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Research Article

## Formulation and Evaluation of Sustained Release Tablet of Metformin by Ionic Gelation Technique using *Sida acuta* Gum as Release Retardant

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### Abstract

This research was done to formulate and assess the sustained release property of metformin tablets prepared from metformin microcapsules produced by ionic gelation technique using *Sida acuta* gum or sodium carboxymethylcellulose as release retardant. *Sida acuta* gum was produced by isopropyl alcohol precipitation of the filtrate obtained from distilled water maceration of powdered dried *Sida acuta* leaves. Metformin and *Sida acuta* gum compatibility was determined using FTIR. Metformin microcapsules were prepared by ionic gelation technique using sodium alginate alone or with either *Sida acuta* gum or sodium carboxymethylcellulose as release retardant. The microcapsules were evaluated for % yield and flow properties. The size and surface morphology of the microcapsules were determined using scanning electron microscopy. Metformin tablets were prepared from the microcapsules using direct compression technique. The tablets were evaluated for hardness, friability and in vitro dissolution. There was no major incompatibility between metformin and *Sida acuta* gum. The microcapsules have excellent flow property and were of micrometer size range. They have rough surfaces. The friability of the tablets ranged from 0.4-1.6% while the hardness was from 3.82-11.17 Kgf. The tablets from formulations M2 failed both friability and hardness test. About 44.5-47.1% of metformin was released from the tablet formulations after 6 h while 86.0-100% was released after 10 h. All the tablet formulations showed sustained release ability.

**Keywords:** Microcapsules, metformin, *Sida acuta* gum, sustained release, ionic gelation

## INTRODUCTION

Most of the medications that are administered to patients are given through the oral route.<sup>1, 2</sup> Drugs taken orally are meant for immediate or modified release. Modified release includes controlled release, sustained release and site targeted release etc. Sustained release drug delivery includes any of the dosage forms that maintain the therapeutic blood or tissue levels of drugs by continuous release of medication for a prolonged period of time after administration of a single dose.<sup>3</sup> Sustained release describes the release of drug substance from a dosage form or delivery system over an extended time interval. It is also known as prolonged release (PR), slow release (SR), sustained action (SA), prolonged action (PA) or extended release.<sup>4, 5</sup> Sustained release delivery system is designed to decrease the frequency of dosing, enhance the effectiveness of drug through its localization at the action site, reduce dose required, decrease side effects and provide uniform drug delivery and better patient compliance.<sup>5</sup> It has the disadvantages of increased cost, toxicity due to dose dumping, unpredictable and often poor in-vitro- in-vivo correlation.

Oral sustained release dosage forms can be designed using the following techniques; (a) Dissolution controlled release e.g microencapsulation or encapsulated dissolution control (soluble reservoir system), matrix dissolution control (soluble matrix system) and multi-layer matrix tablet (b) Diffusion controlled release e.g Reservoir device and matrix device (c) Dissolution and diffusion controlled systems e.g Ion-exchange resins, pH-dependent formulations, osmotically controlled release and altered density formulation.

Microencapsulation is a type of technique used to achieve sustained release of drug from dosage forms. Microencapsulation is a means through which solids, liquids and gases may be covered with microscopic particles forming thin membrane around the substance.<sup>6, 7</sup> Microparticles or microcapsules are made up of two components, a core material (active ingredient) and surrounded polymeric shell or core material dispersed in polymeric matrix.<sup>8</sup> Microcapsules usually have a dimension of few micrometers to few millimeters (5µm-5mm) in diameters.<sup>9</sup> The coat can retard drug release and modify the availability of the core material.<sup>10, 11</sup> Microencapsulation of a substance is done to protect the encapsulated substance from the negative effects

