



## Date mucilage as co-polymer in metformin-loaded microbeads for controlled release.

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### ABSTRACT

Mucilage from the fruit of the date palm (*Phoenix dactylifera*) was characterized and evaluated for the use as a polymer in controlled release metformin-loaded microbeads. Metformin-loaded (1% w/v) microbeads were formed by the ionotropic gelation method using blends (2% w/v) of date mucilage: sodium alginate in varying concentrations (20:80 C4, 25:75 C3, 33:67 C2, 50:50 C1) using zinc chloride (10% w/v) as a crosslinking agent. Bead size and morphology, swelling index, entrapment efficiency and release properties were then measured. The dissolution profiles were fitted to kinetic equations to determine the kinetics and mechanisms of drug release while the similarity factor,  $f_2$  was used to determine formulations with similar drug release patterns. The results showed that the date mucilage had crude fat content of 2.5%. The microbeads formed were spherical with bead sizes ranging from 0.44 to 1.99 mm except for the one prepared using blend C4 which was ellipsoidal. Drug entrapment efficiency ranged between 25.0 and 91.1% w/w with alginate alone giving the least entrapment. Microbeads formulated with blends C2 and C3 had the slowest dissolution rates at  $t_{15} < 9\%$  in 240 hours. C3, however, had a higher entrapment efficiency and was considered the optimum formulation. All microbead formulations fitted the Korsmeyer-Peppas model with super case II transport mechanism except for the one made of sodium alginate alone, which had an anomalous (non-Fickian) diffusion. Secondary parameters of the Korsmeyer-Peppas' model showed that microbead formulations C2 and C3 provided controlled release for longer than 24 hours. Similarity factor,  $f_2$  showed comparable release profiles between C2 and C3 ( $f_2=94.2$ ). This study shows that mucilage from the date fruit could potentially be used as a polymer in the formulation of controlled release metformin-loaded microbeads.

**KEY WORDS:** Date palm mucilage, metformin, microbeads, controlled release, *Phoenix dactylifera*, excipients

### INTRODUCTION

The design of controlled drug delivery systems involves the use of diverse polymers in combination with an active pharmaceutical ingredient (API) to obtain a desired release pattern. One approach for controlled release formulation of APIs is the production of polymeric gel beads (1). Microbeads provide accurate

delivery of potent drugs and reduce the concentration of the drug at sites other than the target tissue (2). In addition, microbeads provide sustained release properties and a more uniform distribution of the API within the gastrointestinal tract as well as, increased drug bioavailability.

Metformin Hydrochloride is an oral anti-diabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of Type 2 diabetes, particularly in obese people with normal kidney function. Metformin is an ideal candidate for the preparation of extended-

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release and slow release formulations due to its relatively short plasma half-life, low absolute bioavailability and gastric irritation of the mucosal wall of the intestine.

Possible therapeutic benefits of formulating metformin microbeads into a controlled release dosage form includes lower cost, simple processing, improved efficacy, reduced adverse effects, flexibility in terms of the range of release profiles attainable, increased convenience, patient compliance and improved adherence to medication (3). Microbeads for controlled release have been prepared from a wide variety of materials including polysaccharides and proteins from natural and synthetic sources. Among them are chitosan (4), albumin (5), sodium alginates (6), starch (7) and gums (8).

The date palm (*Phoenix dactylifera* L.) also called Nakhla and 'tree of life' by the Arabs (the Nigerian local name in Hausa-Dabino) is a member of the palm family Arecaceae or Palmae (9). It is believed to be indigenous to the countries around the Arabian Gulf. The date palm is one of the oldest cultivated fruit trees and has been used as staple food in the Middle East for over 6000 years (10). Dates and their constituents play a role in the prevention of diseases through anti-oxidant (11), anti-inflammatory and anti-bacterial activity (12). Rahmani *et al.*, also reported the therapeutic effects of date fruits in the prevention of cancer via modulation of anti-tumour activity (13). Dates are known to contain a high concentrations of polysaccharides, proteins, fats and edible fibre (14). The presence of polysaccharides, safety, availability, and usefulness as food has made dates of interest in excipient development for pharmaceuticals. For example, Ngwuluka *et al.*, used dried and milled date fruit as a binding agent in a paracetamol tablet formulation at a concentration of 2 - 20% w/w. The tablets had acceptable mechanical properties at 20% w/w. The authors also reported that dried milled date fruit conferred longer disintegration times, thus, indicating a probable controlled release ability (15).

