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Original Research Article

Design and Evaluation Of Ibuprofen-Loaded Microspheres Using Acid-Thinned Sweet Potato Starch As A Co-Polymer For Controlled Release

Oluwamayowa O. Agho[1], Adebimpe R. Akinsipe[2], Eniola G. Babafemi[2], Adenike Okunlola[2]*

[1]*Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Lead City University, Ibadan, Nigeria*
[2]*Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, University of Ibadan, Ibadan, Nigeria*

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ABSTRACT

Microsphere formulations can control the delivery of drugs in a sustained manner using polymers as carriers. Combining indigenous sweet potato starch (SP) with commercial polymers such as sodium alginate and hydroxypropyl methylcellulose (HPMC) produces microspheres with improved properties, including drug entrapment and release. This study aims to explore the use of acid-thinned starch of SP as a more affordable, release-retarding copolymer in ibuprofen microspheres. The microspheres were prepared by the ionic gelation method using acid-thinned SP starch in combination with sodium alginate and HPMC at ratios 1.0:1.0:1.0, 1.5:1.0:0.5. 1.5:0.5.1.0, and at polymer: drug ratios 3.0:1.0; 4.0:1.0 and 6.0:1.0. The microspheres were characterized for morphology, swelling index, entrapment efficiency and dissolution time (t_{50}). A 3^2 factorial design was used to analyse the influence of polymer blend type and polymer: drug ratio on these properties. Spherical microspheres with size range of 0.56±0.03 to 0.92 ±0.09 mm was obtained. FT-IR analysis revealed ibuprofen was well entrapped with no incompatibility between the drug and the polymer blends. Entrapment efficiency ranged from 74.00±4.35 to 90.00±6.00 %. The time taken for 50% drug release (t_{50}) was 4.00±0.15 to 10.00±0.87 h. Polymer type and polymer: drug ratio had positive influence on size, entrapment and t_{50} ($p < 0.05$). Formulation F_9 containing starch: alginate: HPMC, 1.5:0.5:1.0, with polymer: drug ratio of 6.0:1.0, was the optimized formulation with acceptable particle size, swelling, highest entrapment, and the most sustained drug release. Acid-thinned sweet potato starch showed potential as a copolymer for controlled delivery of ibuprofen in microspheres.

Keywords: Acid hydrolysis, Factorial design, Ibuprofen, Microspheres, Sweet potato starch

Introduction

The long duration and high cost of drug discovery and development necessitate the need for the pharmaceutical industry to make the most of existing dosage forms of currently available drugs, with the aim of improving their safety, efficacy and cost effectiveness while enhancing patient compliance.[1] The ideal drug delivery system would be that, in which the drug is localized and controlled to improve efficacy, while minimizing toxicity. Factors such as the route of administration, drug release mechanism, polymer type and targeting ability are important in controlled release formulations.[2] The advancement of material science and pharmaceutical technology has led to the development of micro and nano drug formulations that accomplish controlled drug delivery. Owing to their precision, biocompatibility, reduced dosing frequency, reduced side effects, reproducible drug absorption and controlled dosing, microspheres are ideal drug delivery devices for controlled delivery to improve drug therapy.[3,4] Ibuprofen is a non-steroidal anti-inflammatory drug used for various chronic inflammatory diseases such as arthritis, primary dysmenorrhea, and fever.[5,6] The typical ibuprofen dose is 400 to 800 mg. Ibuprofen's conventional formulations are rapidly absorbed, with a drug elimination half-life of about 2-3 hours. As a result, the drug is given frequently (three or four times per day) to achieve effective plasma concentrations over a 24-hour period.[7] Controlled drug delivery is therefore required to reduce dose and dosing frequency, thereby improving patient compliance. Formulating ibuprofen in microspheres using appropriate polymers is a suitable technique for prolonging its release, reducing the frequency of administration, and the occurrence of side effects.

Sweet potato (SP) (*Ipomoea batatas* Lam) is an affordable indigenous crop that is cultivated extensively for its nourishing value in many parts of the world, including Nigeria.[8,9] Nigeria is the one of the highest producers of sweet potato in sub-Saharan, with an estimated annual production of 3.69 million metric.[8] The tuber has a relatively high percentage starch content of 58-76% and has shown potential as excipients in tablet formulations.[10] Acid-thinning (hydrolysis) randomly breaks α-1,4 and α-1,6 links in starch, shortening the polymeric chains. Acid thinning occurs in two stages: an initial stage where hydrolysis targets the amorphous regions of granules at a fast rate, and a later stage when hydrolysis occurs at a slower rate in the crystalline region.[11,12] Hydrolysis rate and starch modification depend on the ratio of amylose: amylopectin, size and shape of starch granules.[13,14] Acid treatment can decrease the molecular mass, increase crystallinity while affecting the gelling properties of some starch.[13,15] In a previous study, acid thinned sweet potato starch was found suitable in the design of starch-urea-borate polymer with potential as a hydrophobic polymer in drug formulations.[9] Being a natural product, incorporating starch can enhance the biocompatibility of microspheres. In addition, drug release can be improved, potentially resulting in a more sustained release profile.