of the environment as it moves to its site of action. It is used to cause sustained or prolonged drug release; for masking the organoleptic properties like taste and odour of many drugs and thus enhance patient compliance,<sup>9, 11</sup> to convert liquid drugs into a free flowing powder, to protect drugs that are sensitive to moisture, light and oxygen or helps to prevent incompatibility between drugs.<sup>9, 11</sup> Microencapsulation can be achieved through techniques such as interfacial polymerization, *in situ* polymerization, spray drying and spray congealing, solvent evaporation, pan coating, ionic gelation technique, etc. Ionic gelation technique depends on poly-electrolytes' ability to crosslink in the presence of counter ions to produce hydrogel beads called gelispheres. Gelispheres are spherical cross-linked hydrophilic polymeric substances that can form gel extensively, swell in simulated biological fluids and its drug release controlled by polymer relaxation. The hydrogel beads are produced by dropping a drug loaded polymeric solution into an aqueous solution of polyvalent cation.<sup>12</sup> Natural and semi-synthetic polymers, e.g alginate, gellan gums, chitosan, pectin and sodium carboxyl methylcellulose are widely used for encapsulation of drugs by this techniques. These polymers also act as release retardant.

*Sida acuta* is a shrub that belongs to the family, Malvaceae. The plant is found mainly in the subtropical regions especially in bushes, in farms and within habitations. The plant is an erect, perennial under shrub or shrub, 1.5 m high with linear to lanceolate leaves and flower, yellow solitary or in pairs.<sup>13</sup> *Sida acuta* gum is isolated from the powdered dried leaves of *Sida acuta*.<sup>14</sup> *Sida acuta* gum has been used as binder,<sup>15</sup> as suspending agent<sup>16</sup>, as polymer matrix former<sup>17</sup> and as mucoadhesive polymer.<sup>18</sup>

Metformin is a biguanide antihyperglycemic agent which is used with proper diet and exercise program to improve glucose tolerance in Type 2 (non-insulin dependent) diabetes mellitus patients and lower both basal and postprandial plasma glucose. It reduces hepatic glucose production and glucose intestinal absorption, and improves insulin sensitivity by enhancing peripheral glucose uptake and utilization.<sup>19, 20</sup> The molecular formula of metformin is C<sub>4</sub>H<sub>11</sub>N<sub>5</sub> (Diamide N,N-dimethylimidodicarbonimidic diamide, N,N-dimethyl or 1,1-Dimethylbiguanide mono hydrochloride).<sup>21</sup> It has an absolute oral bioavailability of 40-60%. It has apparent complete gastrointestinal absorption of 6 h after ingestion. It is distributed very fast after absorption and does not bind to plasma proteins. It is excreted through the kidney and has a mean plasma elimination half life after oral administration of

between 4-8.7 hours.<sup>5, 19</sup> Therapeutic levels may be 0.5 to 1.0 mg/L in fasting state and 1-2 mg/L after a meal.

This study was done to formulate metformin microcapsules by ionic gelation technique using *Sida acuta* gum as release retardant and to assess the sustained release property of the metformin tablets produced using the microcapsules.

## MATERIALS AND METHODS

### Materials

Sodium bicarbonate (Guandong Guanghua Science Technology Co-Limited), microcrystalline cellulose (Kores Chemical Limited India), metformin HCL (Kores Chemical Limited India), sodium hydrogen phosphate (Guandong Guanghua Science Technology Co-Limited), disodium hydrogen phosphate (Guandong Guanghua Science Technology Co-Limited), silicon dioxide (Kores Chemical Limited India), magnesium stearate (Kores Chemical Limited India), sodium alginate, sodium carboxyl methylcellulose All chemicals used were of analytical quality

### Isolation of *Sida acuta* gum

The method of<sup>14</sup> was used. A 150 g quantity of powdered dried *Sida acuta* leaves was macerated for 9 hours using 1.5 litres of distilled water. It was heated for one (1) hour, thereafter, allowed to cool and filtered using a clean muslin cloth. The filtrate (1 litre) was precipitated using equal volume of isopropyl alcohol. The mixture was continuously stirred for 45 minutes to ensure proper contact between the filtrate and alcohol. It was kept for another 15 minutes and the gum was collected by passing through a muslin cloth. The gum was washed twice using isopropyl alcohol (sufficient quantity) and once with acetone (sufficient quantity). It was dried and kept in an airtight container.

