Ray diffractometry was done to evaluate the starches' polymorphism, both native and modified form (Zobel H.F, 1998). The crystallinity index was calculated by Segal's method as,

Crystallinity index CrI (%) = $\frac{Ic-Ia}{Ic}$ x 100 ----------(4)

Where Ic represents the intensity of the main crystalline peak (Leach et al, 1959)

Ia is the amorphous background intensity.

Assessment of emulsion capability

An established method of Omojola *et al*, (2010) was adopted. Two-gram quantity of the *Vigna subterranea* starch was mixed in 25 ml of distilled water with the aid of a vortex mixer (Scientific Industries Vortex Geni 2) for 30 s. followed by the addition of 25 ml of sunflower oil. The mixture was centrifuged at 1,600 rpm for five minutes. Emulsion capacity was calculated as the amount of oil retained per gram of sample.

Emulsion capacity (ml/g) = $\frac{V1-V2}{2}$ ---------- (5)

Where V_1 is the volume of oil added (ml)

V_2 is volume of oil decanted after centrifugation (ml)

Drug-excipient compatibility studies

Fourier Transform Infra-Red (FTIR) analysis

Three batches of drug-excipient mixtures in a 1:1 ratio was prepared and tested. The batches were stored at room temperature in a dry environment for four weeks while corresponding admixtures were prepared with 5% moisture added and stored at the same temperature. Another batch was stored at elevated temperature and humidity (40 ºC/ 75% RH) FTIR spectroscopy was employed to investigate the compatibility between pure diclofenac sodium and the excipients (native and annealed starches). FTIR spectra of diclofenac sodium, starch samples, emulsifying wax, and their physical mixtures were recorded and compared to detect any significant changes in the characteristic absorption band pointing towards drug-excipient interaction. This was done for all the batches using transmittance mode, A.

Preparation of topical diclofenac sodium 1% w/w cream

Method described by Chime *et al* (2013 was used in the formulation of diclofenac topical cream with slight modification. Oil and aqueous phases were prepared separately. The oil phase containing oily ingredients was heated to about 70ºC while the aqueous phase containing the dissolved preservatives and other water-soluble components were heated to the same temperature. The oily phase was gradually incorporated into the aqueous phase with continuous stirring. Diclofenac sodium cream was incorporated and the cream was allowed to cool at room temperature. Diclofenac sodium creams were prepared using starch- based Pickering stabilization (with both native and annealed starches) and compared with emulsifying wax-based formulation.

Evaluation of diclofenac cream formulation properties

The prepared creams were evaluated for appearance, texture, homogeneity, pH, viscosity, spreadability, globule size, and emulsion stability, and content of active pharmaceutical ingredients using standard

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pharmaceutical procedures.

In vitro drug release study

The release of the optimized topical diclofenac sodium cream, *in vitro,* was systematically investigated using cellulose membrane diffusion across semi-permeable biological barrier with PBS, 500 ml as a dissolution medium (Kenechukwu *et al*, 2018) The cumulative amount of diclofenac sodium recovered in the receptor medium at predetermined time intervals was used to quantify drug release from the cream formulations. The release study was conducted under controlled thermal and hydrodynamic conditions hot plate magnetic stirrer at a temperature of 37° +/- 0.2° C and rotation speed of 100 rpm as previously described (Barkin R, 2015). A measured quantity of each cream formulation, 0.005 g, was accurately weighed and enclosed within a dialysis membrane possessing a molecular weight cut-off of 6000-8000 Da, (Breda, The Netherlands). The loaded membrane securely sealed with a heat resistant thread and subsequently placed in the dissolution medium. Aliquots of 5 ml were withdrawn from the release medium at predetermined time interval, (0, 0.16, 0.5, 1, 2 , 3, 4 , 5 , and 6 hour) and replaced with 5 ml of freshly prepared PBS to maintain sink condition.(Momoh *et al*, 2013) To monitor the temporal release profile, the absorbance of the aliquot was taken in ultraviolet spectrophotometer (6405, JENWAY, UK) at 290 nm wavelength. Amount of released drug per sampling point was determined from a pre-validated calibration curve. The cumulative percentage drug release was determined using the following relationship:

Cumulative Diclofenac sodium release rate

$$= \frac{Cummulative\ anount\ of\ diclofenac\ sodium\ cream\ released}{Initial\ amount\ of\ diclofenac\ sodium} \text{ x } 100\% \text{ ---------- (6)}$$

Analysis of drug release kinetic, and mechanism

The *in vitro* release data were fitted into various established drug release kinetic models, (Costa & Lobo, 2001) including, zero order, first order, Higuchi and Korsmeyer- Peppas to study the kinetics and mechanisms of release.(Wojcick- Pastuszka *et al*, 2019) The best fitting model the release data based on correlation coefficient (R^2) was taken to be the release kinetics of the diclofenac sodium creams. The release mechanism was gotten by the gradient, n (release exponent), of the graph of Korsmeyer- Peppas model. The magnitude n, was used to infer the dominant release mechanism.

Membrane diffusion study

The extent of diclofenac sodium diffusion across the cellulose membrane was evaluated by determining the cumulative amount of drug diffused over time.