Hydroxypropyl methylcellulose (HPMC) is a hydrophilic polymer that can form films useful for coating microspheres and other drug delivery devices. Due to its high hydrophilicity, HPMC can absorb and retain water, making it useful for drug delivery.[16, 17] The swelling capacity of

***Corresponding author. E mail: adenikeokunlola@gmail.com
Tel: +2348023351064

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HPMC can also enhance the drug-loading capacity of the microspheres. Sodium alginate has been used as a polymer to improve the ability of microspheres to adhere to mucosal surfaces, such as the intestinal lining, producing longer drug residence time at the target site. Crosslinking sodium alginate with chelating agents such as calcium chloride creates a matrix that controls drug release.[18] Acid-modified *Ipomoea batatas* starch is a relatively affordable and ecologically-friendly polymer that has improved physicochemical properties such as good flowability, high mechanical strength, modified hydrophobicity with surface roughness and increased surface area that can enhance the encapsulation.[19] Combining HPMC (hydroxypropyl methylcellulose), sodium alginate and starch allows for the formulation of microspheres ~~with improved~~ with improved mechanical strength, enhanced water absorption, better drug loading capacity, and sustained drug release properties. Thus, this research study aims to prepare microspheres of ibuprofen using acid modified sweet potato starch as a copolymer with sodium alginate and HPMC at different blend combinations and polymer: drug ratios.[9] A 3^2 full factorial design was used to determine the effects of independent variables polymer type and polymer: drug ratio on response variables particle size, swelling, entrapment efficiency and dissolution time (t_{50}).

Materials and Methods

Ibuprofen was obtained from Xunsua Ltd CAS# 15687-27-1 (China). Sodium Alginate was obtained from Minerals-water Ltd (United Kingdom). HPMC was from Tennesy Company, China. Calcium Chloride was obtained from Loba Chemie Pyt Ltd (India). Sweet potato tubers were obtained from local farmers (9WHW+2R7 Motunde Village, Ibadan, 200113, Oyo State, Nigeria).

Extraction of starch

Five kilogram (5 Kg) of sweet potato tubers were thoroughly washed to remove remnants of soil, washed with distilled water, peeled, and cut into small pieces. The cut tubers were milled into a fine paste using a laboratory mill, and then strained through a muslin cloth.[20] The filtrate was left to settle while the supernatant was decanted at 12-hour intervals, and the starch slurry was re-suspended in distilled water. Sodium metabisulphite was added in order to prevent color change due to oxidation.[20] The starch paste was collected after 72 hours and dried in a hot air oven at 50.0°C for 48.0 hours. The dried mass was pulverized using a laboratory blender and then screened through a mesh sieve of 250 micrometers size. The yield of starch (%w/w) was calculated from the ratio of the weight of dried starch to the weight of whole peeled tubers.

Modification of sweet potato starch by acid-hydrolysis

Native sweet potato starch (300g) was hydrolyzed by incubating the starch in 600 ml of a 6.0% HCl solution for 192.0 h without stirring at 27.0± 2.0°C. The suspension was neutralized with a 10.0% (w/v) NaOH solution (Okunlola, 2015), and the starch slurry was washed several times with distilled water before drying in a hot air oven at 40 C for 24.0h.[20,21] The starch was blended into powder using a laboratory blender and passed through a sieve with a mesh size of 125 micrometers.[22] The yield of acid-thinned sweet potato starch (%w/w) was calculated from the ratio of the weight of dried modified starch to the weight of dried native starch (300g).

Morphology of native and acid-thinned sweet potato starches

A scanning electron microscope was used to examine the morphology of the starches at an accelerating potential of 10 kV (Hitachi SU8030 FE-SEM Tokyo, Japan).[9,23]

FTIR analysis

The native and modified starches were analyzed using FTIR (Thermo Nicolet Nexus 870 Madison, WI, USA) in transmission mode, with at least 64 scans and 8 cm^{-1} resolutions in the spectral range 4000 cm^{-1}

Formulation of ibuprofen-loaded microspheres containing acid-thinned starch using the ionic gelation technique

Microspheres were prepared from a gel blend of acid-modified sweet potato starch, sodium alginate, and HPMC at ratios 1.0:1.0:1.0, 1.5:1.0:0.5. 1.5:0.5.1.0, respectively, to obtain a total polymer concentration of 3 %w/v. Appropriate quantity of the drug (1.0, 0.75, and 0.5g) was added to the polymer blend in order to obtain dispersions of polymer: drug ratios of 3.0:1.0; 4.0:1.0, and 6.0:1.0, respectively. To ensure homogeneity, the drug-loaded polymer solution was stirred continuously for 30.0 minutes with a magnetic stirrer.[20] The uniform solution obtained was then manually extruded into 500 mL of calcium chloride (10.0%w/w) in a 1-liter beaker using a syringe with a 21.0 G needle. This was done under constant stirring (500 rpm) at room temperature (27.0 ± 2.0°C). After curing for 15 min, the formed microspheres were collected, washed with distilled water, and then dried for 24.0 h in an oven at 40°C.[24] The total polymer concentration, concentration of crosslinking agent, needle size, dropping height, drop rate, and curing time were kept constant.

Characterization of ibuprofen-loaded microspheres

Percentage Yield

The percentage yield of the microspheres was calculated using the following equation.

$$Yield\ of\ microspheres\ = \frac{M}{Mo} x\ 100 \quad (1)$$

Where M = weight of microspheres

Mo = total weight of drug and polymers

Morphology

The size and shape of the microspheres were observed using a scanning electron microscope (Hitachi SU8030 FE-SEM Tokyo, Japan) at an accelerating potential of 5.0 kV.