### Preparation of Metformin Microcapsules

Metformin microcapsules were formed following the formulation ratio in Table 1 by using the method of<sup>21</sup> with slight modification. A 10 g quantity of metformin was dissolved in a mixture of 20 g sodium alginate and 100 ml distilled water, and this drug loaded polymer was introduced in drops using a 21G needle into a beaker containing 5% w/v calcium chloride solution. The solution was stirred continuously using a magnetic stirrer to form the microcapsules. Microcapsules formed were collected, washed, dried and stored in an airtight container. The other microcapsules formulation (M2 and M3) were prepared according to formulation ratio in Table 1.

Table 1 Composition of metformin microcapsules (ratio)

| Formulation | Drug (metformin) | Polymer A (Sodium alginate) | Polymer B (Sodium carboxyl methylcellulose) | Polymer C ( <i>Sida acuta</i> gum) |
|-------------|------------------|-----------------------------|---|------------------------------------|
| M1          | 1                | 2                           | -   | -                                  |
| M2          | 1                | 1.5                         | 0.5   | -                                  |
| M3          | 1                | 1.5                         | -   | 0.5                                |

### Evaluation of Microcapsules

The microcapsules were evaluated based on % yield, flow properties, SEM and FTIR.

### Microcapsules yield

The microcapsules yield was calculated using method by previous researchers.<sup>7, 22</sup> Microcapsules yield (%) was expressed as a ratio of the mass of microcapsules obtained

from the ionic gelation technique to the mass of initial solid content (drug and polymers) used.

### Bulk density

A 3 g quantity of metformin microcapsules was transferred into 10 ml measuring cylinder and the bulk volume recorded. The bulk density was calculated using equation 1.<sup>23</sup>

$$\text{Bulk density} = \frac{\text{weight of microcapsules}}{\text{volume occupied}} \dots 1$$

### Tapped density

A 3 g quantity of metformin microcapsules was poured into a 10 ml measuring cylinder and this was tapped 100 times on a padded surface and the tapped volume was recorded. The tapped density was calculated using equation 2.<sup>23</sup>

$$\text{Tapped density} = \frac{\text{weight of microcapsules}}{\text{volume occupied}} \quad \dots \quad 2$$

### Hausner ratio

This was calculated using equation 3.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \dots \quad 3$$

### Carr's index

This was calculated using equation 4.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \quad \dots \quad 4$$

### Angle of repose

A 10 g quantity of microcapsules from formulation M1 was weighed and made to flow through a funnel onto a flat horizontal surface so that it formed a conical heap. The height and the base of the cone formed were measured and recorded. This was done in triplicate. This procedure was repeated for formulations M2 and M3.<sup>24</sup> The angle of repose was calculated using equation 5.

$$\tan \theta = \frac{2h}{d} \quad \dots \quad 5$$

Where  $\theta$  is angle of repose; h is height of cone formed by the microcapsules and d is the diameter of the cone.

### Scanning Electron Microscopy (SEM) Analysis

The morphology of the metformin microcapsules was determined at different magnifications using Phenom ProX SEM model (Phenomworld Eindhoven, The Netherlands).<sup>25</sup>

### Fourier-Transform Infrared (FTIR) Spectroscopy Analysis

This was done by preparing pellets of metformin crystals and potassium bromide (KBr) and applying pressure of 15 tons in a hydraulic press. The pellets were scanned over a wavelength range of 400- 4000  $\text{cm}^{-1}$  using the Shimadzu spectrophotometer FTIR-8400s at a resolution of 4  $\text{cm}^{-1}$  and with a scanning speed of 2 mm/s.<sup>8, 26</sup>

### Formulation of Sustained release tablets of metformin

Metformin sustained release tablets were produced using direct compression technique following the formula in Table 2. The metformin microcapsules, sodium bicarbonate and microcrystalline cellulose were mixed thoroughly in a mixing bottle for five (5) minutes, thereafter, magnesium stearate and silicon dioxide were added and mixed for 1 min. A 600 mg quantity of sample was compressed into tablet using 16 stations rotary tableting machine (Clit Jemkay Eng. Pvt. Ltd. Ahmedabad, India) having 13 mm punches.