RESULTS AND DISCUSSIONS

Effects of annealing on the physicochemical properties of *Vigna subterranea* starch

The physicochemical properties of the native and annealed starches were assessed to determine the impact of annealing on their functional characteristics and pharmaceutical suitability. The results of these analyses are presented in Table I.

Table I: Some physicochemical properties of native (BST Native) and annealed *Vigna subterranea* starch (BST)

Parameter	Physicochemical properties	
	Native BST	BST
pH	6.9	5.9

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Hydration capacity	3.4	2.5
Wettability (%)	50.0	55.0
Swelling index	0..61	1,3
Mean particle size (μm) ±SD	19.67 ± 1.19	23.32 ± 3.01
Emulsion capacity (ml/g)	1.7	0.2
Crystallinity index (%)	64	66
Gelatinization peak temperature (ºC)	80	85
Viscosity of 2% starch dispersion	22.0	29.0

Table I, shows that annealing produced modified starches with improved structural integrity, increased crystalline perfection and enhanced functional performance towards its use as stabilizer. The increased crystallinity index observed following annealing may be attributed to enhanced molecular mobility and reorganization of starch chains under sub-gelatinization conditions. This facilitates improved alignment and packing of amylopectin chains into more ordered double helical structures. Annealing also decreased the hydration capacity. This is in keeping with the reported finding of Adebowale *et al*, (2011) where it was showed that annealing decreased swelling power and reduced hydration capacity of starch granules due to stronger molecular organization and increased crystallinity. Annealing treatment was also found to increase the wettability of the starch samples. This is consistent with a previously reported work by Wiacek A (2015) where it was observed that there were changes in contact angle of modified starch film. Annealing also had a statistically significant ($p<0.05$) impact on capacities of the starches to form emulsions. This is also in keeping with Folade and Ayetigbo (2015). The starch molecules demonstrated increase in the viscosities of 2% dispersions. This is because the starches had high wettability, which means the water penetrates granules more easily making granules to swell more which in turns will manifest as increase in viscosity. Annealing treatment significantly ($p<0.05$) altered the starch granules diameters. These happened because, during annealing, water penetrates the amorphous region of the starch granule. This resulted in internal molecular rearrangements and relaxation of chain and still keeping the external shape intact. These results are in keeping with the findings of Fonseca *et al* (2022**).** Particle size increased with annealing and this affects viscosity, spreadability, skin feel and how the starch interacts with oil and water. ($p<0.05$). Table I also shows the effects of annealing on the thermal properties of starch samples. Changes in polymorphic arrangements after annealing treatment can affect water absorption, swelling behaviour, viscosity and thermal stability. Evaluating the polymeric pattern will help determine if the annealing treatment preserved or improved the structural organisation of the starch granule which are important in ensuring consistency, compatibility and effectiveness in pharmaceutical formulations. In starch, annealing relaxes double helixes, break weak crystalline domain and increase heterogenicity in short range resulting in broader peaks. (Alvani e*t al*, 2014) This suggests that annealing promoted molecular reorganization and homogenization. Thus, there will be controlled drug release and improved rheological stability. Polymorphic nature and crystallinity index of starch are key structural attributes that influence its physicochemical and functional behaviour in pharmaceutical formulation systems. The balance between crystalline (ordered), and amorphous (disordered) regions, affect characteristics such as swelling, solubility, thermal stability and interactions with other formulation components.

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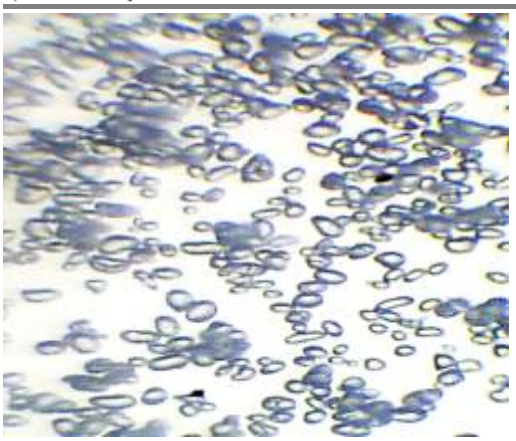
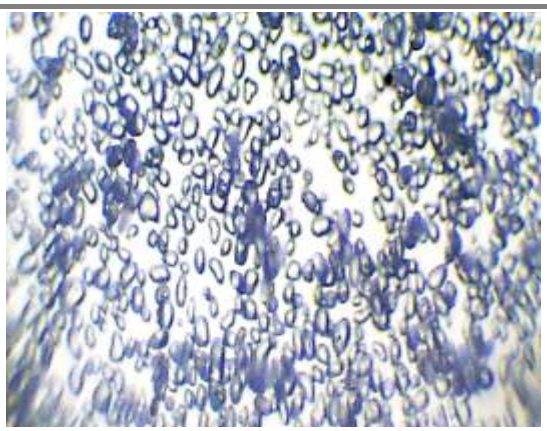


Native BST



BST

Fig I and II: Photomicrographs of native *Vigna subterranea* starch (Native BST) and annealed *Vigna subterranea* starch (BST)