FTIR analysis

Sodium alginate, HPMC, acid-thinned starch, pristine ibuprofen and ibuprofen-loaded microspheres were analyzed using FTIR in transmission mode (Thermo Nicolet Nexus 870 Madison, WI, USA). At least 64 scans with 8 cm^{-1} resolutions were recorded in the spectral range of 4000 cm^{-1}.[25]

Swelling Index

One milliliter of a bed of microspheres was immersed in phosphate buffer (pH 6.8) made up to 10.0 mL in a 10-mL measuring cylinder for 12 hours. The swelling index was calculated from the ratio of volume obtained after 12 hours to the original volume.[25]

Entrapment Efficiency

One hundred milligrams of microspheres were crushed, and suspended in 50.0 mL of pH 6.8 phosphate buffer for 24.0 h. The solution was filtered, diluted with buffer and analyzed using a UV/VIS spectrophotometer (Spectrum lab 752s UV-VIS spectrophotometer, No 752S12090, China) at 270 nm. The drug entrapment efficiency (E) was calculated using Equation 2:

$$E\ (\%) = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} x\ 100 \quad (2)$$

Drug release study

The paddle method was used to conduct *in vitro* dissolution studies. The paddle was rotated at 50 rpm in 900 mL of pH 6.8 phosphate buffer, which was kept at 37.0 ± 0.5°C. Samples (5.0 mL) were drawn at regular intervals and replaced with equal amounts of fresh medium. Using a UV spectrophotometer at 270 nm wavelength, the amount of ibuprofen released was measured (Spectrum lab 752s UV-VIS Spectrophotometer, No 752S12090, China).

All results are presented as mean ± standard deviation using three determinations.

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Factorial design

A full 3^2-factorial experimental design was used, with two factors at three levels. Table 1 below shows the nine possible combinations. Polymer type (X1) and polymer to drug ratio (X2) were the independent variables while the responses particle size, swelling index, entrapment efficiency, and dissolution time (t_{50}) were the dependent variables [20,26] The main effects (X1, X2) are the average results of changing one factor at a time from low to high value. The statistical software Minitab 22 Software USA (Minitab Inc., USA) was used to design the experiments. The data was analyzed using ANOVA at $\alpha_{0.\ 05..}$ The polynomial equations below were derived through multiple regression analysis of data:[27]

Size = 0.8865+ 0.07580 X1+0.03345 X2 - 0.02890 X1X2+ 0.02255 $X1^2$ - 0.003201 $X2^2$ (3)

Swelling = 1.692 - 0.1028 X1 + 0.2677 X2 - 0.02676 X1X2+0.1381 $X1^2$- 0.01931 $X2^2$ (4)

Entrapment = 9.192 + 0.3050X1 + 0.1801X2 +0.1047X1X2+0.1045$X1^2$ – 0.02268 $X2^2$ (5)

t_{50} = 2.587 - 0.1664 X1- 0.3739 X2+ 0.0460X1X2 - 0.05537 $X1^2$- 0.002398 $X2^2$ (6)

Table 1: The 3^2 factorial design showing formulation code, coded values, actual values and responses

Formulation	Coded values		Actual values		Size	Swelling Index	Entrapment	t_{50}
	X1	X2	Polymer blend (Starch: Alginate: HPMC)	Polymer: drug ratio	(mm)	(v/v)	(%)	(h)
F1	-1	-1	1.0:1.0:1.0	3:1	0.56 ± 0.03	2.25 ± 0.15	74.00 ± 4.35	4.00 ± 0.15
F2	-1	0	1.0:1.0:1.0	4:1	0.65 ± 0.05	3.50 ± 0.33	79.20 ± 5.00	6.00 ± 0.35
F3	-1	+1	1.0:1.0:1.0	6:1	0.77 ± 0.08	4.05 ± 0.22	83.90 ± 6.15	7.90 ± 0.67
F4	0	-1	1.5:1.0:0.5	3:1	0.79 ± 0.06	1.75 ± 0.09	84.60 ± 7.30	4.70 ± 0.25
F5	0	0	1.5:1.0:0.5	4:1	0.82 ± 0.07	2.00 ± 0.35	86.30 ± 5.00	6.30 ± 0.50
F6	0	+1	1.5:1.0:0.5	6:1	0.87 ± 0.09	3.70 ± 0.40	88.40 ± 9.10	8.50 ± 0.55
F7	+1	-1	1.5:0.5:1.0	3:1	0.85 ± 0.06	2.10 ± 0.05	85.30 ± 5.00	6.10 ± 0.48
F8	+1	0	1.5:0.5:1.0	4:1	0.88 ± 0.07	3.00 ± 0.23	89.40 ± 7.10	7.80 ± 0.56
F9	+1	+1	1.5:0.5:1.0	6:1	0.92 ± 0.09	4.00 ± 0.20	90.00 ± 6.00	10.00 ± 0.87

Results and Discussion

Characterization of native and acid-modified sweet potato starches: Yield, morphology and Fourier Transform Infra-red (FTIR) analysis

Sweet potato tubers gave a yield of 18.55%w/w of native starch, whereas the yield of the acid-modified sweet potato starch was 78.50%w/w.[22] The yield is the amount of acid-thinned starch produced divided by the amount of native starch used. This yield may vary according to the type of starch, the acid used, and the duration of the acid treatment. In general, studies have shown that acid thinning can result in a yield of approximately 80 to 100%.[28,29]