In the present study, mucilage from the date fruit was extracted and its potential as a controlled-release polymer in metformin-loaded microbeads was evaluated. The overall objective was to reduce the

frequency of the use of the metformin, by providing a controlled release formulation for patients with type 2 diabetes.

## MATERIAL AND METHODS

### Materials

The materials used include Metformin hydrochloride BP (gift from Fidson Healthcare Plc., Nigeria), sodium alginate (viscosity - 445 mPas, Art. No. 9180.2, Carl Roth GmbH + Co., Karlsruhe, Germany), zinc chloride (Alfar Aesar GmbH & Co., Karlsruhe, Germany), *Phoenix dactylifera* dried date fruit (locally obtained from Zaria, Kaduna State in the Northwestern part of Nigeria).

### Extraction and purification of mucilage from dried date fruit

The method of Akin-Ajani *et al.*, was used to extract and purify the mucilage (16). Dried fruit (500 g) of *Phoenix dactylifera* were deseeded, cut into pieces and soaked in 4 L of chloroform-water DS for 36 hours. This was then sieved with a muslin cloth to remove the extraneous matter. Ethanol (90% v/v) was used to precipitate the mucilage. The mucilage thus collected was washed three times with diethyl ether to further purify it. The mucilage was dried at 40°C in a hot air oven for 18 hours. After drying, the mucilage was pulverised and passed through a sieve with mesh size 250 µm. It was then stored in an airtight container until needed.

### Physicochemical properties of the polymer

Proximate analysis (moisture content, ash content, crude fibre, crude fat) and swelling power were determined using methods described previously (17). The polymer obtained from the date fruit and blends with sodium alginate 20:80 C4, 25:75 C3, 33:67 C2, 50:50 C1, were prepared and the viscosity determined using a Brookfield Viscometer (RVDV-II+P, Middleboro, USA) using spindle 4 and a shear rate of 100 RPM at 27°C ± 3°C. The swelling rate of the parent polymers and polymer blends were also determined over a 24-hour period.

## Elemental Analysis of the polymer

Date mucilage was analysed for twelve elements using Atomic Absorption Spectroscopy (Perkin Elmer, AAnalyst 200 AA Spectrophotometer UK (AAS)). The instrument conditions are shown in Table 1. Microwave-assisted acid digestion method was used with slight modification (18). Samples, 2.0 g each was placed in polytetrafluoroethylene (PTFE) flasks (25 mL). A mixture (20 mL) of acid ( $\text{HNO}_3$  – 65%) and oxidant ( $\text{H}_2\text{O}_2$  – 30%) in a ratio of 2:1 was added to each flask. The flasks were kept at room temperature for 1 hour, then placed in a covered Teflon container, placed in a domestic microwave oven and heated at 600 W for 5 minutes. After cooling the digestion flasks, the resulting solutions were evaporated to a semidried mass to remove excess acid. The mass obtained was diluted with 0.2 M nitric acid solution and kept as stock sample solution. The blank was also prepared using the same procedure.

**Table 1** Operating conditions of the AAnalyst 200 AA

Oxidant: Air; oxidant flow	10.0 L min <sup>-1</sup>
Fuel: Acetylene; acetylene flow	2.5 L min <sup>-1</sup>
Nebulizer aspiration flow rate	4 – 6 mL min <sup>-1</sup>

The samples were each placed in the AAS with the blank and the results are shown in ppm. Equation 1 was used to determine the concentration of the elements in mg/g.

$$\text{Element (mg/g)} = \frac{\left(\frac{CV \text{ df}}{W}\right)}{1000} \quad \text{Eq. 1}$$

Where, C is the concentration of element in the sample solution in mg/L, V is the volume of undiluted sample solution in mL, W is the sample weight in g and df is the dilution factor.

## Preparation of metformin hydrochloride microbeads

Microbeads embedded with metformin hydrochloride were prepared by the ionotropic gelation technique. Blends of the *Phoenix* mucilage and sodium alginate (as stated previously) were prepared. Metformin

hydrochloride (1% w/v) was added and stirred continuously until a dispersion was obtained (2 g polymer:1 g drug).