As shown in Fig 1 and II, the starch granules largely retained their native shapes, confirming that annealing did not cause gelatinization or rupture of granules. Morphological features of starch play an important role in determining its functional and pharmaceutical properties. Granule shape, size, surface characteristics and arrangement can affect water absorption, swelling capacity, viscosity, and the interaction with other excipients present in the topical cream formulation. This also determines their efficiency as stabilizers in Pickering emulsions, especially, the consistency and stability of the formulation. Additionally, starches with predominantly spherical or oval –shaped granules exhibits superior interfacial adsorption due to their ability to pack closely and uniformly around oil droplets. Starch granules have been classed as large (> 25 µm), medium (10-25 µm), small (5-10 µm), and very small (≤ 5µm). (Loden M, 2003) Smaller particles increase Brownian motion and slow sedimentation. *Vigna subterranea* starch exhibits elliptical shaped granules with smooth surfaces and the particle size ranged from 17.58µm- 23.73µm with mean of 19.662 µm meaning that the particle sizes are large with significantly reduced surface area.

Drug-excipient compatibility

The physical mixtures of drugs and excipient remained stable throughout the observation period suggesting that there was no incompatibility. FTIR spectra of diclofenac sodium, starches, and emulsifying wax were overlaid to enable direct visual assessment of characteristic absorption band, peak shifts, disappearance, broadening, or emergence of new peaks. The FTIR spectra overlays are presented in Figs III-V

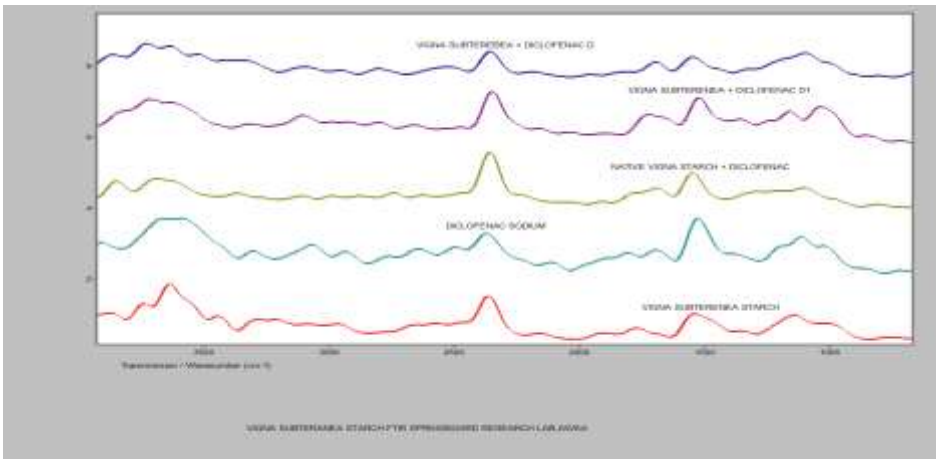


Fig III: Over lay of FTIR spectra of Diclofenac sodium, *Vigna subterranea* starch and 1:1 mixtures of Diclofenac sodium and *Vigna subterranea* starch samples (D), and another 1;1 mixture containing 5% moisture (D1)and kept 25°C, and at 40°C and 75% RH for four weeks.

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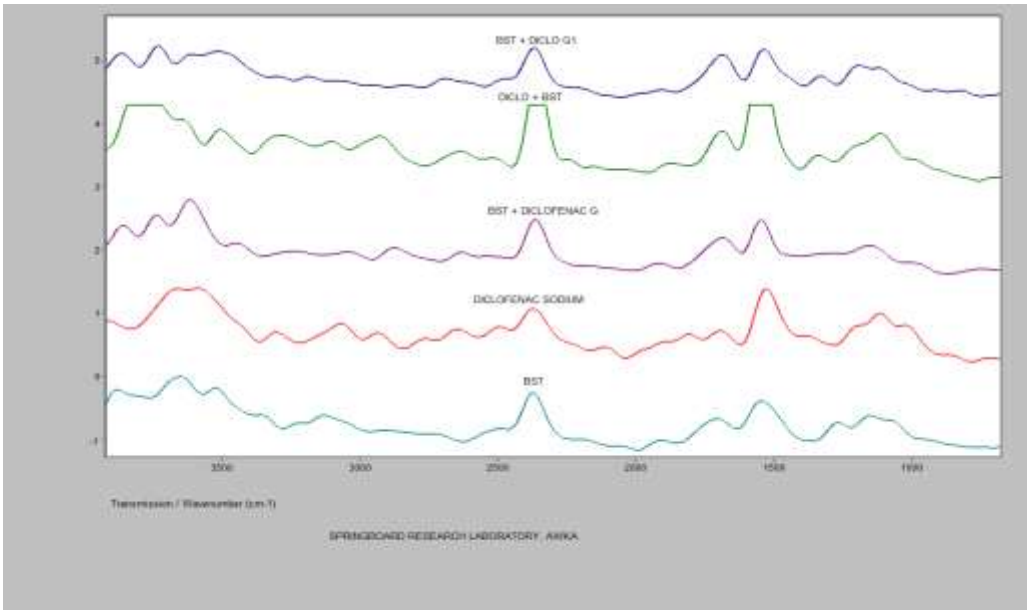

Fig IV: Over lay of FTIR spectra of Diclofenac sodium, Annealed *Vigna subterranea* starch and 1:1 mixtures of Diclofenac sodium and Annealed *Vigna subterranea* starch samples (G), and another 1;1 mixture containing 5% moisture (G1) stored at temperature of 25°C, and at 40°C and 75% RH for four weeks RH for four weeks.

