

Evaluation of freeze-dried pregelatinized Chinese yam (*Dioscorea oppositifolia*) starch as a polymer in floating gastroretentive metformin microbeads

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Pregelatinized Chinese yam (Dioscorea oppositifolia) starch has been evaluated as a polymer for the formulation of floating gastroretentive beads for the controlled delivery of metformin hydrochloride. Floating microbeads were prepared by the ionotropic gelation method using a blend of modified Chinese yam starch and sodium alginate at different ratios. Sodium bicarbonate was added as a gas-generating agent. The floating microbeads were characterized by SEM, DSC, FTIR analyses and the drug entrapment efficiency and floating ability was evaluated. Drug release was investigated using in vitro dissolution test and the results were fitted to various kinetic models to determine the mechanism(s) of release. Spherical, discrete and free flowing microbeads were obtained from the modified starch-alginate blends. Minimum lag time (< 20 s) was observed for the floating microbeads containing starch and buoyancy was maintained for 12 h. The release of MET from the floating microbeads appeared to be controlled by varying the starch to alginate polymer ratio. In general, the formulations followed diffusion and erosion mechanisms of drug release. The results suggest that modified Chinese yam starch-sodium alginate blend can be useful for the formulation of floating gastroretentive system for metformin hydrochloride.

Key words: Metformin hydrochloride – Chinese yam starch – Floating microbeads – Controlled drug delivery – Release kinetics.

Oral sustained drug delivery system is complicated by limited residence time in the stomach and proximal portion of the small intestine. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine [1]. To overcome these limitations, several controlled oral drug delivery systems with prolonged gastric residence times floating drug dosage systems [1-3], swelling or expanding systems [4], mucoadhesive systems [5, 6], modified-shape systems [7], high-density systems [8], and other delayed gastric emptying devices have been reported. Among these systems, floating drug dosage systems have been most commonly used. Floating drug dosage systems have a lower density than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration [9]. Floating gastroretentive delivery systems offer a number of other advantages. The controlled, slow delivery of drug to the stomach may provide sufficient local therapeutic levels for drug delivery to the stomach (e.g. anti-ulcers), thus reducing drug wastage and untoward side effects since the systemic exposure to the drug will be limited. Moreover, the prolonged gastric availability may also reduce the dosing frequency [9, 10].

Metformin hydrochloride (hereafter referred to as MET) is an orally administered biguanide derivative widely used in the treatment of non-insulin dependent diabetes mellitus [11, 12]. In humans, MET is incompletely absorbed and mainly excreted in the urine with a half-life of 4-6 h [13]. The absorption window of MET is predominantly in the small intestine and follows a saturable dose-dependent mechanism [11, 14]. Thus, its absorption after oral administration is likely to be site specific and its release after the small intestine would be of no therapeutic value [11, 12, 15]. The immediate release formulations of MET available require administration 2-3 times daily and are associated with a high incidence of side effects [15]. Studies have

shown that the extent of absorption of MET is improved when the gastrointestinal motility is slow [15, 16]. In order to optimize therapy and patient compliance, various efforts have been made to develop controlled release formulations of MET. However, burst release of MET has been previously reported for controlled release tablets which is undesirable. A time independent drug release is desirable in sustained release formulation in order to optimize drug therapy. The development of a gastroretentive formulation will reduce burst release and prolong the release of MET and thus provide a better alternative to the conventional sustained release tablet formulations [10].

Various methods have been used to prepare the floating dosage forms [3, 17]. The most commonly used excipients are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene [3]. Sodium alginate, a polysaccharide which contains varying amounts of 1,4-linked -D-mannuronic acid, -L-guluronic acid residues is one of the most commonly used polymeric backbone for the formulation of beads. As biocompatible and biodegradable biopolymer, it forms a bio-adhesive and stable gel with divalent cations such as Ca²⁺, Sr²⁺, and Ba²⁺ [18].

Starch is known to produce low toxicity and low cost products that are biodegradable and stable in biological environment [19]. Starches have been added to different polymers to modulate release of drugs from mucoadhesive microbeads, although most studies have been limited to widely available starches such as corn, potato and rice [20-22]. Starches containing mainly amylopectin and traces of amylose have been shown to possess great potential as novel mucoadhesive polymer because of the free hydroxyl groups which opens up the possibility for the starch to be crosslinked with other polymers for controlled delivery [22]. Research has shown that sweet potato starch-alginate blends used to prepare ibuprofen microbeads have provided relatively slow release at low pH suggesting that the drug was thoroughly encapsulated by the microbeads [21]. However, the release pattern of ibuprofen was biphasic, characterized by initial burst release followed by slow release. In another study, hydrogel beads containing a blend

of pregelatinized glutinous (Bora) rice starch and sodium alginate was formulated for the controlled delivery of metformin hydrochloride [22]. However, starch-alginate blend possessed low entrapment efficiency and controlled release was achieved only when the microbeads were coated with HPMC. It has been established that starches from different botanical sources vary in their composition, physicochemical and functional properties which provide opportunities for their use for various purposes [23].

Recent studies have shown that starches from the tubers of *Dioscorea oppositifolia* L (Chinese yam) consist of polygonal granules with small particle size and high specific surface area [24]. The starch contains 21.6:78.4 amylose:amylopectin ratio and showed good potential as excipients for direct compression, as well as good disintegrant and binder properties in tablet formulations [26-27]. Chinese yam starches, modified by pregelatinization followed by freeze drying, have shown potential as directly compressible excipients for controlled drug delivery [25]. The results showed that pregelatinization improved the swelling, compressibility and flowability of the native starches. The freeze dried pregelatinized starches generally showed higher compactibility and produced tablets which were non disintegrating indicating a potential for application as excipients for controlled drug delivery. So far, no work has been done to evaluate the usefulness of pregelatinized Chinese yam starch as a polymer for the formulation of floating gastroretentive microbeads. Thus, in the present study, a gastroretentive controlled release system of MET is formulated using a blend of freeze-dried pregelatinized Chinese yam starch and sodium alginate in order to increase the residence time of the drug in the stomach and modulate its release behavior. The potential of the blend of modified Chinese yam starch and alginate as natural polymers for pharmaceutical drug delivery systems has been evaluated.