The dispersion was extruded into a beaker containing zinc chloride (10% w/v) using a 5 mL hypodermic syringe with a 23 G needle at a rate of 2 mL/30 s stirring at 300 RPM for 15 minutes. The microbeads were left to stand for about 7 minutes to allow for further cross-linking. The beads were collected by decantation, washed with distilled water and allowed to solidify by air drying at room temperature and further drying at 40°C for 6 hours. The microbeads formed were then stored in airtight containers until required. The ratio of sodium alginate to date mucilage in the formed microbeads was not determined.

## Physicochemical properties of the microbeads

The bead size of the microbeads was determined by optical microscopy (Olympus Model 312545, Japan). The morphology and surface characteristics of the microbeads were analysed using scanning electron microscopy (SEM) (Hitachi Model S- 2460N, Japan) at an accelerating voltage of 25 KV. The surfaces of the samples were sputter-coated with a thin gold layer in an argon atmosphere to prevent charging.

For determining the swelling index, 100 mg of microbeads were soaked in 20 mL of a phosphate buffer at pH 6.8 and the weight of the beads was determined after 3 hours. The swelling index was calculated using Equation 2:

$$\text{Swelling index (\%)} = \frac{\text{Change in weight (mg)}}{\text{Initial weight (mg)}} \times 100 \quad \text{Eq. 2}$$

To determine the entrapment efficiency of the drug-loaded microbeads 50 mg (equivalent to 25 mg of metformin hydrochloride) was weighed and crushed in a mortar with a pestle and suspended in 50 mL of a phosphate buffer at pH 6.8. The mixture was then filtered and the absorbance of the filtrate was carried out using a UV spectrophotometer (UV spectrophotometer, Gransmore Green, Felsted Dunmow Essex CM6 3LB England) at 233 nm to determine the amount of the drug present in the

weighed microbeads using Equation 3:

$$E (\%) = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad \text{Eq. 3}$$

Where, E is the Entrapment Efficiency.

### Drug release study

The *in-vitro* dissolution studies were performed using the paddle method (19) rotated at 100 RPM in 900 mL of phosphate buffer at pH 6.8, maintained at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . Microbeads equivalent to 500 mg of metformin hydrochloride were placed in the dissolution vessel. Samples (10 mL) were withdrawn at different time intervals and replaced with equal amount of fresh medium. The sample was filtered and diluted and the amount of metformin hydrochloride released was determined using UV spectroscopy as described above. The dissolution profiles of the different formulations were obtained.

### Kinetic modelling of release profiles

The comparison of the release studies data fitted into various kinetic equations is presented in Table 5. Kinetic modelling of the release data was performed by fitting to different Equations, that is, zero order, first order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas equations to determine the kinetics and mechanism of drug release. Values of correlation coefficients were used to identify the model of best fit.

### Data presentation and analysis

All experiments were performed in triplicate and the data is presented as mean  $\pm$  SD. Statistical analysis was performed using one-way Analysis of Variance (ANOVA) using GraphPad Prism<sup>®</sup> 5 (GraphPad Software Inc., San Diego, USA). Dunnett's Multiple Comparison Test was used to compare the individual differences between the physicochemical properties. At 95% confidence interval,  $p < 0.05$  was considered significant. Additionally, the microbead formulations obtained using alginate alone and the different polymer blends were analysed using the similarity factor ( $f_2$ ) on DD Solver (Microsoft Excel add-in, Excel, 2016).

## RESULTS AND DISCUSSION

### Proximate and elemental composition of the date mucilage

Moisture content, crude fibre, crude ash and crude fat content of the mucilage were  $6.12 \pm 0.28$ ,  $0.60 \pm 0.03$ ,  $3.00 \pm 0.15$  and  $2.50 \pm 0.12$  respectively. The moisture content was set at a limit of  $\leq 15.0\% \text{ w/w}$  for natural gums and mucilages (20, 21). The swelling power, defined as the swollen sediment weight (g) per g of dry sample, was  $13.74 \pm 0.69$ .

The elemental composition of the *Phoenix dactylifera* date fruit mucilage for monovalent, polyvalent and heavy metals is shown in Table 2. The mucilage exhibited measurable concentrations of iron and sodium. Its heavy metal concentrations were below the level of detection (LOD).