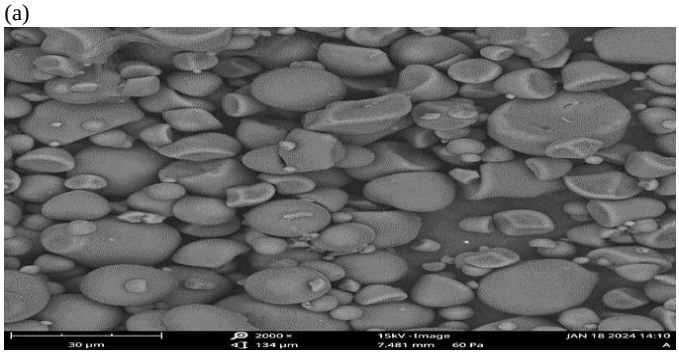
Figure 1 shows the scanning electron micrographs (SEM) of the native and acid-thinned sweet potato starches.[9] The micrographs revealed that the native starch granules were oval in shape, while the acid-modified starch showed irregularly shaped and aggregated granules. Acid-modification of the starch is expected to disrupt the semi-crystalline structure of the native starch granules due to the destruction of their helical structure by the process of acid-thinning, resulting in a more amorphous or less ordered structure.[9,30]

Figure 2 is the FTIR spectra of the native and acid-thinned sweet potato starches. The FTIR spectrum of acid-thinned starch was different from that of native form. While some peaks persisted, shifts in intensity and position indicated changes in chemical bonds and structure. Acid treatment weakened the intermolecular bonds within starch granules, resulting in a more amorphous structure and potentially altering the hydroxyl and C-H stretching regions in the modified starch's spectrum.[20] The sharp band at around 2900 to 2950 cm^{-1} corresponded to C-H stretching, with a slight decrease in intensity. The peaks around 1700 cm^{-1} that are related to carbonyl groups (C=O) indicated the formation of esters while bands related to C=C stretching in the anhydro glucose ring of starch showed altered intensity due to the acid modification.[31]

Characterization of ibuprofen-loaded microspheres

The method used to prepare microspheres affects their size, entrapment, and drug release characteristics.[32] The ionic gelation technique was used in this study because it offers several advantages for preparing microspheres, and these include its simplicity, low cost, and avoidance of the use of organic solvents. Furthermore, this method achieves high encapsulation efficiency and provides numerous functionalization options, increasing the versatility and potential for various applications.[33]

(a)



(b)

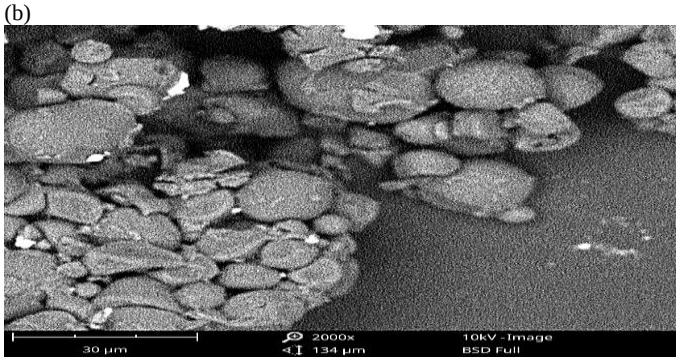


Figure 1: The Scanning Electron Micrographs (SEM) of (a) native and (b) acid-thinned sweet potato starches (mg 2000x), scale bar = 30 µm *SEM images revealed the acid-modified starch granules exhibited rougher, more porous, and aggregated surfaces compared to the smooth, discrete, and oval and polyhedral particles of the native starch.

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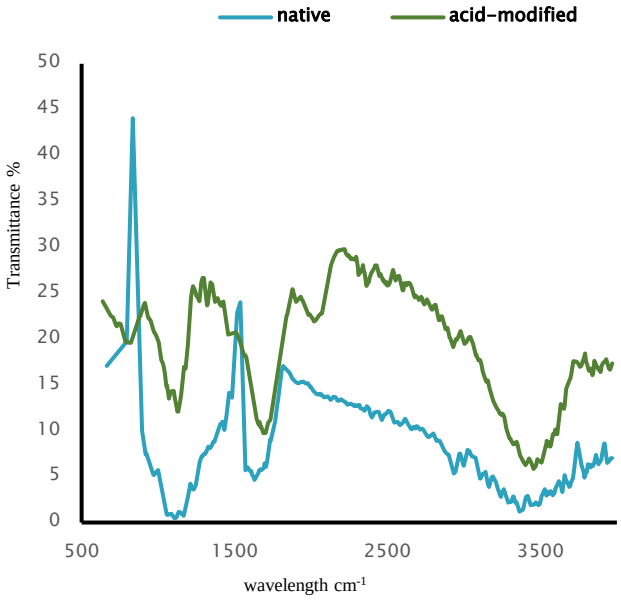