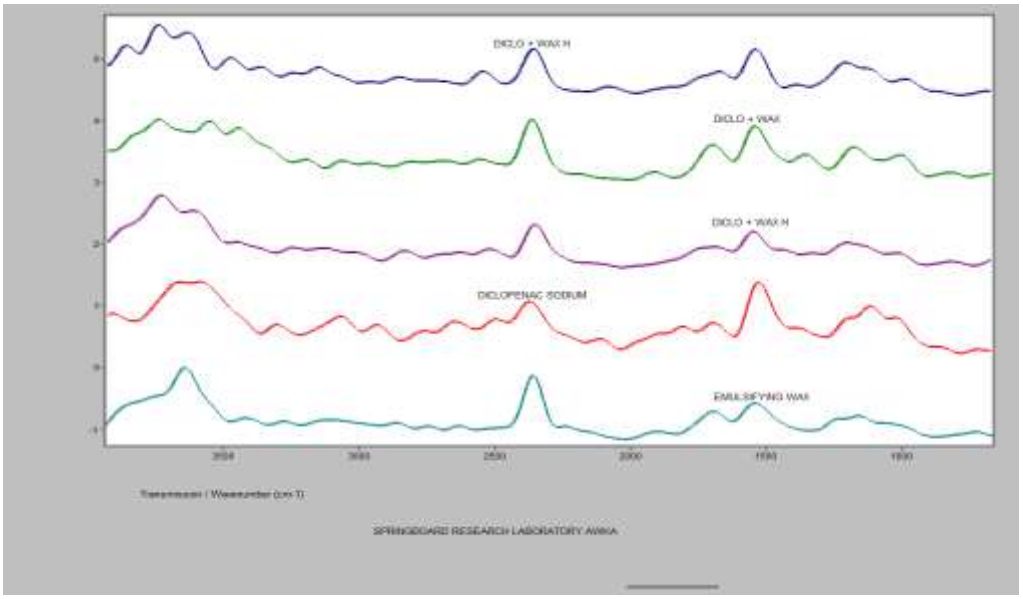

Fig V: Over lay of FTIR spectra of Diclofenac sodium, Emulsifying wax, 1:1 mixtures of Diclofenac sodium and Emulsifying wax samples (H) , and another 1:1 mixture containing 5% moisture (H1) stored at temperature of 25°C, and at 40°C and 75% RH for four weeks

In Fig III, The FTIR overlay confirms that diclofenac sodium is chemically compatible with native *Vigna subterranea* starch. The retention of characteristic functional group peaks and the absence of new absorption bands indicate that they are compatible. There were slight peak broadening and minor intensity variations seen in the hydroxyl stretching region (about 3400 cm^{-1}) and fingerprint region (approximately 1150-1020 cm^{-1}), in the 1:1 mixture of diclofenac sodium and *Vigna subterranea* starch. These changes are as a result of physical interaction such as hydrogen bonding and molecular association. The FTIR analysis in Fig IV shows that the characteristic functional groups of both diclofenac sodium at 1600, 1570 and 1450 cm^{-1} and annealed *Vigna subterranea* at 3200 – 3400, 1150- 1000 cm^{-1} were retained in the combined spectra. The absence of new absorption bands or disappearance of major peaks confirms chemical compatibility between diclofenac sodium and annealed *Vigna subterranea*. Minor shifts observed in the hydroxyl stretching region may be attributed to physical interactions such as hydrogen bonding. In the overlay spectra in Fig V, all major characteristic peaks of diclofenac sodium were retained. Including the band at approximately 3400 cm cm^{-1}, 1570 cm^{-1}, and

1500cm^{-1}, alongside emulsifying wax absorption band at approximately 2920 cm^{-1}, 2850cm^{-1}, and 1735cm^{-1}. Characteristic peaks were retained and no new peaks were formed. Therefore, no chemical incompatibility existed between diclofenac sodium and emulsifying wax.

Formulation of Diclofenac topical cream

Table II: Formulation composition of 100g of 1% (w/w) diclofenac sodium topical cream

Composition (%)	F1	F2	F3	F4	F9	F11
Diclofenac sodium	1.0	1.0	1.0	1.0	1.0	1.0
Emulsifying wax	-	-	-	-	-	7.5
Native BST	-	-	-	-	7.5	-
BST	1.0	2.5	5.0	7.5	-	-
Emulsifier	10.0	10.0	10.0	10.0	10.0	10.0
Fixed oil	5	5.0	5.0	5.0	5.0	5.0
Preservative	0.15	0.15	0.15	0.15	0.15	0.15
TEA	1.0	1.0	1.0	1.0	1.0	1.0
Solubilizer	10.0	10.0	10.0	10.0	10.0	10.0
Deionizer	100	100	100	100	100	100

Table II shows that the formulations differed primarily in the type of stabilizer employed, (with native *Vigna subterranea* starch, annealed *Vigna subterranea* starch, and emulsifying wax), while all other excipients and drug concentration were kept constant. This design ensured that any observed differences in physicochemical properties and invitro drug release could be attributed to the nature of the stabilizer rather than variations in the formulation composition.