Table 2: Composition of metformin sustained release tablets

| Ingredients                     | M1         | M2         | M3         |
|---------------------------------|------------|------------|------------|
| Metformin microcapsules (mg)    | 250        | 250        | 250        |
| Sodium bicarbonate (mg)         | 40         | 40         | 40         |
| Microcrystalline cellulose (mg) | 301        | 301        | 301        |
| Magnesium stearate (mg)         | 3          | 3          | 3          |
| Silicon dioxide (mg)            | 6          | 6          | 6          |
| <b>Total (mg)</b>               | <b>600</b> | <b>600</b> | <b>600</b> |

### Evaluation of Sustained release tablets of metformin

#### Friability

Ten tablets from formulation M<sub>1</sub> were jointly weighed and placed at the right hand side of the DBK friability test apparatus, while ten tablets of formulation M<sub>2</sub> were jointly weighed and placed at the left hand side. The apparatus was set to make 100 revolutions in 4 minutes, after which the tablets were re-weighed. This was repeated for formulation M<sub>3</sub>.

#### Uniformity of weight

Twenty (20) tablets randomly chosen from formulation M<sub>1</sub> were weighed individually and the mean weight determined. The percentage deviation of each tablet from the mean weight was determined. This was repeated for M<sub>2</sub> and M<sub>3</sub> and values were recorded.

#### Hardness, thickness and diameter

These were done using Veego digital tablet test apparatus (Veego Instrument Corporation, Mumbai India) and respective values were recorded.

#### Dissolution test

An in-vitro dissolution test was carried out in dissolution test apparatus (Erweka) for ten (10) hours at  $37 \pm 1^\circ\text{C}$  and at 50 rpm. One tablet from each formulation was placed in the

basket of the dissolution test apparatus. Simulated gastric acid medium (0.1N HCl) was used as the dissolution medium for the first 2 hours while for the remaining 8 hours, phosphate buffer pH 6.8 under same condition was used. A 5 ml quantity of sample was withdrawn from dissolution medium and replaced with 5 ml fresh medium to maintain constant volume every 1 hour. After filtration, the sample solutions were analyzed at 232 nm for metformin hydrochloride using DBK U.V spectrophotometer (DBK, India).

#### Statistical analysis

Data was analyzed using Microsoft excel and expressed as mean  $\pm$  SD.

## RESULT AND DISCUSSION

### Percentage yield of Gum

The percentage yield of *Sida acuta* gum was 7.03%.

### Yield of Microcapsules

The results of the loading efficiency of the different microcapsules formulation are shown in Table 3. The loading efficiency for formulation M<sub>2</sub> was relatively low/poor. This was due to difficulty in filtration and drying. The yield for formulation M<sub>1</sub> and M<sub>3</sub> were relatively higher.



Table 3 Percentage yield of microcapsules

| Formulation | Percentage yield |
|-------------|------------------|
| M1          | 37.6             |
| M2          | 12.4             |
| M3          | 32.7             |

**Evaluation of microcapsules**

The results for Carr's index and Hausner ratio for the microcapsules are shown in Table 4. Carr's index values of 0-10% and Hausner ratio of 1.00-1.11 signifies excellent flow, therefore, formulations M1, M2 and M3 have excellent flow properties.

Table 4: Micromeritic evaluation of microcapsules

| Formulations | Bulk density (ml) | Tapped density (ml) | Hausner ratio | Carr's index (%) | Angle of Repose (degree) |
|--------------|-------------------|---------------------|---------------|------------------|--------------------------|
| M1           | 0.48              | 0.52                | 1.08          | 7.7              | 35                       |
| M2           | 0.59              | 0.63                | 1.07          | 6.3              | 25.5                     |
| M3           | 0.55              | 0.58                | 1.05          | 5.2              | 30.6                     |

**SEM Analysis**

The SEM images of formulation M1 at magnification of x500, x1000 and x1500 are shown in Figures 1a – 1c respectively;

that of formulation M2 are shown in Figures 1d – 1f, while that of formulation M3 are shown in Figures 1g -1i respectively. The images have rough surfaces and were of micrometer ranges. This shows presence of microcapsules.

