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Evaluation of fonio and sweet potato starches, and sodium alginate blends as polymers in metformin microbead formulation

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ABSTRACT

To achieve sustained release of metformin, microbeads were prepared using fonio and sweet potato starches blended with sodium alginate via ionotropic gelation. Blends were made in ratios of 1:1, 1:2, 1:3, and 1:4. The viscosity of the blends ranged from 212.0 to 862.0 cP, with fonio being less viscous than sweet potato. Microbead sizes ranged from 1,325.5 to 1,912.5 µm, with fonio starch microbeads being smaller. Sweet potato starch microbeads had better drug entrapment (up to 93.2%) and a lower swelling index compared to fonio. The highest metformin release (48% at 4 hours) was from the 1:1 sweet potato blend, although release decreased with higher starch ratios. At a 1:4 ratio, fonio starch microbeads reached a maximum of 30% drug release. The drug release mechanism was through relaxation, indicating that both starches can support the sustained release of metformin.

Keywords: fonio starch, metformin, microbeads, sweet potato starch, sustained release

INTRODUCTION

In recent years, substantial research has focused on developing microbeads using a wide range of natural and synthetic polymers. Starch-based materials have attracted attention in controlled-release drug delivery systems due to their

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biocompatibility, biodegradability, abundance, and excellent drug entrapment efficiency[1]. The use of polymers in microbead formulations has facilitated the sustained and controlled release of therapeutic agents. Microbeads not only offer prolonged drug release but also improve drug bioavailability and ensure a more uniform distribution throughout the gastrointestinal tract[2]. Many natural and synthetic polymers, including alginic acid, sodium alginate, chitosan, and pectin, have been successfully employed to produce such drug delivery systems[3,4].

Controlled drug release occurs when the drug is incorporated within a polymeric matrix that modulates its release predictably over time. The release profile is mainly affected by the physicochemical properties of the polymers used[5].

Fonio (*Digitaria exilis*), a cereal native to West Africa, is gaining recognition for its unique starch properties and nutritional value. Known locally as findi (Fulani), acha (Hausa), and "hungry rice" (English), fonio is an underutilised grain with notable pharmaceutical potential[6,7]. Fonio starch is characterised by a small granule size and a high amylose content, which may contribute to favourable controlled-release properties[8]. Fonio starch used in the polymer blend to produce microbeads is distinct for its "better-packed" molecular structure, which confers remarkable structural stability and resistance to shearing and heating[9]. The exceptionally small granule size of fonio starch (~8 μm) provides a high specific surface area, enhancing water retention and swelling power beyond those of other starches, such as corn starch[8]. When integrated into an alginate matrix, this starch is expected to reduce porosity and increase the complexity of the internal network, thereby facilitating a more controlled release of encapsulated material[10]. Modified fonio starch has shown excellent compressional properties, including a faster onset of plastic deformation when compressed and prolonged disintegration times in tablet formulations. These features suggest its suitability for sustained-release drug delivery[8]. Furthermore, fonio starch nanoparticles have been incorporated into topical gel systems for antifungal drug delivery, demonstrating additional versatility[11].

Sweet potato (*Ipomoea batatas*) is another crop rich in starch, widely cultivated in tropical and subtropical regions. Although native to Central America, its adaptability has made it a vital agricultural product in Africa, Asia, and South America. Industrially, the primary application of sweet potato is starch production, with starch content ranging from 6.9% to 30.7% (wet basis)[12,13] . Sweet potato starch has exhibited good binding properties in tablet

formulations and has also been explored in nanoformulations, supporting its potential in advanced drug delivery systems[14,15]. In a study using a blend of pregelatinized sweet potato starch and alginate to produce ibuprofen-loaded microbeads showed that various formulation variables affected the mean particle size of the microbeads produced[16].

Metformin hydrochloride is a widely prescribed oral antihyperglycemic agent in the biguanide class, primarily used for treating type 2 diabetes mellitus. Sustained-release formulations of metformin offer several therapeutic advantages, including improved efficacy, reduced dosing frequency, minimised side effects, and better patient compliance[17].

The present study, therefore, aimed to develop and evaluate metformin hydrochloride-loaded microbeads using locally sourced fonio and sweet potato starches, combined with sodium alginate. The goal was to formulate a cost-effective, biocompatible, and efficient sustained-release drug delivery system utilising underutilised indigenous starches.