Organoleptic, mechanical, and physical characteristics of the formulated creams

Sensory evaluations of the creams were carried out in order to ensure products are aesthetically acceptable as it will ensure acceptability by patients and compliance. All the creams were oil-in-water, non- greasy, white in colour, odourless and had smooth texture. They were homogenous with no sign of phase separation even after centrifugation. The physical and mechanical properties of the formulated creams were assessed to evaluate their quality, stability, and performance. The results of the evaluations are presented in table III.

Table III: Properties of the formulated diclofenac sodium 1 % topical creams

Formulation batch	Mean globule size (µm) ± SD	PH	Mean Drug content (%)	Spreadability (%)	*Invitro* occlusivity	
					24hr	**48 hr**
F1	51.36 ± 0.03	7.3	93.0	381	20.48	17.30
F2	43.37± 1.31	7.3	101.0	328	24.09	20.51
F3	43.37± 2.06	7.5	102.0	368	21.69	17.95
F4	41.86± 1.19	7.7	95.0	360	25.30	24.36
F9	50.41± 3.18	7.8	89.66	320	26.50	24.36
F11	42.70± 0.96	7.4	93.7	370	37.30	37.20

From Table III, the pH of the formulated creams was from 7.3 to 7.8 which are in line with some formulation reports. (Manian et al, 2022) pH values of the creams were within acceptable range for preparation intended for topical use. (Walters & Roberts, 2002) The slight variations in pH among the formulations may be attributed to the differences in the type and concentration of the stabilizers used in the cream base. Moreover, the USPNF revision notice for diclofenac had it that topical diclofenac must not necessarily have a particular pH value as long as the pH value is near neutrality (USP convention, 2021) (diclofenac topical gel- access data.fda.gov). The spreadability values ranged from 320 to 381%. This is in line with the work published by Ahmed Moglad et al. (2021). As shown in table III, Variation in spreadability among the formulations reflects differences in

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viscosity and internal consistency resulting from the type and concentration of the polymeric base used. Knowledge of spreadability helps to ascertain uniform dose and distribution of the creams upon application to the skin. Higher spreadability values indicate easier and more uniform application to the skin surface. All formulations displayed spreadability within an acceptable range for topical semi solid preparations, confirming good mechanical and rheological characteristics suitable for effective dermal application. This also ensures good patient compliance and ease of use. The content of API for all the diclofenac cream formulations ranged from 93.0% to 102% and was within BP specification (British Pharmacopoeia, 2009). The occlusivity values obtained indicate that the oil -in-water cream formulations provided moderate occlusive properties. An occlusive cream is meant to enhance the skin water retention and inhibit trans epidermal moisture loss by formation of thin film upon skin application. (Loden M, 2003) This ensures good penetration of drug via opening of corneocyte's restricted channels. (Nnamani *et al*, 2021)

In vitro drug release of optimized formulations

The invitro drug release profiles of the formulated creams were evaluated by plotting the cumulative percentage of drug released against time. This enabled the comparison of the three formulations and determination of the influence of annealed starch on the release behaviour of diclofenac. The cumulative drug release profiles are presented in Fig VI