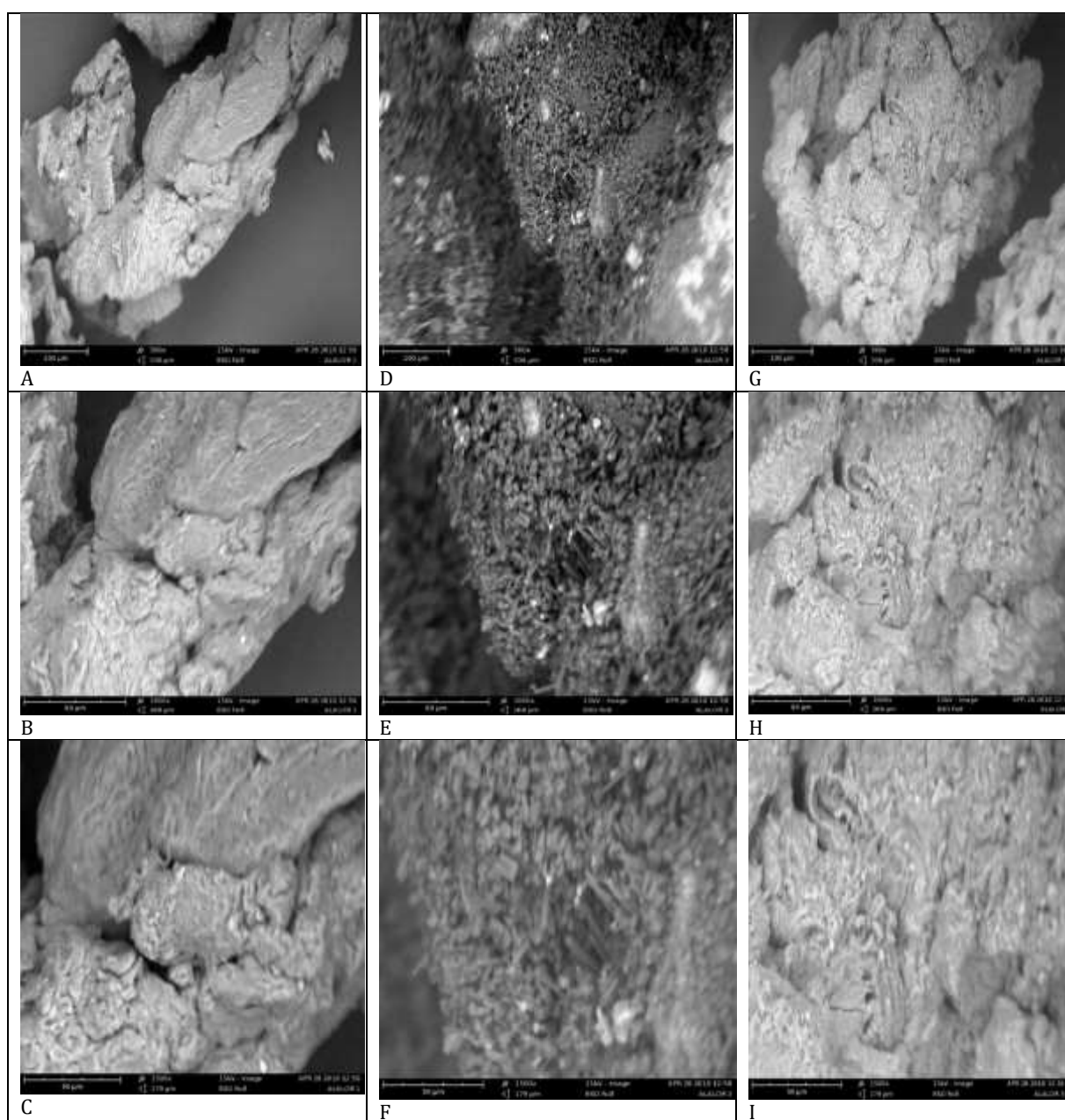


Figure 1: SEM images; (a) x500 magnification of formulation M1, (b) x1000 magnification of formulation M1, (c) x1500 magnification of formulation M1, (d) x500 magnification of formulation M2, (e) x1000 magnification of formulation M2, (f) x1500 magnification of formulation M2, (g) x500 magnification of formulation M3, (h) x1000 magnification of formulation M3, (i) x1500 magnification of formulation M3

### FTIR

Figure 2a shows the presence of two typical bands associated with N-H primary stretching vibration of metformin at 3384.98  $\text{cm}^{-1}$  and 3300.06  $\text{cm}^{-1}$ , and a band at 3172.68  $\text{cm}^{-1}$  due to N-H secondary stretching. Also, characteristic bands assigned to C-N stretching at 1624.82  $\text{cm}^{-1}$  and 1566.82  $\text{cm}^{-1}$  were observed in the FTIR spectrum of metformin. The FTIR

spectrum of *Sida acuta* gum and metformin in Figure 2b showed similar bands for N-H primary and secondary stretching vibration at 3384.98  $\text{cm}^{-1}$ , 3292.34  $\text{cm}^{-1}$  and 3190.70  $\text{cm}^{-1}$  respectively. The two characteristic bands of C-N stretching were compressed together into one band at 1593.94  $\text{cm}^{-1}$ . This shows that there was no major incompatibility between metformin and *Sida acuta* gum.