**Table 2** Elemental composition of date mucilage

ELEMENT	WAVE-LENGTH (nm)	SLIT (mm)	LIMIT OF DETECTION (mg/L)	CONTENT (mg/g)
Mg	285.21	2.7/1.05	0.004	$7.15 \pm 0.36$
K	766.49	2.7/0.45	0.020	$8.10 \pm 0.41$
Ca	422.67	2.7/0.60	0.062	$2.28 \pm 0.11$
Na	589.00	1.8/0.60	0.007	$230.52 \pm 11.53$
Fe	248.33	1.8/1.35	0.040	$236.52 \pm 11.83$
Cu	324.75	2.7/0.80	0.025	$15.10 \pm 0.76$
Co	240.73	1.8/1.35	0.053	< LOD
Cd	228.80	2.7/1.35	0.010	< LOD
Pb	283.31	2.7/1.05	0.180	< LOD
Ni	232.00	1.8/1.35	0.060	< LOD
Mn	279.48	1.8/0.60	0.016	$45.11 \pm 2.26$
Zn	213.86	2.7/1.80	0.006	$36.76 \pm 1.84$

### Composition and viscosity of the polymer blends

The composition of the polymer blends and their corresponding formulation codes are presented in Table 3. The polymer blend concentration was  $2\% \text{ w/v}$ . Viscosities of alginate, date mucilage and the polymer blends used in making the microbeads are also presented in Table 3. The viscosity of the polymer blends decreased with the increase in date mucilage concentration in the order of  $C1 < C2 < C3 < C4$ . The viscosities of both the date mucilage and sodium

alginate were significantly ( $p < 0.05$ ) lower than those of the polymer blends.

**Table 3** Composition and viscosity of polymer blends

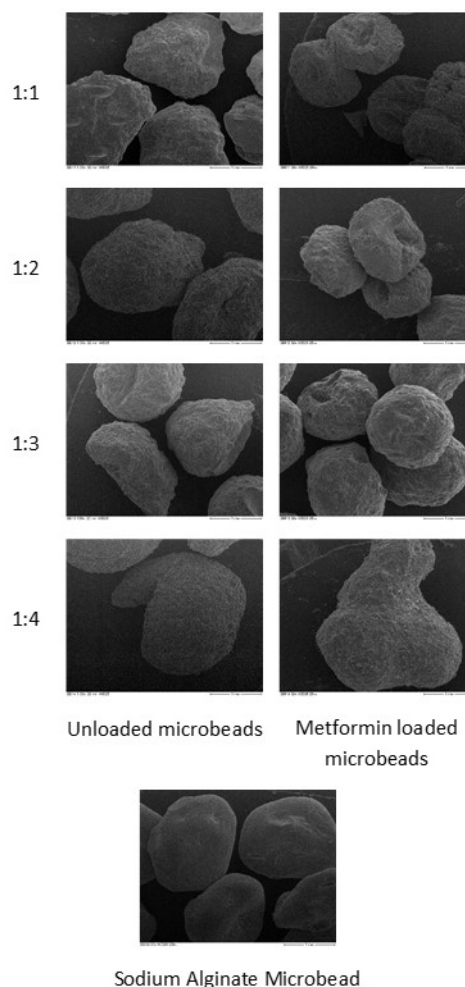
POLYMERS	POLYMER BLEND (%)	FORMULATION CODE	VISCOSITY (MPA.S)
Alginate	100:0	T1	532.0 ± 4.1
Date mucilage	100:0	C0	52.0 ± 0.1
Date: Alginate	20:80	C4	1210.0 ± 0.3
	25:75	C3	964.0 ± 0.2
	33:67	C2	780.0 ± 0.4
	50:50	C1	580.0 ± 0.8

### Physicochemical properties of metformin-loaded microbeads

The SEM showing the shape and morphology of the microbeads are presented in Figure 1. The formulation containing sodium alginate alone as a polymer (T1) produced spherical microbeads with smooth surfaces with a mean particle size of 436.3  $\mu\text{m}$ . The date mucilage alone did not form microbeads. Microbead formulations C1 to C3 were also spherical in shape and similar to that prepared using alginate alone. C4 yielded an ellipsoidal shape. Generally, the beads had rough surfaces. This is consistent with previous studies where the rough surface was attributed to drying and to properties imparted by the embedded drug (8). The mean particle sizes of the microbeads are presented in Table 4. There was a decrease in the microbead size with an increased concentration of the date mucilage in the order of  $C4 > C3 > C2 > C1$ , but these sizes were significantly ( $p < 0.0001$ ) larger than the alginate microbeads. This significant increase in size may have been contributed by the high swelling capacity of date mucilage.