I. MATERIALS AND METHODS

1. Materials

Metformin hydrochloride was kindly provided by Zydus Cadila Healthcare Ltd. (Ahmedabad, India), sodium alginate was obtained from S.D. Fine Chem. (Mumbai, India) while calcium carbonate and sodium bicarbonate were obtained from Finar Chemicals Ltd. (Ahmedabad, India). Tubers of *Dioscorea oppositifolia* L (Chinese yam) were obtained from local farmers in Ibadan, Nigeria, and authenticated. All other reagents used were of analytical grade.

2. Extraction of starch

Fresh tubers of yam were washed with distilled water, peeled, washed again and then cut into small pieces. The pieces were milled into a fine paste using a laboratory mill. The slurry was strained through a muslin cloth and the filtrate was left to settle. The supernatant was decanted at 12 h intervals and the starch slurry re-suspended in distilled water. Sodium metabisulphite was added to the distilled water used to prevent discoloration. The starch cake was collected after 3 days and dried in a hot air oven at 60 °C for 48 h. The dried mass was pulverized using a laboratory blender and then screened through a 120 µm mesh [26].

3. Preparation of freeze dried pregelatinized starches

The pregelatinized forms of the *Dioscorea* starches were prepared using established methods. Twenty percent w/v aqueous starch slurry was heated at 80 °C and stirred for 15 min. The pregelatinized starch was freeze dried in a freeze dryer (Christ GmbH, Osterode, Germany) at -84 °C and pressure of -0.371 bar for 24 h. All the starches were passed through a 125 µm mesh sieve. The description of the physicochemical and material properties of the modified starch has been reported elsewhere [25].

4. Preformulation studies for floating beads

In order to optimize the product characteristics and release profile of the drug from the prepared beads, several preformulation trials were undertaken with varying ratios of the polymers (modified Chinese yam starch: sodium alginate), concentration of cross-linking agent, stirring speed and curing time. The shape, flow properties and buoyancy were used as parameters for the optimization of the process variables in the preparation of the microbeads. The properties of the microbeads prepared at various conditions are presented in Table I.

5. Preparation of floating microbeads

The microbeads were prepared from the gel blend of freeze dried pregelatinized Chinese yam starch and sodium alginate using the ionic gelation method [28]. The required amount of drug was added to the solution containing the modified Chinese yam starch and dispersed thoroughly by stirring on a magnetic stirrer for 60 min. Sodium bicarbonate was added to sodium alginate solution. The two gels were then blended and homogenized to obtain suitable starch-sodium alginate ratio. The resulting dispersion was extruded into calcium chloride solution (10 % w/v) maintained at appropriate stirring speed. After curing for the required period of time, the beads were collected by decantation, washed in ethanol and then dried for 10 h at room temperature and 6 h in hot air oven at 40 °C temperature.

6. Determination of drug content

The content of MET in the microbeads was determined spectrophotometrically using a UV spectrophotometer (UV-1700 Shimadzu, Japan) at 233 nm in phosphate buffer PH 7.4.

7. Characterization of beads

7.1. Size and morphology

The morphology and surface characteristics of the microbeads were analyzed using scanning electron microscopy (XL 30 ESEM, Philips, Eindhoven, Netherlands) at an accelerating voltage of 30 KV while the particle sizes of the prepared microbeads were determined by using optical microscopy method.

7.2. Buoyancy studies

Floating capability was determined by the placing microbeads in a dissolution apparatus containing 0.1N HCl (900 mL). The time taken for the beads to rise to the surface and float was taken as floating lag time (FLT). The duration of time the beads constantly remained on the surface of medium was determined as the total floating time (TFT).

7.3. Swelling index

For estimating the swelling index, 0.5 mL of microsphere bed was soaked in 5 mL of 0.1 N HCl in a 10 mL measuring cylinder. The volume of microsphere bed was determined after 12 h. Swelling index was calculated by using the equation:

$$\text{swelling index} = \frac{\text{volume after 12 h (mL)}}{\text{original volume (mL)}} \quad \text{Eq. 1}$$

7.4. Entrapment efficiency

Fifty milligrams of accurately weighed drug-loaded microbeads were crushed in a glass mortar (using a pestle) and suspended in 10 mL of phosphate buffer, pH 7.4. After 24 h, the solution was filtered. The filtrate was appropriately diluted using phosphate buffer, pH 7.4 and analyzed spectrophotometrically (UV- 1700, Shimadzu, Japan) at 233 nm. The drug entrapment efficiency (E%) was calculated according to the following formula:

$$E (\%) = \frac{\text{(practical drug content/theoretical drug content)} \times 100}{\text{Eq. 2}}$$

Table I - Properties of the microbeads prepared at various conditions.