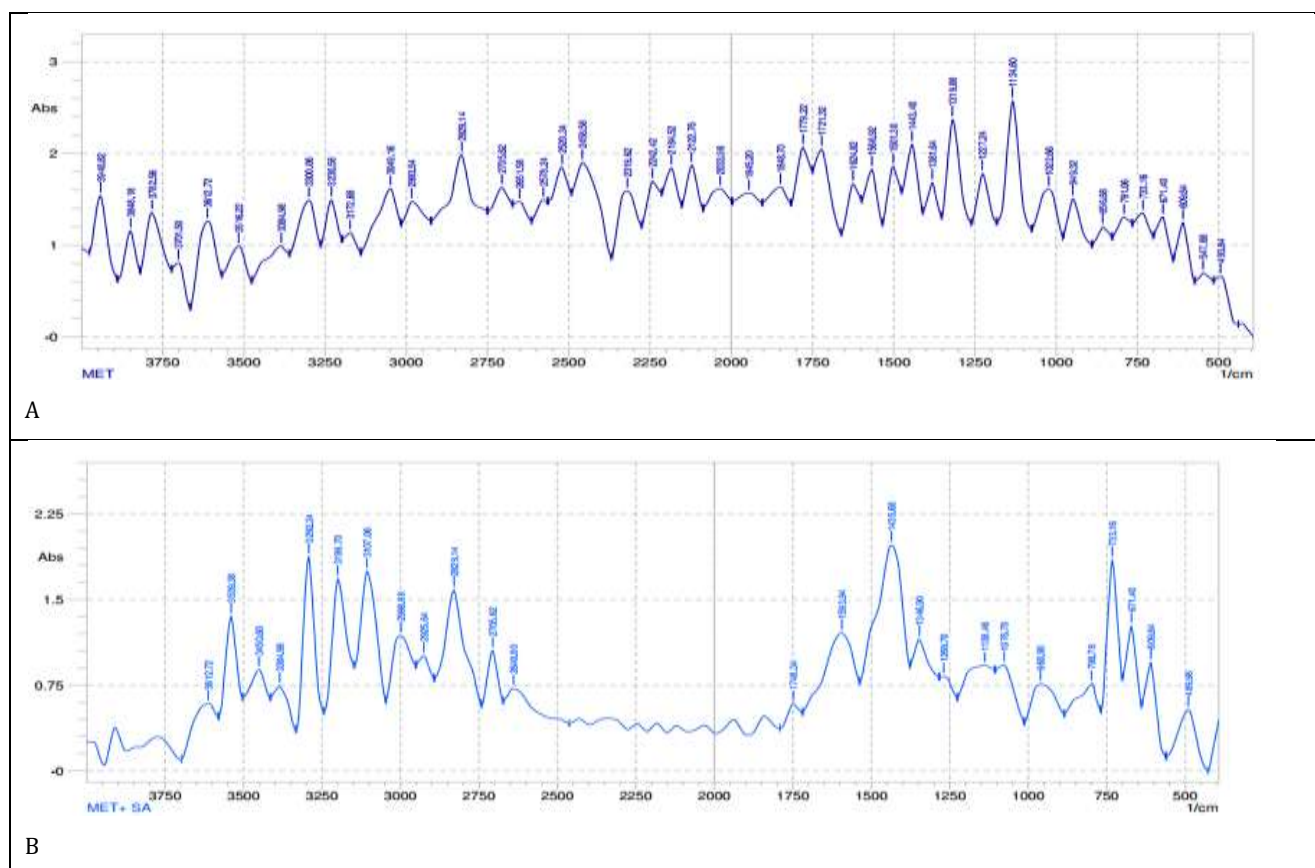


Figure 2: FTIR spectrum of (a) metformin (b) metformin + *Sida acuta* gum

### Evaluation of Sustained Release Tablets of Metformin

As shown in Table 5, metformin tablets from all the formulations except M2 passed the friability and hardness test.

Table 5: Evaluation of Sustained Release Tablets of Metformin

| Formulations | Friability (%) | Hardness (KgF) | Thickness (mm) | Diameter (mm) | Uniformity of weight (mg) |
|--------------|----------------|----------------|----------------|---------------|---------------------------|
| M1           | 0.8            | 11.17          | 3.44           | 12.91         | 0.6027                    |
| M2           | 1.6            | 3.82           | 3.82           | 12.91         | 0.5952                    |
| M3           | 0.4            | 8.40           | 3.20           | 12.91         | 0.5952                    |