Figure 2: FTIR spectra of native and acid-thinned sweet potato starches

Morphology

The scanning electron microscope (SEM) images of ibuprofen microspheres in Figure 3 showed that the microspheres were spherical, with those containing higher amount of acid-thinned starch (F_4 to F_9) having larger sizes with rougher surfaces than those containing the other polymers in other batches at a ratio 1.0:1.0:1.0. (F_1 to F_3).[34] The range of size of the microspheres was from 0.56±0.03 to 0.92 ±0.09 mm as presented in Table 1. Increasing the amount of starch in the formulation generally yielded larger microspheres because the higher amount of the starch polymer increased the density of the polymer matrix and enhanced viscosity, making the microspheres more robust and less prone to shrinkage or deformation during the formation process.[20] The surface morphology revealed that the pores on the microspheres containing the polymers at ratios 1.0:1.0:1.0 (F_1 to F_3) were more prominent than in formulations containing higher ratio of starch to other polymers starch. The presence of pores, or small cavities, on the surface of microspheres can significantly impact their interactions with fluids. The pores usually allow fluids to penetrate the microspheres more easily, leading to a greater degree of swelling, which is important for drug release, since the swelling of microspheres can enhance the rate of drug release into the surrounding.[20,35,36]

FTIR Analysis

Figure 4 shows the FTIR spectra of the pure drug, sodium alginate, acid-thinned starch, HPMC and the drug-loaded microspheres. Ibuprofen typically showed the characteristic peaks of its functional groups, such as the carbonyl stretching vibration around 1700-1750 cm^{-1} and hydroxyl stretching vibrations around 2900-3000 cm^{-1}. The persistence of these peaks suggests a stable drug-polymer formulation. HPMC exhibited characteristic peaks in the FTIR spectra, the main FTIR peaks included 1050 cm^{-1} for the C-O stretching and attributed to the glucose ring; 3390 cm^{-1} for the O-H stretching corresponding to the hydroxyl group; 1370 cm^{-1} corresponding to C-O-H showing the bending of hydroxyl groups; 2930 cm^{-1} for C-H stretching characteristic of methyl and propyl groups and 1450 cm^{-1} for C-H absorptions that can be used to determine the ratio of methyl to glucose content.[37]

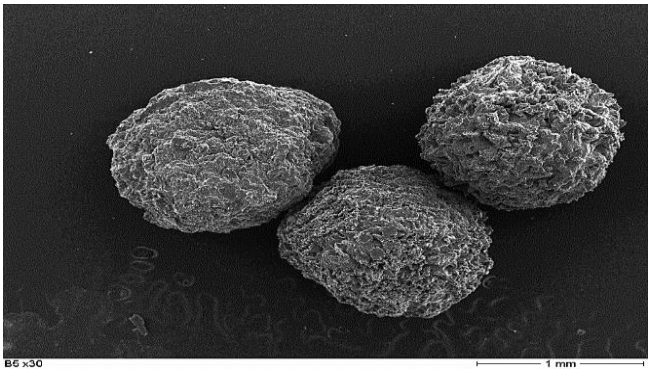

Figure 3: Scanning Electron Micrographs (SEM) of ibuprofen-loaded microspheres containing a blend of acid-thinned sweet potato starch, sodium alginate and HPMC Mg 30x, scale bar 1mm

The FTIR spectrum of sodium alginate exhibited distinct peaks associated with its functional groups. There was a broad band around 3400-3600 cm^{-1} due to O-H stretching characteristic of the hydroxyl groups; bands around 2900 cm^{-1} for C-H stretching indicative of C-H stretching vibrations in the methylene groups (-CH2) of the alginate structure; peaks around 1635 cm^{-1} for the asymmetric COO stretching attributed to the carboxylate groups (-COONa) and 1420 cm^{-1} (symmetric COO stretching) (Rai et al, 2013). Additionally, peaks between 1100 and 1000 cm-1 are attributed to C-O stretching in the pyranose ring.[38] The peak around 884 cm^{-1}, related to the mannuronic acid residue in the alginate structure, was also observed. The spectra revealed there were no interactions between ibuprofen and the polymer blends, confirming drug entrapment within the polymer blend.[20]

Swelling Index

Polymer swelling in microspheres influences drug release by enhancing diffusion and potentially altering release kinetics.[39] The swelling index values of the microspheres are presented in Table 1. The results revealed that microspheres containing the lowest concentration of acid-thinned starch i.e., polymer blend of Starch: Alginate:HPMC ratio 1.0:1.0:1.0 (F_1 to F_3) had more swelling than the formulations containing high amount of starch (F_4 to F_9). The controlled swelling of the more hydrophobic acid-thinned starch will allow drug release to be tailored to achieve a sustained release profile.[40] This can be accomplished through cross-linking, the modification of starch, and the combination of starch with other polymers. Alginate, a natural polysaccharide, typically swells more rapidly than HPMC when exposed to aqueous environments.[41] This rapid swelling is due to the way alginate chains interact with water and the porous structure that was formed. Concentration of sodium alginate, the cross-linking agents used, and the presence of other polymers also have an impact on swelling and drug release. However, sodium alginate microspheres can be less mechanically robust due to their porous structure and rapid swelling, which may lead to breakage or degradation. HPMC offers a more controlled and extended swelling behavior, making it suitable for sustained release applications. Swelling produces a gel-like layer of HPMC that can act as a barrier to drug diffusion, slowing release.[42,43] HPMC's hydrophilic nature and extended swelling capability allow it to absorb more water and expand the microspheres. On the other hand, the swelling of starch in the microspheres is more limited, and therefore retards drug release.[44]