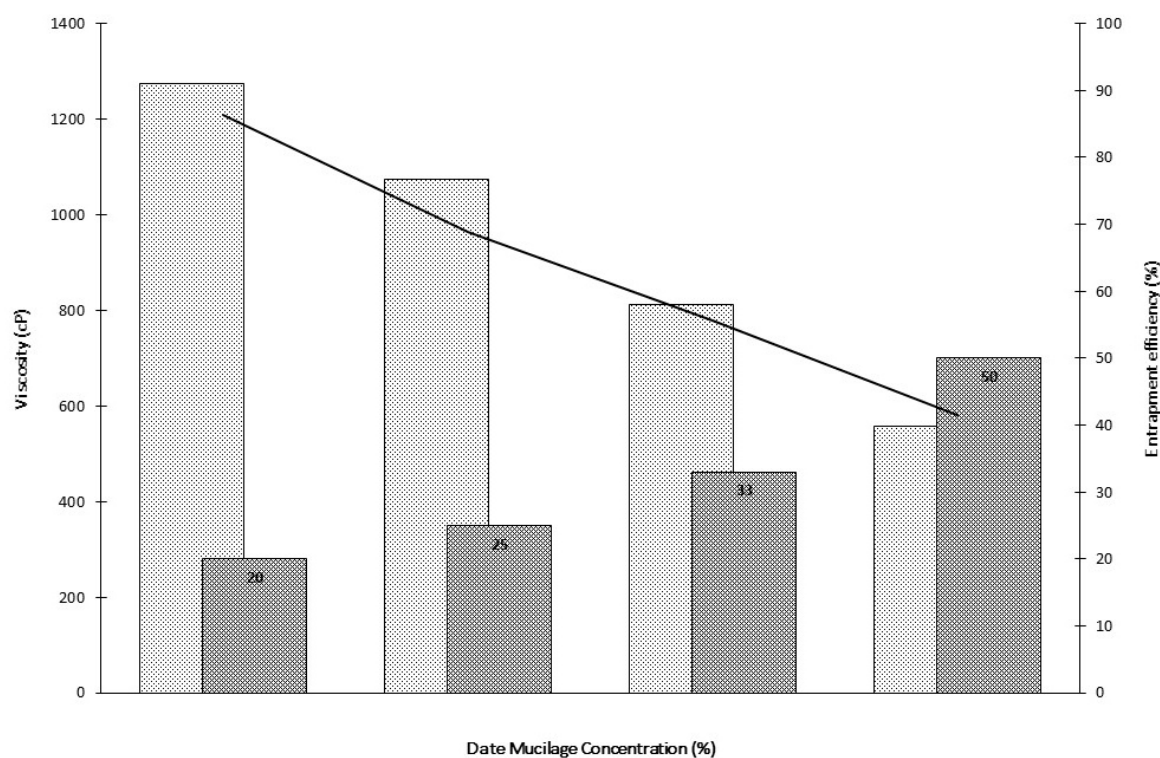
**Table 4** Physicochemical properties of microbeads

FORMULATION CODE	POLYMER BLEND (%)	MEAN BEAD SIZE ( $\mu\text{m}$ )	SWELLING INDEX (%)	ENTRAPMENT EFFICIENCY (%)	t15 (min)
C4	20:80	2147.9 ± 9.1	360.8	91.1	105
C3	25:75	1992.7 ± 7.5	142.8	76.8	-
C2	33:67	1633.4 ± 8.6	121.7	58.1	-
C1	50:50	1528.5 ± 6.4	105.5	39.8	90
T1	100:0	436.3 ± 6.3	25.7	25.0	120



**Figure 1** SEM of microbeads of different polymer concentrations (Mag. x 30)

The swelling index of the microbeads is also presented in Table 4. Microbeads prepared with sodium alginate alone had a swelling index of 25.7%. As the concentration of the date mucilage in the polymer blends increased, there was a corresponding decrease



**Figure 2** Plot showing relationship between viscosity and entrapment efficiency as date mucilage concentration increases

in the swelling index of the microbeads. However, they were still greater than that of the sodium alginate. The high swelling index was probably due to the presence of the date mucilage, a plant hydrocolloid (22). Mucilages are known to have a high water-binding ability due to the high concentration of hydroxyl groups in the polysaccharide (23).