### Dissolution profile

The percentage drug release was between 44.5 to 47.1% after 6 hours and 86.0 to 100% after 10 hours (Figure 3). All formulations showed sustained release capabilities, however, unlike M1 that released 100% of metformin at 10 h, M2 released 85.96% and M3 released 90.4%

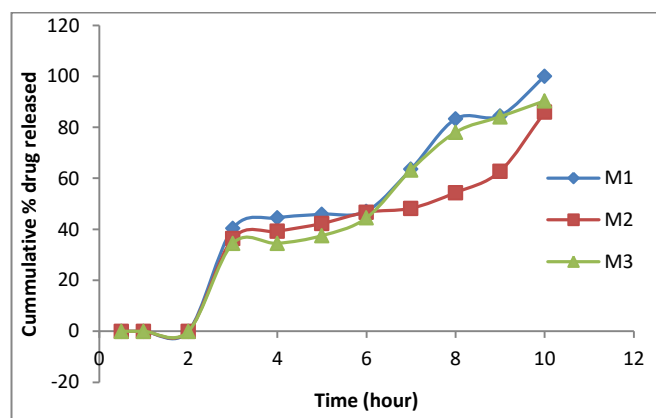


Figure 3: Dissolution profile of metformin sustained release formulations M1-M3

### CONCLUSION

Metformin microcapsules were formed by ionic gelation technique using sodium alginate alone or with either NaCMC or *Sida acuta* gum. Tablets prepared using the microcapsules showed good sustained release property, however, tablets prepared with microcapsules formed using *Sida acuta* gum or NaCMC were comparable and better than those formed using sodium alginate alone.

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### CONFLICT OF INTEREST

The authors reported that there was no conflict of interest.

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