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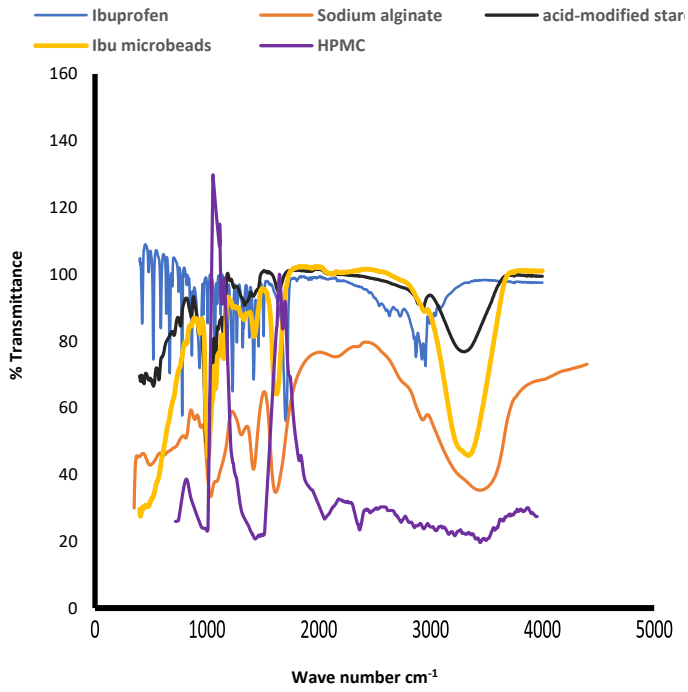

Figure 4: FTIR of pristine ibuprofen, alginate, HPMC, acid-thinned starch and ibuprofen-loaded microspheres*The persistence of the characteristic peaks of ibuprofen's functional groups such as the carbonyl stretching vibration around 1700-1750 cm^{-1} and hydroxyl stretching vibrations around 2900-3000 cm^{-1}, suggests no interaction with the acid-thinned starch and other polymers, drug entrapment and a stable drug-polymer formulation

Entrapment Efficiency

The drug entrapment efficiency of microspheres is a critical index of drug delivery and is useful for assessing their capacity for drug loading.[45] The results of entrapment efficiency for the formulations) are presented in Table 1 which showed high drug entrapment that ranged from 74.00 ± 4.35 to 90.00 ± 6.00%. The presence of starch in the microsphere formulations appeared to enhance entrapment of drug within the microspheres. As the amount of acid-thinned starch increased, entrapment efficiency increased (F_4 to F_9). The higher amount of starch created a denser material with substantial cross-linking of molecules, allowing the system to entrap the drug more effectively.[25,46] HPMC also showed good entrapment, especially at higher concentrations, because of its hydrophilic nature, swelling capacity, and ability to form a stable hydrogel.

Drug release

The plots of cumulative drug release versus time for the ibuprofen-loaded microspheres are shown in Figure 5. The dissolution plots were used to determine the time required for 50% drug release (t50) and are presented in Table 1. No burst release was observed for all batches containing the acid-thinned sweet potato starch. Burst release denotes an unpredictable and uncontrolled release of encapsulated drugs from carriers when introduced to a release medium, in which ≥ 20% of the drug is released in the first hour.[47] The complex formed between the hydrophobic acid-thinned starch and the hydrophilic polymers served to increase the rigidity of the microspheres. Formulations with a greater amount of polymer materials gave a lower percentage of drug release because the dissolution medium entered the microspheres slower[25]. As polymer concentration increased, the viscosity of the polymer gel increased, making it more resistant to diffusion and erosion, increasing the path length of diffusion and reducing the diffusion coefficient of the drug, with consequent reduction in the rate of release of the drug.[25,48] The size of the microsphere can also impact drug release. Larger microspheres with a higher amount of starch gave slower drug release rates due to the increased density and resistance to erosion. The combination of acid-thinned starch with HPMC and alginate has proven useful in retarding release, resulting in controlled release of ibuprofen that is more prolonged than its biological half-life.

Factorial design

The 3^2 factorial experimental design highlighted the quantitative impacts of two parameters, polymer blend type (X_1) and polymer: drug ratio (X_2), on response variables the size, swelling, entrapment efficiency, and dissolution time (t_{50}) of the microspheres.[25] The use of factorial design for formulation optimization enabled the two chosen factors to be varied at the same time, permitting the evaluation of the impact of each factor at different levels, as well as the interactions between them.[49]

Table 2 shows the individual and interaction coefficient values, along with the p-values. The coefficients of X_1 (polymer type) and X_2 (polymer: drug ratio) for microsphere size were 0.076 and 0.034 respectively and were both positive, indicating that the use of the acid-thinned starch at higher composition and lower content of alginate in the blend produced significantly larger microspheres ($p = 0.005$) while increase in polymer to drug ratio from 3.0:1.0 to 4.0:1.0 and then to 6.0:1.0, also significantly enlarged the microsphere size ($p = 0.048$).[50] This is due to an increase in the viscosity of the dispersed phase as the polymer to drug ratio increased, which produced larger droplets that eventually transformed into larger microspheres.[27,51] The larger value of the X_1 coefficient indicates that the polymer type had a greater influence on microsphere size than polymer: drug ratio. The results also showed that the two factors interacted (X_1X_2) to significantly reduce microsphere size ($p= 0.040$).