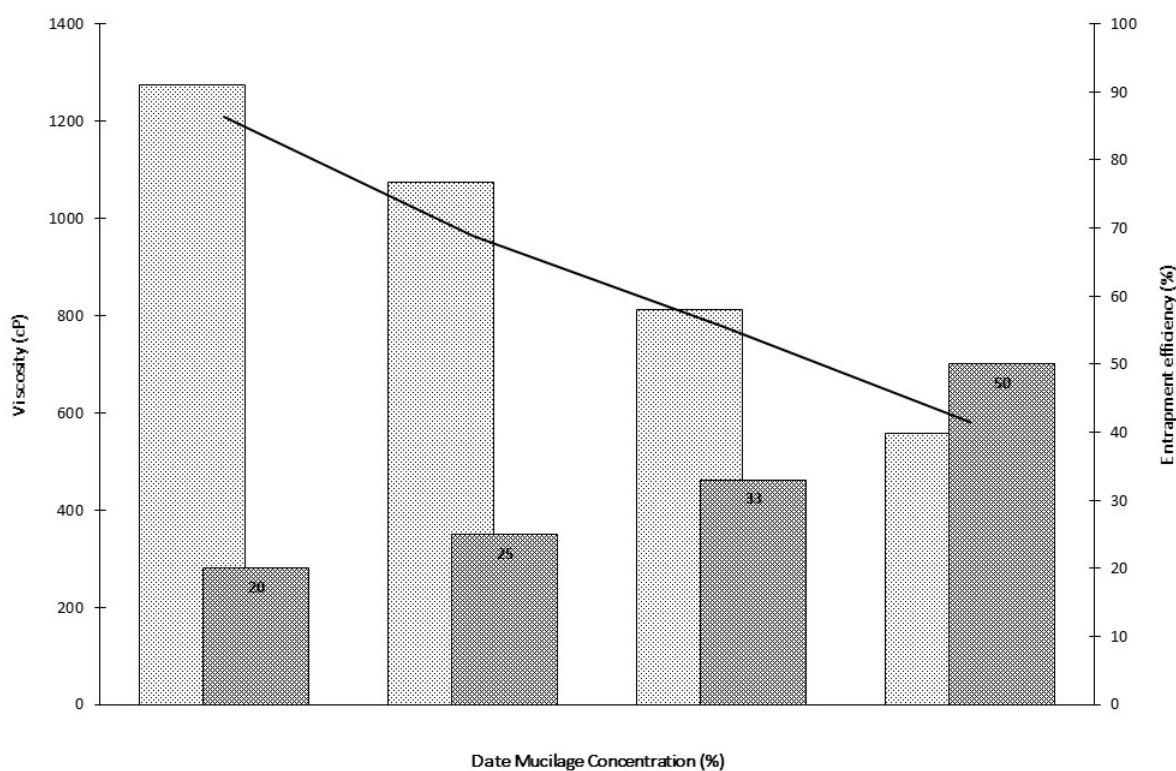
The entrapment efficiency shows the extent to which the drug is embedded in the polymer network and it is an essential parameter for assessing drug loading of microbeads. Table 4 shows that the entrapment efficiency ranged from 39.8% to 91.1% in the microbeads made from date:alginate polymer blends indicating that the presence of the date mucilage in the formulations improved the entrapment of the metformin compared to that using alginate alone. Entrapment efficiency also increased with a decrease in concentration of the the date mucilage in the order 50:50 < 33:67 < 25:75 < 20:80. The lower entrapment efficiency for blends C1 and C2 could be due to the metformin hydrochloride being a freely soluble drug in water and the lower viscosities of polymer blends of

C1 and C2, thus causing diffusion of the drug during curing. This is consistent with the viscosity of the polymer blends as shown in Figure 2. Diffusion has been shown to be inversely proportional to viscosity (24, 25). The increase in viscosity indicates increase in polymer-polymer interaction and thus increase in junction zones to which drug can be attached (26).

#### Release properties of metformin-loaded microbeads

Drug release from microbeads depends on the extent of cross-linking, morphology, size and density of the drug as well as the presence of adjuvant. Drug release from particulate systems involves three mechanisms, that is, release from the surface of particles, diffusion through the swollen rubbery matrix and a release due to polymer erosion which usually does not occur independently. In cases of release from the surface, absorbed drugs instantaneously dissolve upon contact with the release medium, this type of release leads to a burst effect (27).