Formulation code	Starch:sodium alginate ratio	Calcium chloride conc. (% w/v)	Stirring speed (rpm)	Curing time	Shape and flow	Physical state after floating for 12 h
A1	7:1	2	200	15	Irregular	-
A2	7:1	2	400	15	Irregular	-
A3	7:1	2	200	30	Irregular	-
A4	7:1	10	400	30	Spherical and sticky	-
A5	4:1	10	200	15	Irregular	-
A6	4:1	10	400	30	Spherical and sticky	-
A7	4:1	10	200	30	Irregular	-
A8	4:1	10	400	15	Spherical and aggregated	Intact
A9	3:1	2	200	15	Irregular	-
A10	3:1	2	400	15	Irregular	-
A11	3:1	2	200	30	Spherical and sticky	-
A12	3:1	2	400	30	Spherical and sticky	-
A13	3:1	10	200	15	Irregular	-
A14	3:1	10	400	15	Spherical and aggregated	Intact
A15	3:1	10	200	30	Spherical and aggregated	Flattened at the end
A16	3:1	10	400	30	Spherical and aggregated	Flattened at the end
A17	2:1	2	200	15	Spherical and aggregated	Flattened at the end
A18	2:1	2	400	15	Spherical and aggregated	Flattened at the end
A19	2:1	2	200	30	Spherical and aggregated	Flattened at the end
A20	2:1	2	400	30	Spherical and free flowing	Flattened at the end
A21	2:1	10	200	15	Spherical and aggregated	Flattened at the end
A22	2:1	10	400	15	Spherical and free flowing	Intact
A23	2:1	10	200	30	Irregular	-
A24	2:1	10	400	30	Spherical and free flowing	Flattened at the end
A25	1:1	2	200	15	Spherical and aggregated	Flattened at the end
A26	1:1	2	400	15	Spherical and free flowing	Flattened at the end
A27	1:1	2	200	30	Spherical and aggregated	Flattened at the end
A28	1:1	2	400	30	Spherical and free flowing	Flattened at the end
A29	1:1	10	200	15	Spherical and sticky	-
A30	1:1	10	400	15	Spherical and free flowing	Intact
A31	1:1	10	200	30	Spherical and aggregated	Flattened at the end
A32	1:1	10	400	30	Spherical and free flowing	Flattened at the end

7.5. Fourier transform infrared (FTIR) spectroscopy

FTIR spectra were taken to investigate chemical interactions between drug and polymer. The beads were analyzed by FTIR (FTIR-8400S, Shimadzu, Japan) in transmission mode. A single bead was mixed with KBr (40 mg) and then formed into a disc in a press. Transmission spectra were recorded using at least 20 scans with 2 cm⁻¹ resolution, in the spectral range 4700–340 cm⁻¹.

7.6. Differential scanning calorimetry (DSC) analysis

DSC was performed on modified starch (a); sodium alginate (b); MET (c) and drug-loaded microbeads (d). The analyses were performed on a DSC 60 (Shimadzu Asia Pacific, Japan) using sealed aluminum pans. The sample pan and the reference pan were heated from 35 to 300 °C at a scanning rate of 20 °C/min, held for 2 min at 300 °C and cooled to 35 °C at 20 °C/min.

8. Release study

The *in vitro* dissolution studies were carried out using the paddle method (USP 21), rotated at 50 rpm in 900 mL of dissolution medium (0.1 N Hydrochloric acid, pH 1.2) maintained at 37 ± 0.5 °C. The quantity of microbeads containing 200 mg of MET was used in each case. Samples (10 mL) were withdrawn at intervals of 1 h and replaced with equal amounts of fresh medium. The sample was diluted and the amount of metformin hydrochloride released was determined at wavelength of 233 nm, using a uv/visible spectrophotometer (Schimadzu 1700, Japan, UV-VIS spectrophotometer). Determinations were done in triplicates.

9. Modeling and comparison of release profiles

Data obtained from *in vitro* release studies were fitted to various

kinetic equations to find out the kinetics and mechanism of drug release from floating microbeads as well as that of the marketed brand of sustained release tablet of MET (brand X).

The drug release mechanism for all the formulations in 0.1 N HCl was fitted to zero order, first order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas models.

- Zero order [29]:

$$Q_t = Q_0 + K_0 t \quad \text{Eq. 3}$$

where Q_t is the amount of drug released at time t , K_0 is the apparent dissolution rate constant or zero order release constant, and Q_0 is the initial concentration of the drug in the solution resulting from a burst effect.

- First order [29, 30]:

$$\ln Q_t = \ln Q_0 + K_1 t \quad \text{Eq. 4}$$

where K_1 is the first order release constant; in this case the drug released at each time is proportional to the residual drug inside the dosage form.

- Higuchi [31]:

$$Q_t = K_H \sqrt{t} \quad \text{Eq. 5}$$

where Q_t is the amount of drug released at time t and K_H is the Higuchi release rate; this is the most widely used model to describe drug release from pharmaceutical matrices.

- Hixon-Crowell [32]:

$$Q_0^{1/3} - Q_t^{1/3} = K_S t \quad \text{Eq. 6}$$

where Q_0 is the initial amount of drug in the pharmaceutical dosage form, Q_t is the amount of drug remaining in the pharmaceutical dosage form at time t , and K_s is a constant incorporating the surface/volume ratio. - Korsmeyer-Peppas [33]:

$$Q_t/Q_\infty = K_k t^n \tag{Eq. 7}$$

where K_k is a constant incorporating structural and geometric characteristics of the drug dosage form and n is the release exponent, indicative of the drug release mechanism. Q_t/Q_∞ is the fraction of drug released at time t .

The model of best fit was identified by comparing the values of correlation coefficients in drug release graphs.

10. Comparison of dissolution profiles

The formulations of floating beads of MET were compared to a marketed brand of sustained release tablet of MET, Glyciphage SR, manufactured by Franco-Indian Pharmaceuticals Pvt Ltd., Mumbai, India (brand X). The dissolution profiles were compared using a similarity factor, (f_2), as shown in Equation 8 [34]. The similarity factor is a logarithmic reciprocal square root transformation of one plus the average mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products over all time points:

$$f_2 = 50 \times \log \left\{ 1 + \frac{1}{n} \sum_{j=1}^n [R_j - T_j]^2 \right\}^{-0.5} \times 100 \tag{Eq. 8}$$

where n is the number of dissolution time points and R_j and T_j are the reference and test dissolution values at time t . Two dissolution profiles are considered similar when the f_2 value is 50 to 100. Values less than 50 indicate that the two products do not have similar dissolution behavior.