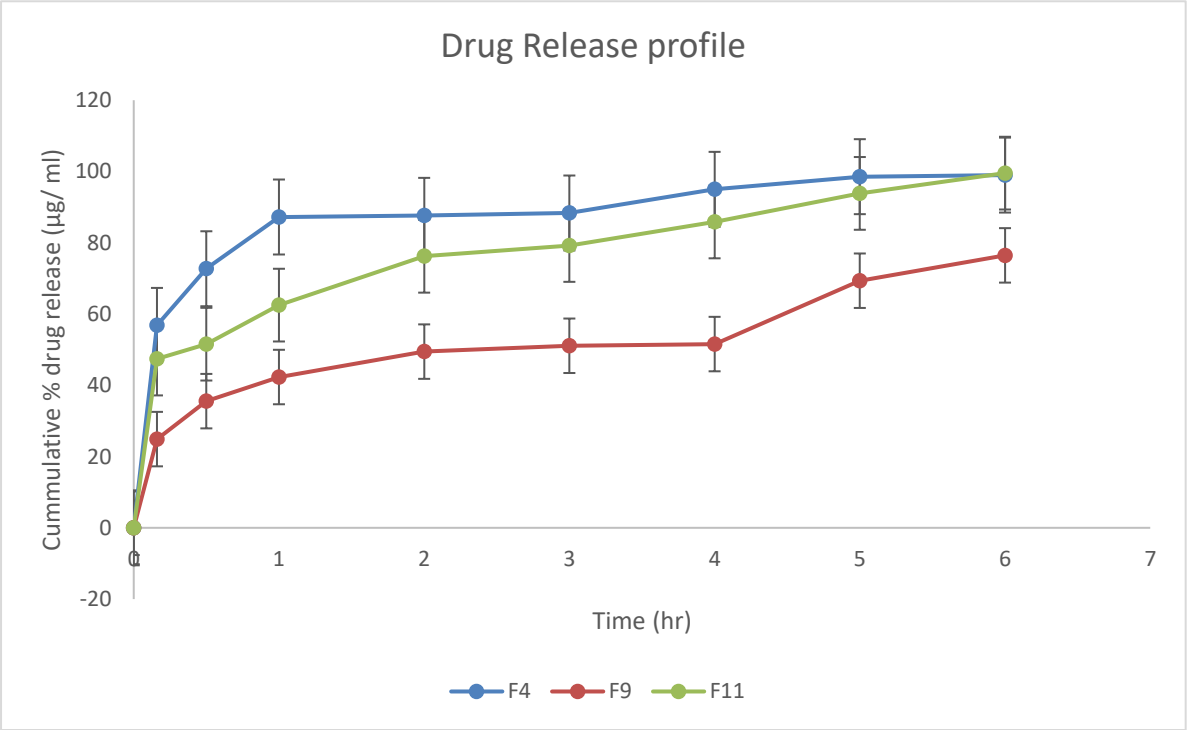

Fig VI: Drug release profile of the optimised formulations

In Fig VI, F4 exhibits a pronounced initial burst with most of the drug released within the early sampling period, followed by a plateau. This rapid release could be due to smaller globule sizes that may have exposed the drug to a larger surface area. F11 exhibited a more gradual release than F4 while still achieving a high cumulative release by the end of the study period. F9 demonstrated the slowest and most controlled release throughout the study with the lowest cumulative release at the final time point. The cream matrix in F9 retained the drug more effectively, providing controlled release. The onset of action being slower shows that the formulation is capable of maintaining drug levels for a longer period.

Drug Release kinetics, and mechanism

Understanding the mechanism and rate at which API's are released are essential as this helps to predict *in vivo* performance and optimizing formulation design for desired therapeutic outcomes.

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Table IV: Release kinetics and mechanism of release.

Formulation batch	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer Peppas	
				R^2	n
F4	0.684	0.802	0.793	0.879	0.14
F9	0.796	0.778	0.874	0.944	0.25
F11	0.951	0.807	0.989	0.965	0.21

Table IV shows the kinetics and mechanisms of diclofenac sodium release from the optimized topical cream preparations. Drug release is best described by Higuchi kinetic model for all the formulations. F11 shows the highest and best fit (R^2 = 0.989) indicating a diffusion-controlled release from a matrix system. The Korsmeyer-Peppas n values (≤ 0.45) confirm Fickian diffusion as the dominant release mechanism, which is in keeping with many reported topical and transdermal formulations. (Rahul et al, 2016; Qadir *et al*, 2024; Prasanth & Sharma, 2022)

Drug release Parameters

Drug release parameters helps to know if the excipients are performing as intended. This directly affect its safety, efficacy, and quality. It is desired that a drug be released at the right rate to achieve effective blood concentration.

Table V: Summary of *in vitro* drug release performance of the diclofenac topical cream formulations.

Formulation batch	AUC (%)	Release efficiency (%)	Mean dissolution time, MDT (hr)
F4	527.58	87.93	0.67
F9	313.42	52.24	1.33
F11	465.22	77.54	2.00

Table V summaries the invitro drug release performance of the optimized diclofenac sodium cream formulations. The area under curve, AUC, reflects the total amount of drug release throughout the study period, while the release efficiency represents the percentage of the maximum possible release achieved over the same period. Mean dissolution time, MDT, is the average time required for the drug to be released from the formulation. Among the formulations, F4 exhibited the highest AUC (527.58), and release efficiency (87.93%) indicating that it provided the greatest drug release. The lowest MDT (0.67h) further suggests that diclofenac sodium was released more rapidly from F4 than from the other formulations. This may be attributed to the globule sizes of the F4 which are smaller and provided a higher surface area for drug diffusion. F9 on the other hand, showed the lowest AUC |(313.42) and release efficiency (52.24%) indicating the least cumulative drug release during the experimental period.. Its MDT of 1.33h suggests a slower release than F4, implying greater resistance of drug diffusion, possibly due to the large globule sizes which made for a more compact microstructure. F11 demonstrated intermediate release performance, with an AUC of 465.22 and release efficiency of 77.54%. Interestingly, despite releasing more drug, than F9, F11 had the highest MDT (2.00 hours), indicating that drug release occurred gradually over time. These points to a more sustained release profile which may be of advantage when prolonged topical drug availability is desired.

Comparative performance of the formulations

The performances of the starch- based Pickering and emulsifying wax- based diclofenac sodium creams were assessed by comparing their physicochemical characteristics and invitro drug release behavior. All formulations produced pharmaceutically acceptable creams with desirable appearance. Analysis of variance revealed a statistically significant difference ($p<0.05$) among formulations at different time points, indicating the drug release profile were meaningfully affected by formulation composition. The release efficiency differed significantly among the formulations (One- way ANOVA $p< 0.05$). The order of release performance based on release efficiency and AUC and as also shown in Fig VI is F4 >F11> F9 whereas the order of MDT was

F11>F9> F4. So, F4 was the fastest and most efficient drug releasing formulation, while, F11 provided the most prolonged release, and F9 exhibited the slowest and least efficient release.