The plots of percent drug released for the different

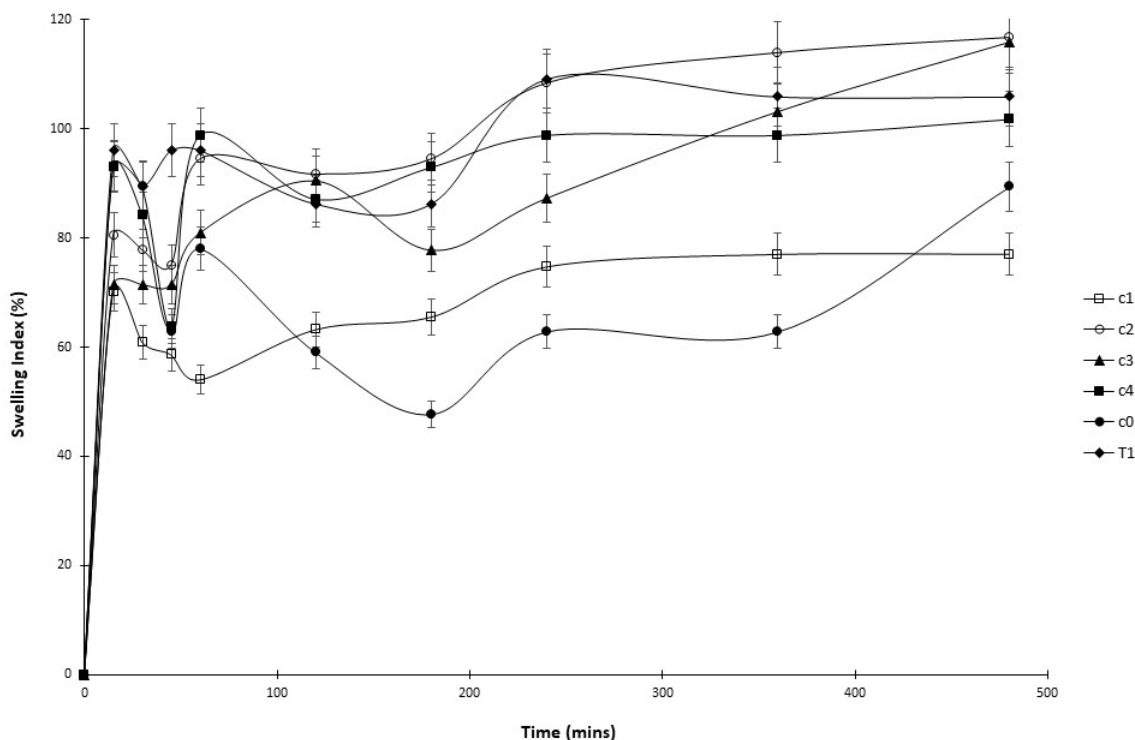


**Figure 3** Plots of % metformin released against time (min) for microbeads prepared with blends of date and alginate

polymer ratios is shown in Figure 3 while the values of  $t_{15}$  (time required for 15 % metformin to be released) is presented in Table 4. The microbeads had significantly ( $p < 0.0001$ ) different release properties depending on the polymer ratio used in the formulation. Formulation C2 had an initial lag time of over 30 minutes during which the drug release was less than 1%. This is of considerable significance as the formulation is intended for controlled release. Burst release, designated as the release of more than 15% of the drug in the first hour was not observed. The  $t_{15}$  values ranged from 90 to 120 minutes, that is, 105 minutes for C4, 90 minutes for C1, 120 minutes for T1, while C2 and C3 had not released up to 15 % at 240 minutes suggesting effective entrapment (28).

The dissolution time for the formulations followed the order of  $C3 < C2 < T1 < C4 < C1$ . The optimum polymer ratio, at which metformin release was slowest, appeared to be 25:75. Both C3 and C2 at 4 hours had released less than 9% while the other ratios including alginate alone had released  $\geq 26\%$ . The polymer structure of

hydrogels is such that it is able to retain the solvents absorbed by forming a swollen gel phase and, in cross-linked systems, will not dissolve regardless of the solvent (29). Matrix dissolution reduces the diffusion path in the polymer and counteracts the swelling process (30). The swelling index of the polymer blends behaved differently over time as shown in Figure 4. Both parent polymers and the polymer blends swelled to  $\geq 70\%$  within the first 15 minutes, after which, the swelling was not significantly different between the polymers. Nevertheless, there was a marked difference in the swelling patterns. Polymer blend C1, after the initial swelling to 70% within 15 minutes continued to swell to only 77% by the 8 hours. Within the first 15 minutes C2 attained 80% swelling and continued swelling slowly to 116% after 8 hours, which was the highest swelling attained among the polymer blends. In the case of C3, after swelling to 71% in the first 15 minutes it had a lag period of about 45 minutes after, which it continued to swell to 115% after 8 hours. Polymer blend C4 also swelled to 92% in the first 15 minutes but did not exceed 101% after 8 hours. At 24