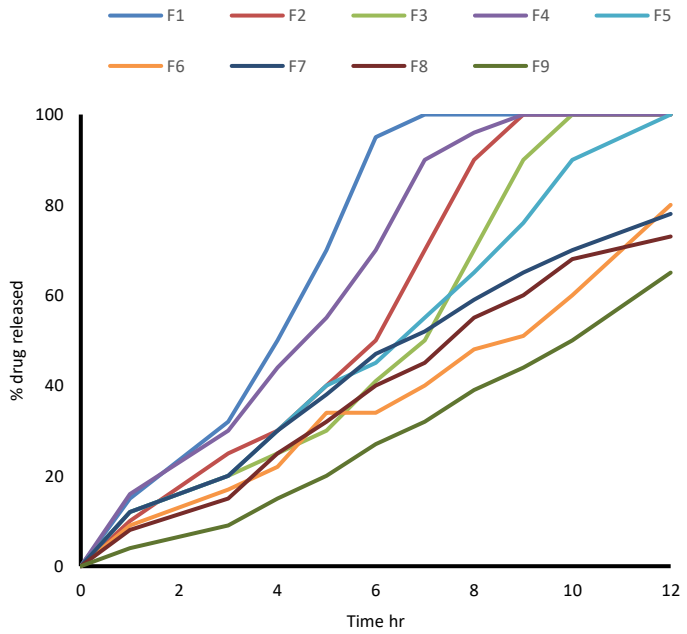

Figure 5: Dissolution plots of the nine formulations of Ibuprofen-loaded microspheres

The coefficient of X_1 (polymer type) for swelling was 0.103 and negative, indicating that a change in polymer type from 1.0:1.0:1.0 blend of starch, alginate and HPMC to 1.5:1.0:0.5 (higher amount of acid-thinned starch), produced a reduction in swelling.[25] The coefficient of X_2 for swelling was 0.268 and positive with a higher influence on swelling than X_1 ($p = 0.005$) indicating that increasing the polymer: drug ratio also improved swelling. The interaction coefficient (X_1X_2)

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for swelling was negative, indicating that the two factors interacted, though not significantly (p = 0.060), to decrease swelling.

X_1 and X_2 coefficients for entrapment efficiency had values 0.305 and 0.180, respectively, and were positive. Furthermore, the coefficient was higher for X_1, indicating that the polymer blend type had a greater influence on entrapment (p = 0.031) than polymer: drug ratio. The improvement in drug entrapment efficiency of microspheres with a change in polymer blend from that with low to higher starch content, and increasing polymer: drug ratio could be attributed to the higher viscosity of the matrix which caused a delay in the number of drug molecules migrating to the surrounding fluid.[52] The coefficients showing the individual effects of polymer type (X_1) and polymer: drug ratio (X_2) on t_{50} were 0.166 and 0.374 respectively, and were positive (p = 0.000), implying that the presence of the acid-thinned starch retarded the quantity of drug released and the time of drug release was extended with higher starch content and polymer: drug ratio.[53] The diffusional resistance created by a higher polymer: drug ratio is capable of retarding the ability of the drug to diffuse out of the microsphere matrix.[54] The interaction coefficients for t_{50}, X_1X_2, was positive, indicating that the two factors interacted to significantly (p = 0.030) prolong the time at which ibuprofen was released from microspheres.

Table 2: Summary of the individual and interaction coefficients of the variables on the particle size, swelling index, entrapment and dissolution time of ibuprofen-loaded microspheres

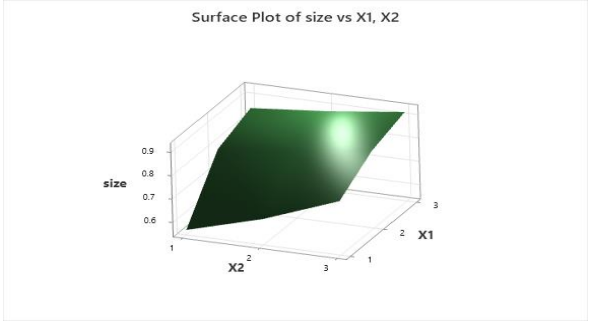
Factor	Coefficient	Particle size	Swelling index	Entrapment	t_{50}
X_1	Effect	0.076	-0.103	0.305	0.166
	p-value	0.005	0.085	0.006	0.000
X_2	Effect	0.034	0.268	0.180	0.374
	p-value	0.048	0.005	0.031	0.000
X_1X_2	Effect	-0.029	-0.027	0.105	0.046
	p-value	0.040	0.060	0.008	0.030

Surface response plots demonstrates the graphical correlation between the response and the independent variables, showing the interactive effects of X_1 and X_2 on size, swelling, entrapment, and t_{50}.[55] The surface plots generated are shown in Figure 6 and these aligned with the polynomial terms, providing insights into the influence of polymer blend type and polymer: drug ratio. Acid-thinned sweet potato starch had different impacts on the parameters of the microspheres. Initially, when the concentration of starch in the formulation increased, from ratio 1.0:1.0:1.0 polymer blend of starch, alginate and HPMC to 1.5:1.0:0.5, there was an increase in size, entrapment, and dissolution time but a decrease in swelling. However, as the starch content remained unchanged but the HPMC content increased (1.5:0.5.1.0), there was an increase in swelling too. The predicted and experimental values of drug entrapment efficiency are shown in Table 3. The formulation F9 containing the blend of starch: alginate: HPMC blend 1.5:0.5:1.0 and polymer: drug ratio of 6.0: 1.0 was chosen as the optimized formulation for evaluation studies based on the criteria of attaining high swelling, highest possible entrapment, and the most prolonged drug release, comparable to the predicted values.