METHODOLOGY

Materials

Metformin hydrochloride (Fidson Healthcare Plc., Nigeria), sodium alginate (Carl Roth GmbH & Co., Karlsruhe, Germany), zinc chloride (Alfar Aesar GmbH & Co., Karlsruhe, Germany), *D. exilis* grains (obtained from Zaria, Kaduna State, Nigeria), and *I. batatas* tubers (obtained from Offa, Kwara State, Nigeria).

Extraction and physicochemical properties of the polymers

The starches were extracted according to established procedures, and the proximate composition and functional properties of fonio and sweet potato had been determined earlier[8]. The polymer blends of sodium alginate: fonio or sweet potato starch in the ratios 1:1, 1:2, 1:3, and 1:4 were prepared and their viscosity determined using spindle 4 on a Brookfield Viscometer (RVDV-II+P, Middleboro, USA) at 27°C ± 3°C and a shear rate of 100 RPM.

Preparation of the microbeads

The ionotropic gelation method was used to prepare microbeads incorporated with metformin hydrochloride[18]. An aqueous solution of sodium alginate and fonio or sweet potato starch (in their desired ratios – 1:1, 1:2, 1:3, and 1:4) was prepared with distilled water, with constant stirring using a magnetic stirrer to form a homogenous mixture. Metformin hydrochloride (1% w/v) was added with constant stirring to attain a homogeneous dispersion. Using a 23 G

needle, the suspension was extruded into a beaker, which contained 10% w/v zinc chloride while being stirred at 300 rpm for 15 minutes at a rate of 1 mL/15 s. It was then further cross-linked for roughly 7 minutes. After decantation, washing with distilled water, the beads were collected, air dried first to solidify at room temperature, and then dried at 40°C for 6 hours in an oven[19].

Characterization of microbeads

Microscopical analysis

The particle size and morphology of the starches had been studied earlier using scanning electron microscopy (Hitachi Model S-2460N, Japan) at an accelerating voltage of 25 KV[8]. The microbeads were, however, analysed for size and morphology using the same scanning electron microscope.

Swelling index

Microbeads (100 mg) were weighed to determine the swelling index. After 3 hours in 20 mL of phosphate buffer (pH 6.8), the swelling index was calculated using equation 1.

$$\text{Swelling Index (\%)} = \frac{\text{Change in Weight (mg)}}{\text{Initial Weight (mg)}} \text{ X } 100 \quad \text{[Eq 1]}$$

Drug loading efficiency

After crushing 50 mg of drug-loaded microbeads with a mortar and pestle, they were suspended in 50 mL of phosphate buffer at pH 6.8. Once the mixture was filtered, the absorbance of the filtrate at 233 nm was measured using a UV spectrophotometer (Gransmore Green, Felsted, Dunmow, Essex CM6 3LB, England). Equation 2 was then used to determine the drug concentration in the weighted microbeads.

$$\text{E (\%)} = \frac{\text{Practical Drug Content}}{\text{Theoretical Drug Content}} \text{ X } 100 \quad \text{[Eq 2]}$$

Drug release and mechanism

The paddle technique[17], was used for *in vitro* dissolution tests, which involved revolving at 100 rpm in 900 mL of phosphate buffer at pH 6.8 and maintaining a temperature of 37 ± 0.5°C. Ten millilitre samples were collected at various intervals and substituted with an equivalent volume of new media. After filtering and diluting the samples, the quantity of metformin hydrochloride released was measured at 233 nm. The measurements were carried out in triplicate.

Statistical analysis

Statistical analysis was performed using one-way Analysis of Variance (ANOVA) in Microsoft Excel, with the difference considered statistically significant at $p<0.05$. All experiments were performed in triplicate, and the data are presented as mean ± SD.

RESULTS and DISCUSSION

Percentage yield of polymers

The yield of fonio and sweet potato starches was 8.4 and 46.0% $^{w}/_{w}$, respectively. The yield of fonio and sweet potato starches was lower and higher, respectively, than that stated in recent studies[20,21]. Location and source have been adduced as reasons for this.