11. Data analysis

Each experiment was conducted in triplicate and the mean determined. Statistical analysis was carried out using the analysis of variance (ANOVA) on a computer software GraphPad Prism 4 (Graphpad Software Inc. San Diego, CA, United States) to compare the differences between the formulations. At 95 % confidence interval, probability p values less than or equal to 0.05 were considered significant.

II. RESULTS AND DISCUSSION

1. Preliminary formulation studies

The results of the effects of stirring speed, concentration of cross-linking agent, polymer concentration and curing time on the MET microbeads are presented in Table 1. At low stirring speed (200 rpm), the microbeads formed were generally irregular in shape but became more spherical as the stirring speed is increased to 400 rpm. Increasing the concentration of the cross-linking agent (calcium chloride) from 2 %w/v to 10%w/v produced microbeads that were more spherical in shape and more buoyant in acidic medium. Generally, it can be observed that a starch to alginate ratio of 7:1 produced microbeads with irregular shapes. The microbeads become more spherical and more buoyant as the ratio of starch to alginate was reduced.

The results also showed that the entrapment efficiency of the beads decreased as the curing time for the preparation of microbeads was increased. The microbeads became more irregular and aggregated when the curing time was increased. Thus, for the optimized microbeads, the time of curing was kept at a minimum (15 min) where they showed improved drug entrapment and spherical beads were obtained. Furthermore, the floating abilities of the beads were observed to increase with the concentration of the gas-forming agent (data not shown). The stirring speed also affected the shape of the microbead with microbeads prepared at a stirring speed of 400 rpm giving more spherical and free

Table II - Composition of optimized floating of metformin hydrochloride microbeads.

Content	A8	A14	A22	A30	A0
Metformin hydrochloride (mg)	500	500	500	500	500
Calcium chloride (%w/v)	10	10	10	10	10
Sodium bicarbonate (mg)	100	100	100	100	100
Sodium alginate (mg)	80	100	133.3	200	400
Starch (mg)	320	300	266.7	200	-

floating microbeads. Optimized floating microbeads containing sodium alginate alone (A0) and the modified Chinese yam starch-alginate blends which yielded spherical microbeads that remained intact after floating for 12 h (formulations A8, A14, A22 and A30) were used for further studies and their compositions are presented in Table II.

2. Physicochemical properties

The SEMs of the microbeads containing sodium alginate and starch-alginate blends at ratios 1:1 and 4:1 are shown in Figure 1. The shapes and surface characteristics of the microbeads observed from the micrographs shows that the beads were spherical and discrete. Microbeads containing only sodium alginate exhibited smoother surfaces (Figure 1a) which is in agreement with previous works done [19, 35]. The surface of the microbeads appeared rougher and porous as the amount of starch increases. Thus, the porosity of the microbeads increased with the amount of starch in the formulation as observed in Figure 1c.

The FT-IR spectra of MET (a), modified starch (b), sodium alginate (c) and metformin loaded beads (d) are presented in Figure 2.

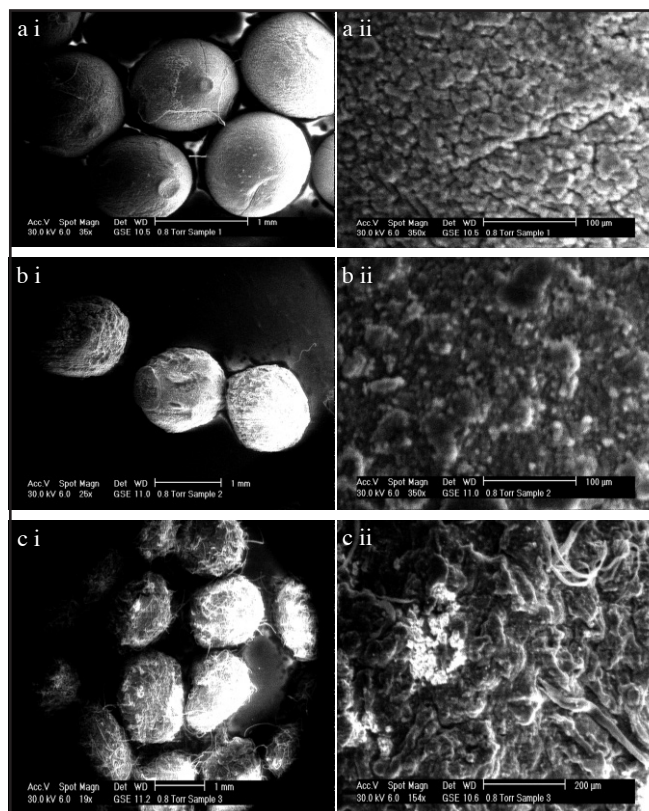


Figure 1 - SEM images showing shape and the surface characteristics of floating microbeads of metformin hydrochloride containing: (a) sodium alginate only, A0; (b) modified Chinese yam starch: sodium alginate (1:1), A30; (c) modified Chinese yam starch:sodium alginate (4:1), A8.