CONCLUSION

There were no differences in appearance of the formulations, showing that both starch-based Pickering systems and emulsifying wax systems were capable of producing pharmaceutically acceptable topical creams. Annealing changed the functional properties of starch, altered the creams microstructure and drug release/ diffusion. The annealed starch-based Pickering stabilizer effectively modulated diclofenac sodium release, demonstrating its potential as a natural alternative to emulsifying wax for stabilizer in topical diclofenac sodium creams. Annealing did not only enhance release, but also enhanced subsequent diffusion across the membrane. Therefore, it can be used to tailor the release kinetics of diclofenac in topical formulations. In excipient selection, the choice between F4 and F11 would depend on the therapeutic objectives, either rapid onset of action or sustained release.

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REFERENCES

1. Adebowale, K.O. and Lawal, O.S. (2003) Functional Properties and Retrogradation Behaviour of Native and Chemically Modified Starch of Mucuna Bean (Mucuna pruriens). *Journal of the Science of Food and Agriculture*, 83, 1541-1546 http://dx.doi.org/10.1002/jsfa.1569
2. Adebowale, K. O., Olu-Owolabi, B. I., Olayinka, O. O., and Lawal, O. S. (2005). Effect of heat-moisture treatment and annealing on the physicochemical properties of red sorghum starch. *African Journal of Biotechnology*, 4(9), 928–933.
3. Ahmed M, Fatima F, Anwer M et al(2021). Formulation and in vitro evaluation of topical nanosponge- based gel containing butenafine for the treatment of fungal skin infection. *Saudi Pharm.J.* 29, 467- 477.
4. Almukainzi M, Alotaibi L, Abdulwahab A, Albukhary, N, and El. Mahdy A.M. (2022). Quality and safetyinvestigation of commonly used topical cosmetic preparations. *Scientific Reports,* 12 (1), 18299.
5. Alvani K.O, Qi X, Tester R.F, and Snape C.E (2011). Physico-chemical properties of potato starches. *Food Chemistry*, 125 (3), 958-965.
6. Anida M.M. Gomes A.MM, Mendes da Silva C.E, and Ricardo N.M.P.S (2005). Effects of annealing on the physicochemical properties of fermented cassava starch (Polvilho azedo). *Carbohydrate Polymers*, 60 (1), 1-6.
7. Aulton M.E, and Taylor K.M.G (2017). Aulton's pharmaceutics. The design and manufacture of medicines (5th ed.). Elsevir
8. Badruddoza AZM, Yeoh T, Shah JC, Walsh T (2023). Assessing and predicting physical stability of emulsion- based topical semisolid products: A review. *Journal of pharmaceutical Sciences*: 112(7): 1772-1793.
9. Binks B.P (2002). Particles as surfactants- similarities and differences. *Current Opinions in Colloid and Interface Science,* 7(1-2), 21-41.
10. British Pharmacopoeia Commission. British Pharmacopoeia (2009). The commission Office, London, vol 111, pp6578-658
11. Chime S.A, and Onyishi V.I(2013). Lipid-based drug delivery systems (LDDS): Recent advances and applications of lipids in drug delivery. *African Journal of Pharmacy and Pharmacology*, 7(48), 3034-3059.
12. Compart J, Singh A, Fettke J, and Apriyanto A (2023). Customizing starch properties: A review of starch modifications and their applications. Polymers, 15(16), 3491.