Physicochemical properties of the microbeads

Viscosity of the polymer blends

The viscosity of the polymer blends and their codes is presented in Table 1. The polymer blends' viscosities increased with an increase in starch concentration, irrespective of the starch. However, the polymer blends containing sweet potato starch were more viscous ($p>0.05$) than those composed of fonio starch. In a study on theophylline-loaded microbeads, it was also observed that the size of the microbeads appeared to increase proportionally with the starch content[22].

Table 1. Viscosity of the polymer blends

Polymers	Formulation Code	Polymer Ratio	Viscosity (cP)
Alginate: potato starch	AP1	1:1	322.0 ± 0.3
	AP2	1:2	368.0 ± 0.2
	AP3	1:3	406.0 ± 0.5
	AP4	1:4	862.0 ± 0.4
Alginate: fonio starch	AF1	1:1	212.0 ± 0.2
	AF2	1:2	254.0 ± 0.3
	AF3	1:3	279.0 ± 0.1
	AF4	1:4	342.0 ± 0.6

Particle size and morphology

The particle size of microbeads containing sodium alginate alone (A1) as the polymer has been previously determined and showed that the formulation

produced beads of 436.3 μm in size, which were spherical with smooth surfaces[20].

The morphology and shape of the microbeads are shown in Figure 1. For microbeads produced from polymer blends of alginate: sweet potato/fonio starch, there was an increase in the particle size with an increase in the concentration of starch for both starches. Microbeads prepared using blends of sodium alginate and sweet potato starch were not spherical in most cases and had a sponge-like surface in all cases, although they had a smooth appearance. The microbeads prepared with blends of sodium alginate and fonio starch had oblong shapes in some cases and were spherical in others, although they had rough surfaces. Studies have shown that the incorporation of the drug resulted in a transformation of the microbeads' morphology from a spherical configuration to a form that is partly spherical and irregular in shape[23].

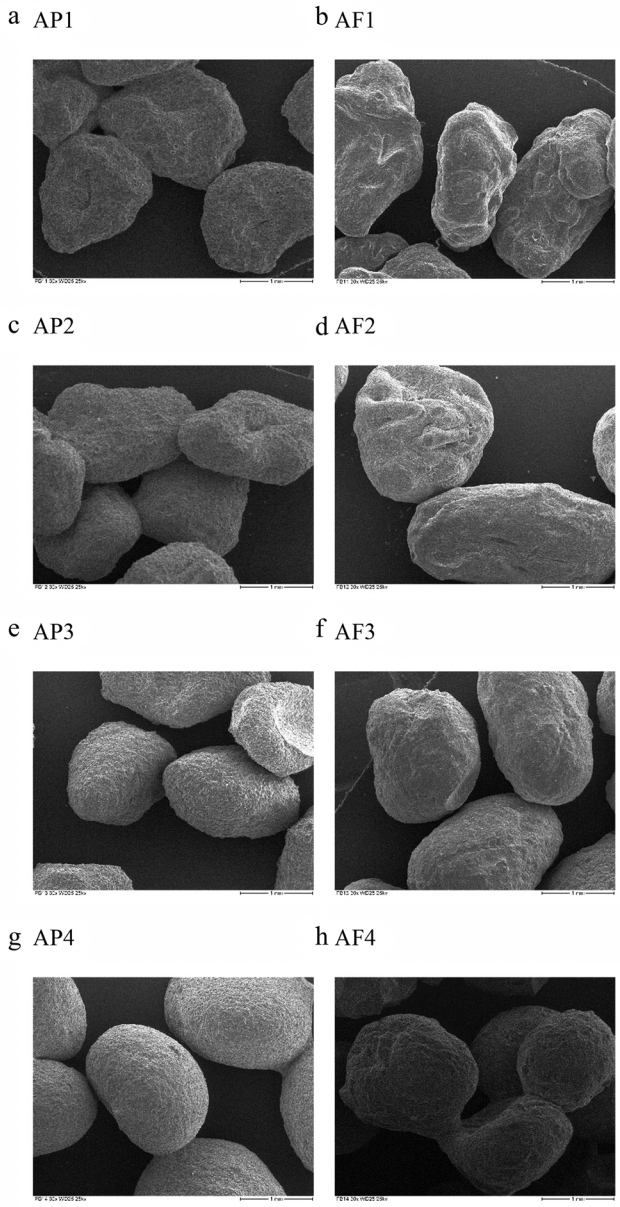

Figure 1. SEM of microbeads of different Alginate: Starch ratios (Mag. 30x). a, c, e, g are alginate: sweet potato in ratios 1:1, 1:2, 1:3, 1:4. Respectively; while b, d, f, h are alginate: fonio in ratios 1:1, 1:2, 1:3, 1:4, respectively.