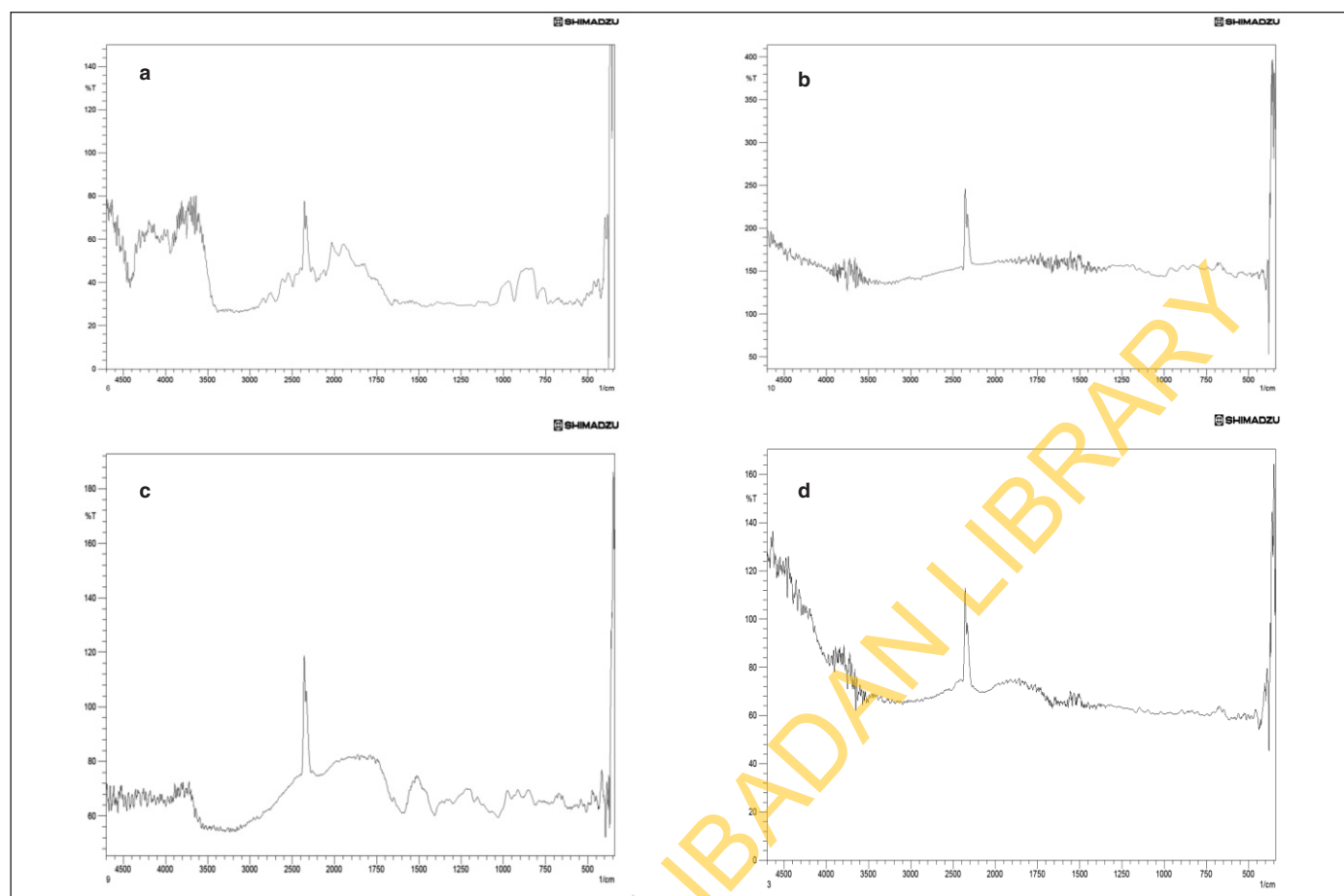


Figure 2 - FTIR spectra for (a) metformin hydrochloride; (b) Chinese yam starch; (c) sodium alginate and (d) metformin-loaded microbead.