13. Costa P, Lobo J.M.S (2001). Modelling and comparison of dissolution profiles. *European Journal of Pharmaceutical Sciences,* 13(2), 123-133.
14. European Medicines Agency (2018). Guideline on the clinical evaluation of cosmetic products.
15. Falade K.O and Ayetigbo O.E (2015). Effects of annealing, acid hydrolysis and citric acid modifications on physical and functional properties of starch from four yam (*Dioscorea* spp.)cultivars. *Food Hydrocolloids*, 43, 529-539.
16. Fonseca L.M, El Halal S.L.M, Dias A.R.G, Zavareze E.R (2021) Physical modification of starch by heat-moisture treatment and annealing and their applications: A review. *Carbohydrate Polymers*; 274: 118665
17. Iliopoulos F, Goh CF, Haque T, Rahma A, Lane ME (2022). Dermal delivery of diclofenac sodium- *in vitro* and *in vivo* studies. *Pharmaceutics*.14(10): 2016.
18. Jin X, Imran M, Mohammed Y. (2022) Topical semisolid products- Understanding the impact of metamorphosis on skin penetration and physicochemical properties. *Pharmaceutics*: 14(11): 2487.
19. Kenechukwu F.C, Attama A.A, Ibezim E.C, and Nnamani P.O, Umeyor C.E, Uronnachi E.M, Momoh M.A, Akpa P.A, and Ozioko A.C (2018). Novel intravaginal drug delivery system based on molecularly PEGylated lipid matrixes for improved antifungal activity of miconazole nitrate. *BioMed Research International,* 3714329.
20. Krueger B.R, Knuston C.A, Inglett G.E and Walker C.E (1987). A differential scanning calorimetry study on the effect of annealing on gelatinization behaviour of corn starch. Journal of Food Science, 52 (3), 715-718.
21. Leach H.W, McCowen L.D, and Schoch T.J(1959). Structure of starch granule.I. Swelling and solubility patterns of various starches. Cereal Chemistry, 36(6),534-544.
22. Mahfouzi M, Zhang H, Haoran L, McClements D.J, and Hadidi M.(2025). Starch-based particles as stabilizers for pickering emulsions: Modofication, characteristics, stabilization, and applications. *Critical Reviews In Food Science and Nutrition, 65*(10), 1841-1856.
23. Manna S, Dhanalakshmi D, Bhowmik M, Jana S, and Jana S(2022). Callulose derivative- based bioadhesive blend patch for transdermal drug delivery. Release kinetics analysis. *Frontiers in Materials*,9,835507.
24. Marto J, Duarte A, Simoes S, Goncalves LM, Gouveia L.F, Almedia A.J, and Ribeiro H.M (2019). Starch-based pickering emulsions as platforms for topical antibiotic delivery: *In vitro* and *in vivo* studies. *Polymers*, 11(1), 108.
25. Marto J, Gouveia L, JorgevI.M, Duarte A, Goncalves L.M, Silva SMC, Antunes F, Pias A.A.C.C, Olivera E, Almeida A.J and Ribeiro H.M(2015) Starch- based pickering emulsions for topical drug delivery: A QbD approach. *Colloids Surf B Biointerfaces*, 135, 183-192.
26. Maru A.D and Lahoti S.R. (2018). Formulation and evaluation of moisturizing cream containing sunflower wax. *International Journal of Pharmacy and Pharmaceutical sciences*, 10(11), 54-59.
27. Momoh M.A, Kenechukwu F.C, and Attama A.A.(2013). Formulation and evaluation of novel solid lipid microparticles as a sustained release system for the delivery of metformin hydrochloride. *Drug Delivery,20(3-4),* 102-111.
28. Nnamani P.O, Ugwu A.A, Nnadi O.H, Kenechukwu F.C, Oforkansi K.C, Attama A.A and Lehr C. (2021). Formulation and evaluation of transdermal nanogel for delivery of arthemether. *Drug Delivery and Transitional Research*, 11, 1655-1674.
29. Nwaogazie F.O, Akinwande B.A, Adebo O.A and Oyeyinka S.A (2024). Application of Annealed Bambara starch as a stabilizer in ice cream production. *Journal of Macromol*. 4(3)10, 533-543.
30. Oladele A.K, and Aina J.O (2007). Chemical composition and functional properties of flour produced from two varieties of tigernuts (Cyperus esculentus). *African Journal of Biotechnology. 6(2), 2473-2476.*
31. Omojola M.O., Akinkunmi Y.O, Olufunsho K.O, Eghareva H.O, and Martins E.O (2010). Isolation and physicochemical characterization of cola starch*, African Journal of Food , Agriculture, Nutrition and Development, 10 (7*), 2884- 2900.
32. Ordu J.I and Onyemelukwe J.I (2018). Evaluation of starch from ginger and cassava as pharmaceutical tablet excipients. *Int J. LifeSci- Scientific Research*, 4(2), 1647- 1654.
33. Rahul S.S, and Praveen D. C (2016). Formulation and evaluation of glimepiride patches for transdermal drug delivery. *Journal of Biomedical and Pharmaceutical Research*, 5(6), 108-120

34. Salehi N., Mortazavi S.M., and Moghimi H (2022). Investigating the changes in cream properties following topical application and their influence on the product efficiency. *Iranian Journal of Pharmaceutical Research, 21(1),* e123946.
35. Shinoda K, and Lidman B (1987). Organised surfactant systems. *Microemulsions*. *Langmuir,* 3(1), 135- 149.
36. Tabosa M.A.C, Cordery S.F, White K.A.J, Bunge A.L, Guy R.H, Delgado- Charro M.B (2022). Skin pharmacokinetics of Diclofenac and co-delivered functional excipients. *International Journal of Pharmaceutics*. 614: 121469.
37. Qadir A, Jan S.U, Shoaib M.H *et al*. (2025). Formulation development and evaluation, in silico PBPK modelling and in vivo pharmacodynamic studies of clozapine matrix-type transdermal patches:. *Scientific Reports*, 15, 1204.
38. United state Pharmacopoeial convention (2021). Diclofenac sodium topical solution (2002)/USP Monograph. In United States Pharmacopeia- National Formulary (USP-NF).
39. United State Pharmacopoeia (2023). USP-NF, General chapter <1151> pharmaceutical dosage forms. Rockvile, MD, USA.
40. Walters K.A, and Roberts M.S (2002). Dermatolgic, cosmetic, and transdermal drug delivery systems. In Dermatologic and transdermal formulations. *CRC Press.*
41. Wiacek A.E,(2015). Effects of surface modification on starch biopolymer wettability. *Food Hydrocolloids*, 48, 228-237.
42. Wojcick-Pastuszka D, Krzak J, Macikowski B, Berkowski R, OsinskiB nd Musiat W (2019). Evaluation of the release kinetics using models including zero order, first order, Higuchi, and Korsmeyer-peppas. *Materials,* 12(8), Article 1202.
43. Zobel H.F (1998). Starch crystal transformations and their industrial importance. Starch/ Starke, 40 (1), 1-7.