Swelling index

The swelling index of the microbeads is presented in Table 2. The swelling index for the beads followed the pattern obtained for the individual swelling power of the starches, as they both had low-fat contents and were thus able to swell[8]. When mixed in increasing ratios with sodium alginate, there was an increase in the swelling index with increasing starch to alginate ratio. This may be due to the loose association of the amylose and amylopectin molecules in the individual polymers[24].

Table 2. Physicochemical properties of the microbeads

Polymers	Formulation Code	Polymer Ratio	Mean Particle Size (μm)	Swelling Index (%)	Entrapment Efficiency (%)	T_{15} (min)	T_{30} (min)
Alginate: potato starch	AP1	1:1	1424.9 ±12.0	186.6	43.7	70.0	130.0
	AP2	1:2	1464.7 ± 6.4	199.2	60.8	-	-
	AP3	1:3	1522.8 ± 8.4	220.4	76.8	-	-
	AP4	1:4	1912.5 ± 9.7	322.0	93.2	-	-
Alginate: fonio starch	AF1	1:1	1325.5 ± 3.9	35.4	44.1	208.0	-
	AF2	1:2	1414.4 ± 9.4	142.8	65.6	-	-
	AF3	1:3	1447.8 ± 3.1	224.8	84.1	-	-
	AF4	1:4	1466.4 ± 5.7	311.3	92.1	130.0	235.0

Entrapment efficiency

The entrapment efficiency of the microbeads is presented in Table 2. The entrapment efficiency indicates how much of the drug is incorporated within the polymer batches. Entrapment efficiency increased with an increase in the concentration of the starch within the blends. Blends containing fonio starch at ratios 1:1, 1:2, and 1:3 had a higher drug entrapment. This was probably because fonio starch is less soluble than sweet potato starch, meaning that it would hold the drug better than sweet potato, which would readily dissolve. However, at the highest starch concentration, potato starch had the highest entrapment efficiency (93.2%), followed by fonio starch (92.1%) ($p>0.05$). This was probably due to the particle sizes of the two starches, with the sweet potato starch, which has a larger particle size, being able to entrap more drug than fonio starch[8], which has a smaller particle size[25]. Blending with sodium alginate, however, did not make this effect pronounced.

Drug dissolution and release mechanism

The degree of cross-linking, the size and form of the microbeads, their density, and the presence of any adjuvants all affect how easily drugs are released from them[26]. Diffusion through the enlarged rubbery matrix, release from the particle surface, and release from the polymer's erosion are the three primary ways that this release takes place. These mechanisms typically do not operate in isolation[19]. When drugs that have been absorbed on the surface are released, they dissolve immediately upon contact with the release medium, resulting in a rapid burst effect[23]. The plots of percentage drug released for the polymers are shown in Figure 2. Although calcium chloride is the preferred cross-linking agent, its high aqueous solubility often leads to rapid and uncontrolled gelation[4]. Zinc chloride, used as the cross-linking agent in the formulation of starch: alginate microbeads, is for more extensive cross-linking and improved mechanical strength[27]. In addition, more controlled release is achieved with zinc chloride[28], as zinc binds more slowly and covalently to alginate than calcium. The type of polymer utilised in the formulation and its concentration had an impact on the microbeads' drug release characteristics. Based on the time needed for 15% of the drug to be released from the plots, there was no burst release (Table 2). Since only AP1 and AF4 had t_{30} (the time it took for 30% of the drug to be released, derived from the plots) values (the earliest being 130 minutes), and only 20% of metformin had been released, it indicated that there was extended drug release. The highest concentration of drug released was by batch AP1 (with an alginate to sweet potato starch ratio of 1:1), 48% at 240 minutes. However, when the concentration of the sweet potato starch increased, the drug release with the alginate: Sweet potato starch batches dropped. Meanwhile, drug entrapment was in the inverse. The alginate to fonio starch batch gave its highest drug release with batch AF4 at 240 minutes, with over 30% drug released. It has been shown that 10 hours is the benchmark for the release of sustained-release metformin tablets, with incremental release targets of 20–40% within the first hour, 35–55% at the second hour, and 65–85% at 6 hours for 750 mg and 1,000 mg formulations[29]. It has also been shown that metformin release from sustained systems usually has an initial burst release of 19-31% within the first 15 minutes[30]. However, maintaining a release of less than 15% of the drug within the first hour is crucial for formulations designed for sustained release, as higher initial release rates are undesirable[31]. Since none of the tested formulations had such a burst release and the highest release at 4 hours was 48%, it can be assumed that it would attain the 80–85% expected within 8–10 hours. The polymer ratios effectively regulated the release of metformin hydrochloride. The metformin-loaded