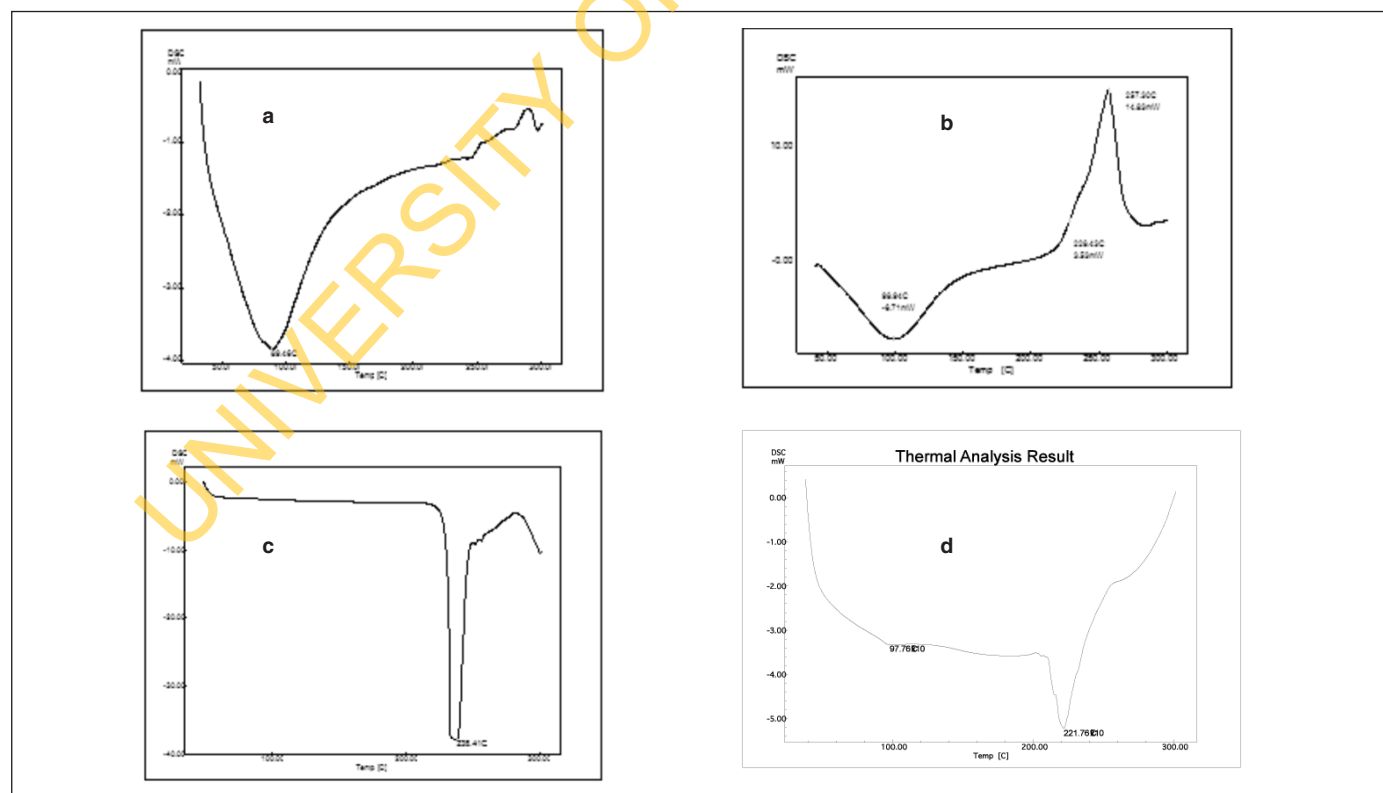


Figure 3 - DSC thermographs for (a) Chinese yam starch; (b) sodium alginate; (c) metformin hydrochloride and (d) metformin-loaded microbead.

Table III - Properties of floating metformin hydrochloride microbeads (mean ± standard deviation, n = 3).

Formulation code	Starch:alginate	Mean size (mm)	Buoyancy		Swelling index	Entrapment efficiency (%)
			FLT (s)	TFT (h)		
A8	4:1	1.475 ± 0.016	5.00 ± 0.03	12.10 ± 0.36	2.12 ± 0.07	51.72 ± 1.37
A14	3:1	1.330 ± 0.011	7.50 ± 0.01	12.35 ± 0.30	2.75 ± 0.18	54.14 ± 1.06
A22	2:1	1.301 ± 0.010	10.00 ± 0.02	12.05 ± 0.23	2.50 ± 0.11	41.91 ± 2.14
A30	1:1	1.198 ± 0.008	18.50 ± 0.02	11.75 ± 0.55	2.25 ± 0.24	37.70 ± 2.03
A0	0:1	1.190 ± 0.009	68.60 ± 0.04	9.80 ± 1.17	1.60 ± 0.57	39.71 ± 1.49

The spectra of the loaded beads suggest that MET contained in the starch-alginate polymeric network was completely entrapped.

The DSC thermograms of modified starch (a), sodium alginate (b), MET (c) and MET-loaded beads (d) are shown in *Figure 3*. For the modified Chinese yam starch, an endothermic peak was observed at 89.46 °C corresponding to melting process while for sodium alginate, an endothermic peak at 99.9 °C was observed. MET showed a large peak around 238.41 °C. The DSC data suggest that changes had taken place in the thermal behavior of metformin hydrochloride. Thus, the entrapment of the drug in the polymeric system resulted in a shift in the peaks.

The properties of the optimized beads are presented in *Table III*. The mean particle sizes of the beads ranged from 1.190 ± 0.008 mm for beads containing sodium alginate alone to 1.47 ± 0.016 mm for those containing starch: alginate ratio of 4:1. Thus, the bead size was directly proportional to the content of the starch in the formulation.

The entrapment efficiency is an essential parameter for assessing the drug loading of microbeads. In this study, the entrapment efficiencies of the MET- loaded microbeads range from 37.70 ± 2.03 % to 54.14 ± 1.06 %. The drug entrapment efficiency was relatively low and this could be attributed to the fact that MET, being highly water soluble, could have diffused out the calcium chloride solution at the time of encapsulation or during curing. It can be observed that the entrapment efficiency generally increased as starch concentration increased; This could be due to the porous nature of the starch gel matrix which allowed considerable drug loading up to a certain concentration beyond which saturation occurred. Thus, there would be competition for space between the swelled starch gel and the drug molecules in the alginate network of the microbeads. Statistical analysis showed that there were significant differences (p < 0.05) in the entrapment efficiency of the microbeads. When related to the particle size of MET-loaded microbeads, the entrapment efficiency was observed to generally increase as the mean particle size of the beads increased.

The floating beads are expected to remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Sodium bicarbonate imparted buoyancy to the formulations in addition to providing the initial alkaline microenvironment for the polymers to gel. The floating lag time (FLT) and total floating time (TFT) of the different formulations are presented in *Table III*. The floating ability can be observed to vary with the starch to alginate ratio. The formulations containing the blend of starch and alginate showed better floating ability than the formulation containing only sodium alginate polymer. This may be related to the surface characteristics of the microbeads as shown in *Figure 1*. The higher porosity of the beads containing starch will enhance fast release of CO₂ and thus accelerate the hydration of the floating beads. The microbeads containing a blend of starch and alginate floated in 0.1 N HCl with a minimum lag time of less than 20 s and remained buoyant for 12 h without any signs of degradation in the test medium. Thus, a major factor contributing to floating appeared to be the concentration of modified Chinese yam starch in the formulation.

3. Release study

The release profiles of the various formulations of floating microbeads are shown in *Figure 4* while the dissolution times are presented

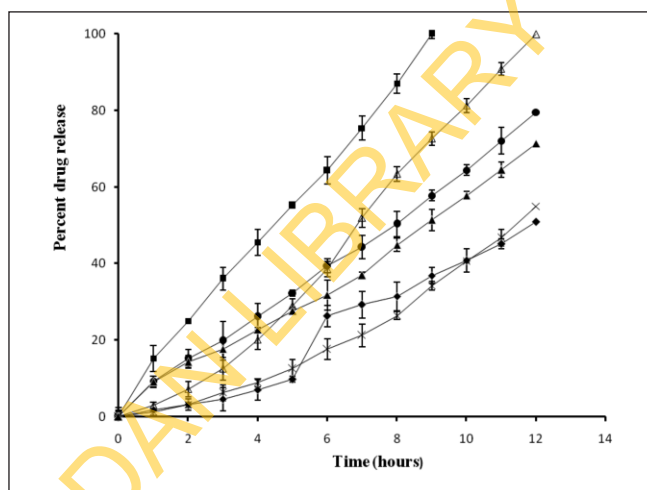


Figure 4 - Plot of percent drug release versus time (h) for marketed sustained release tablet of metformin hydrochloride and floating microbeads: Δ, brand X; ■, A8; ●, A14; ▲, A22; ◆, A30 and X, A0.