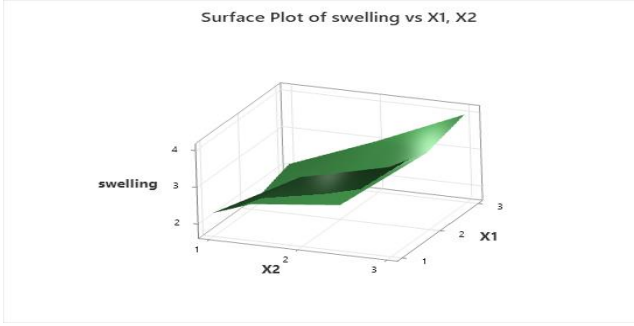
Sweet potato starch, a natural polymer, is abundant, biodegradable, and can be considered a less expensive alternative to some synthetic polymers. It has been established from a previous study that microparticles prepared using sweet potato starch released drugs in a controlled manner, with the rate of release dependent on starch concentration.[56] Acid-modified *Ipomoea batatas* (sweet potato) starch is superior to native starch and some other existing polymers since it has modified hydrophobicity with surface roughness and increased surface area that can improve the encapsulating property of the starch, a useful parameter in drug delivery systems. In addition, the modification improves physicochemical properties such as good flowability, high mechanical strength, and the potential for sustained drug delivery[21]. In this study, acid-modified sweet potato starch effectively controlled the release of ibuprofen, resulting in sustained release profiles over extended periods, which is critical for maintaining therapeutic drug levels and reducing dosing frequency. The combination of increased hydrophobicity, controlled release, mechanical strength as well as its affordability and biodegradability make this novel starch polymer suitable as a copolymer for developing microspheres for a poorly aqueous soluble drug such as ibuprofen, when compared to native starch or the other hydrophilic polymers alone.

This study has contributed to showcasing the potential of sweet potato starch as a viable material for drug delivery, particularly in low-income countries, as obtained in sub-Saharan Africa because of its widespread availability, low cost, and inherent functional properties. The acid-thinned starch of sweet potato tubers has been proven to have potential as a polymer in controlled drug release applications and can be comparable to the available commercial starches.[16] Major challenge include the need for additional research to fully understand the pharmaceutical potential of various varieties of sweet potato, standardize extraction by establishing large-scale processes for commercial availability, and develop modification techniques to optimize functional properties for specific drug delivery applications.

(a)



(b)



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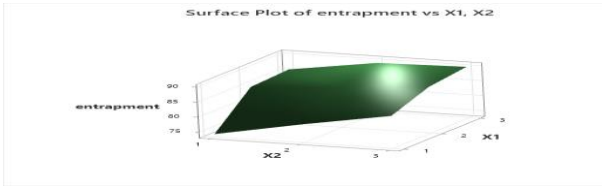
(c)



(d)

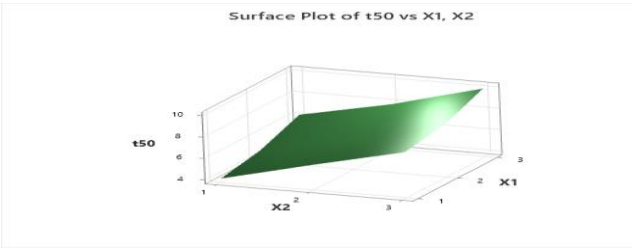


Figure 6: Response surface plots of (a), size (b), swelling (c), entrapment and (d), t_{50}, vs X_1 (polymer type) and X_2 (polymer: drug ratio)

Table 3: Results of the optimized formulation for response variables

Response variables	Predicted value	Experimental value
Size	0.88	0.92
Swelling	4.42	4.00
Entrapment	93.00	90.00
t_{50}	10.70	10.00

Conclusion

Formulations of ibuprofen microspheres containing acid-thinned sweet potato starch, sodium alginate and HPMC as copolymers, were developed utilizing a 3^2 full factorial design to evaluate two variables simultaneously (polymer blend type and polymer; drug ratio) and their interactive effects. The factorial design of ibuprofen microspheres revealed significant results. Microsphere size, entrapment efficiency and dissolution time, t_{50}, were enhanced by the presence of acid-thinned sweet potato starch. The optimized batch had high entrapment efficiency of 90% with drug release (t_{50}) lasting more than 10 hours and therefore considered to have sustained release. The optimized batch's experimental responses closely matched the predicted values. The results reveal the potential of sweet potato starch modified by acid-thinning as a viable alternative polymer for drug delivery.

Future research should concentrate on increasing production, conducting *in vivo* testing to confirm sustained release and patient benefits, investigating different local tuber starches and modification methods for broader applicability. In addition, optimizing manufacturing processes will be important to address the challenges of transitioning from lab-scale to industrial-scale manufacturing in order to make the microspheres commercially viable. Furthermore, ~~conducting~~ clinico-economic assessments should be carried out in addition to examining long-term stability of the sweet potato starch-based microspheres to assure safety and efficacy.

Conflict of interest

The authors declare no conflict of interest.

Authors' declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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