microbeads' dissolution data were fitted into the various drug release kinetic models (Table 2). Except for AF4, which suited the Korsmeyer-Peppas model with a R^2 of 0.9996 and n>1, all showed correlation coefficients of $R^2 \geq 0.9945$ for the Weibull model with β varying between 0.763 and 2.155, indicating a super case II transport (relaxation) release mechanism. This implies that drug release accelerates towards the end of the release process[19]. Among the formulations that conformed to the Weibull model, AF1, AP2, AF2, and AF3 exhibited values of $0.75<\beta<1$, suggesting a non-Fickian diffusion behaviour. In contrast, AP1 and AP3 presented β values greater than 1, which implies a more complex release mechanism involving diffusion, swelling, and/or erosion of the matrix[32]. AP4 had correlation coefficients of 0.9999 for both the Weibull and the Korsmeyer-Peppas models with both β and n>1. This suggests that for both starches at the highest concentration in the microbead, the drug release mechanism was by relaxation.

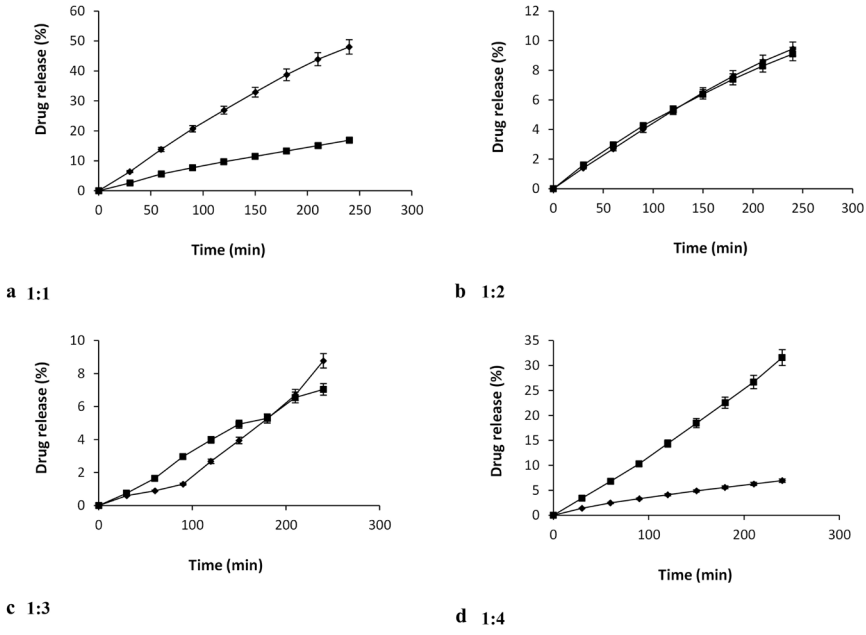

Figure 2. Plots of percentage drug released against time (min) for Alginate to polymer ratios: a 1:1, b 1:2, c 1:3, d 1:4, Alginate: Sweet potato ♦, Alginate: Fonio ■

The polymer blends and microbeads increased in viscosity, swelling and drug entrapment efficiency with the concentration of the starches. Both fonio and sweet potato starches showed potential for sustained release of metformin. Alginate: fonio starch ratios produced microbeads with a primarily non-Fickian release mechanism, whereas those of alginate: sweet potato starch exhibited a more complicated release mechanism. However, at the highest starch concentration, the microbeads had a relaxation drug release mechanism.

STATEMENT OF ETHICS

This study does not require any ethical permission.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

The authors contributed equally to the article.

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