Table IV - Values of t₁₅ and t₅₀ for the branded sustained release tablet and floating microbeads formulations of metformin hydrochloride in 0.1N HCl

Formulation	t ₁₅ (h)	t ₅₀ (h)
Brand X	3.40	6.80
A8	1.00	4.40
A14	2.00	8.00
A22	2.10	8.75
A30	5.40	11.50
A0	5.80	11.20

in *Table IV*. The floating beads showed sustained release of MET in an acidic environment and the drug release patterns obtained were almost linear. For most controlled release preparations, an initial high rate of drug release is usually observed at the beginning of the controlled release process which can be due to a number of mechanisms including surface desorption, pore diffusion or lack of a diffusion barrier to regulate the diffusion process. The initial non-steady period is usually referred to as “burst release” [36]. While burst release of drugs may be utilized in the administration of certain drugs, in controlled release systems, it can have adverse pharmacological effects and can be economically ineffective [36]. The time independent release is often more desirable because the drug is released at a steady state thereby optimizing therapy. The release profile indicated that the beads did not exhibit burst release, indicating that the drugs were embedded in the beads and were not loosely bound to the surface of the beads [21]. For most of the formulations, a steady time independent release rate was observed (*Figure 4*). However, formulation A8 which contained the highest starch concentration, exhibited a release of 15 % within the first hour. This could be due to the increased porosity of the beads.

The t₅₀ values (i.e. the time for 50 % of drug content to be released) for the formulations ranged from 4.40 h (A8) to 11.50 h (A30). There were significant (p < 0.001) differences in the t₅₀ values for the various formulations. The drug release from the floating beads appears to

be controlled by the concentration of starch in the formulation. The higher the concentration of starch in the floating beads, the faster the dissolution rate. This could be due to the fact that the presence of starch renders the gel matrix more porous, thereby facilitating the release of the drug. Thus, the novel starch could be used to modulate the release of MET from the microbeads. Furthermore, it can be observed that formulations A22 and A30 show the best appropriate balance between floating and controlled release although the entrapment efficiency was low. This indicates that these formulations would be useful as gastroretentive dosage form for the delivery of MET.

The marketed brand of MET extended-release tablet (Brand X) comprises a hydrophilic polymer matrix system which allows the drug to be released slowly from the dosage form by a process of diffusion through the gel matrix. The release profile (Figure 4) showed a t_{50} value of 3.4 h. All the floating microbead formulations except A8 showed higher t_{50} values than that of brand X, indicating better sustained release properties.

The kinetics of drug release from dosage forms are important as they influence the dosing interval, bioavailability, overall patient

compliance and in many instance the occurrence of toxic or untoward effects [37]. The graphs of the release kinetic models are shown in Figure 5. The correlation coefficient was used as an indicator of best fit for each of the models considered and the values of the correlation coefficients are presented in Table V. The release of MET followed Korsmeyer-Peppas model for formulations A8 and A0 ($r^2 = 0.998$ and 0.996 , respectively). This indicates drug release from these formulations is controlled by more than one process, usually a combination of diffusion and erosion mechanisms [33]. Drug release from formulations A14 and A22 followed zero order kinetics ($r^2 = 0.997$ and 0.992 , respectively), indicating the release of drug is through progressive erosion and is independent of the time and drug concentration. On the other hand, the release of MET from formulation A30 followed the first order kinetics ($r^2 = 0.960$) indicating that the rate of release is dependent on drug concentration. This indicates that manipulating the concentration of the modified starch can be used to modulate the drug release mechanism from the floating microbeads. The release of MET followed Korsmeyer-Peppas model for brand X ($r^2 = 0.995$).

In recent years, the Food and Drug Administration (FDA) has

Table V - Correlation obtained with different kinetic models.

Formulation	Zero order plot (r^2)	First order plot (r^2)	Higuchian plot		Hixson-Crowell plot	Korsmeyer plot (r^2)
			Slope (n)	r^2		
Brand X	0.983	0.880	31.98	0.846	0.967	0.995*
A8	0.985	0.917	33.40	0.927	0.947	0.998*
A14	0.997*	0.937	23.65	0.917	0.963	0.992
A22	0.992*	0.940	20.91	0.901	0.940	0.978
A30	0.957	0.960*	16.45	0.820	0.910	0.951
A0	0.956	0.923	16.21	0.792	0.948	0.996*

* Highest correlation of drug release pattern in 0.1N HCl.