**Figure 4** Swelling rate of parent polymers and polymer blends

hours (not shown), the rank order for the swelling rate of the polymers was  $C3 > C2 > C4 > T1 > C1 > C0$ . This suggests that each blend behaved differently and was responsible for the drug release profile obtained, which did not correlate with the viscosities of the blends. The features of the penetrant uptake, the drug dissolution process and the drug diffusion through the swelling polymeric network mainly rule the drug release from a polymeric matrix (31). These three phenomena depend, in turn, on the matrix viscoelastic characteristics, the drug solubility, and the drug diffusion coefficient. It is assumed that the incoming penetrant affects the motion of the drug molecules by influencing the drug diffusion coefficient in the gel, and altering the drug flux through the density gradient arising in the matrix during swelling (32).

The batch with the optimal ratio obtained here could therefore be formulated into a controlled-release dosage form of metformin hydrochloride thus minimizing the gastrointestinal irritation associated with the use of

the drug in type 2 diabetic patients and reduce the frequency of administration. Since release rates after 240 minutes were not measured, and the formulation released  $< 10\%$  of the drug at this time, no data is available on the pattern of release of drug after this time.

The correlation coefficients obtained from the various release kinetic models are presented in Table 5. Drug release from all the microbead formulations fitted the Korsmeyer-Peppas model with correlation coefficients,  $r^2 \geq 0.954$ . The Korsmeyer-Peppas model gives an insight into the type of drug release mechanism occurring from swellable polymeric devices (33). This shows that metformin release from the microbeads was governed by mechanisms of diffusion and erosion. Though drug release mechanism from the microbeads formed from alginate alone was anomalous (non-Fickian) diffusion i.e., both diffusion and relaxation (erosion)  $0.5 < n < 1$ , microbeads formed from the date mucilage:alginate blends had Super Case II transport (relaxation) mechanism of



**Table 5** Correlation coefficients obtained from release kinetic mathematical models for the metformin microbeads

FORMULATION CODE	ZERO-ORDER	FIRST-ORDER	HIGUCHI	HIXSON-CROWELL	KORSMEYER-PEPPAS	
					r <sup>2</sup>	n
C4	0.9948	0.9799	0.8368	0.9859	0.9981	1.103
C3	0.9282	0.9234	0.7478	0.9250	0.9535	1.348
C2	0.9891	0.9860	0.8099	0.9871	0.9994	1.187
C1	0.9945	0.9966	0.8310	0.9953	0.9995	1.127
T1	0.9432	0.9634	0.9542	0.9575	0.9960	0.701

$n > 1$ , suggesting accelerated drug release towards the end point of the release (34). Secondary parameters (not shown) from the Korsmeyer-Peppas model also showed that microbead formulations C2 and C3 would have controlled release  $>24$  hours in the order  $C3 < C2$ .

The similarity factor,  $f_2$  measures similarity between pairs of dissolution profiles. Values of  $f_2 > 50$  (50 - 100) are indicative of a similarity or equivalence of the two dissolution profiles and values of 100 indicate identical profiles. Results obtained showed similarity of dissolution profiles between formulations C1 and C4 ( $f_2 = 69.7$ ), C2 and C3 ( $f_2 = 94.2$ ), T1 and C1 ( $f_2 = 50.3$ ) and T1 and C4 ( $f_2 = 60.4$ ). The highest similarity was between C2 and C3. There was dissimilarity between the microbeads made from blends that gave the slowest release and that made from alginate alone, showing that their release profile was clearly different.

## CONCLUSION

Date mucilage as a polymer together with sodium alginate in a formulation of metformin hydrochloride microbeads demonstrated controlled release for polymer blend ratio of 33:67 (C2) and 25:75 (C3). However, C3 had greater drug entrapment efficiency than C2. Therefore, microbeads formulated from date mucilage: alginate blend 25:75 could be used for controlled-release of Metformin Hydrochloride until 10% of the drug is released. More studies are needed to generate release data until a time point is reached when the entire drug has been released.

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## CONFLICT OF INTEREST

The authors hereby declare no conflict of interest.

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