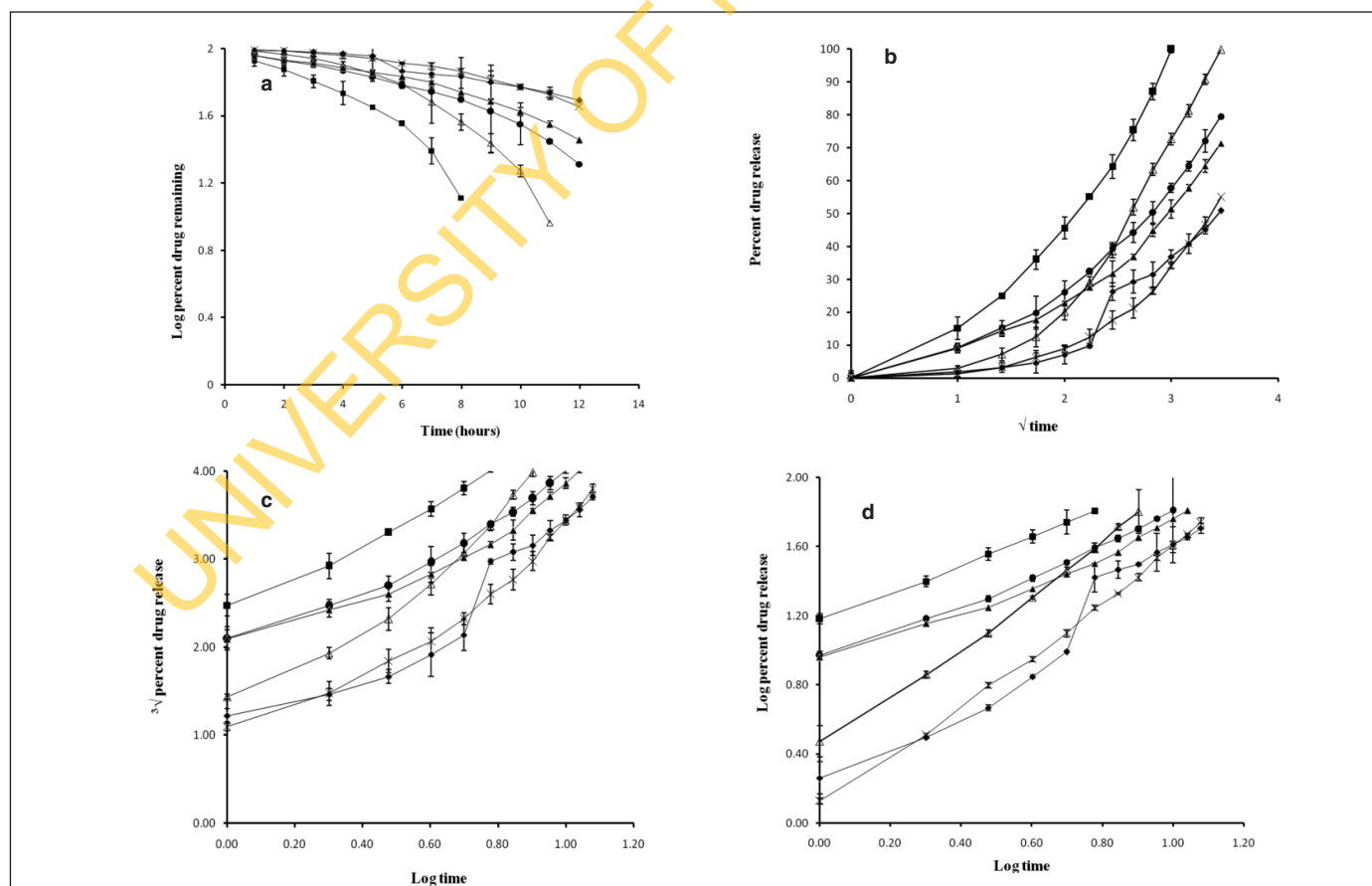


Figure 5 - Kinetic models for marketed sustained release tablet of metformin hydrochloride and floating microbeads: Δ , brand X; \blacksquare , A8; \bullet , A14; \blacktriangle , A22; \blacklozenge , A30 and \times , A0. (a) First order; (b) Higuchi square root law; (c) Hixson-Crowell cube root model; (d) Korsmeyer-Peppas model.

Table VI - Similarity factor (f_2) for dissolution profiles of sustained release tablet (Brand X) and floating beads of metformin hydrochloride in 0.1N HCl.

Formulation	A8	A14	A22	A30	A0
Brand X	25.35	46.11	27.29	39.15	26.67
A8	-	19.33	17.16	11.52	11.28
A14	-	-	61.88	35.39	34.45
A22	-	-	-	42.09	41.19
A30	-	-	-	-	68.55

placed more emphasis on comparison of dissolution profiles in the area of post-approval changes and biowaivers [38]. A dissolution profile comparison between drug products helps assure similarity in product performance and signals bioequivalence. One of the simplest methods for the comparison of dissolution profiles is the factor f_2 , described as a similarity factor [34]. When the two profiles are identical, $f_2 = 100$. An average difference of 10 % at all measured time-points results in an f_2 value of 50. FDA has set a public standard of an f_2 value between 50 and 100 to indicate similarity between two dissolution profiles [38]. The f_2 values obtained from this study are presented in Table VI. In the comparison of the dissolution profiles of the various formulations of microbeads, similarity was observed between the dissolution profiles of formulations A30 and A0 ($f_2 = 68.55$) and formulations A14 and A22 ($f_2 = 61.88$). The results, however, reveal dissimilarity among the release profiles of the starch: alginate microbeads and Brand X as f_2 values were less than 50. Thus, drug release from the starch-alginate beads was not the same as that of the marketed Brand of controlled release tablet. This is expected since Brand X is a controlled release tablet made with hydrophilic polymers while the formulated microbeads are gastroretentive controlled release system.

*

The properties of the starch: alginate microbeads were affected by the stirring speed, ratio of starch: alginate and curing time. The release of MET from the floating microbeads was controlled by varying the starch to alginate polymer ratio. The results show that the release from the microbeads could be modulated by the concentration of the modified starch in the formulation. In particular, formulations A22 (with a ratio of starch to alginate of 2:1) and A30 (with a ratio of starch to alginate of 1:1) showed best appropriate balance between buoyancy and sustained drug release. The results indicate that modified Chinese yam starch - alginate blend can be useful for the formulation of gastroretentive controlled release system of metformin hydrochloride.

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DECLARATION OF INTEREST

The authors report no conflict of interest.

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