Floating Alginate Microbeads Based Formulation For Controlled Oral Delivery Of Glibenclamide

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Abstract: The purpose of designing the floating microbeads based formulation of antidiabetic drugs was to achieve controlled release of the drugs. The floating microbeads based controlled release formulation is expected to aid in reducing the dosing frequency and to increase the gastric residence time. The gastric residence time in present study was induced using the buoynancy characteristics in the gastric fluid. Glibenclamide (glyburide) was selected as a model bioactive which is a second-generation sulfonylurea drug used in lowering blood-glucose in type-II diabetes mellitus. The floating microspheres of Glibenclamide was designed by using polymers including low and high molecular weight grades HPMC, ethyl cellulose, sodium alginate, calcium chloride, calcium and sodium carbonates. The floating microbeads were characterized for their drug entrapment efficiency, percentage yield, shape and surface morphology, particle size, percentage buoyancy, in vitro drug release studies (in acidic buffer pH 1.2), and formulation’s stability. The results of the investigations indicated that ionic cross-linking technique namely ionotropic gelation method can be successfully used to fabricate Glibenclamide loaded floating microbeads. The study demonstrated that formulation of a controlled release floating microbeads of Glibenclamide is a promising approach in reducing the frequency of dosing.

Keywords: Floating Microbeads, Glibenclamide, Alginate, Controlled delivery, Oral route, In vivo study

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I. Introduction

Noninsulin dependent diabetes mellitus (NIDDM) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [1]. Diabetes mellitus (Type 2) makes up about 90% of the cases of diabetes which if not controlled properly initializes with fatigue, hunger, increased thirst and frequent urination to major health issues such as blurred vision, erectile dysfunction, ketoacidosis, liver and kidney damage. In case of type 2 diabetes mellitus, oral hypoglycemic’s are used as first line treatment with an aim to control the blood sugar levels of the subject or patient. Due to their short biological half-life, frequent dosing is required to maintain drug’s therapeutic concentration in the blood plasma. To overcome this issue, majority of research focused during product development is pertaining to control the rate of drug release. The gastroretentive (GR) technology has become a major tool in this direction by controlling the release and thus the systemic availability of the drug. Recently various gastroretentive technologies has been reported, the most prominent once included Qbd-enabled systematic development of multiple-unit microballs of itopride hydrochloride, where optimized GR system employed simple, effectual and cost effective floating microballs in improving gastric residence time and site-specific drug delivery [2]. Further, advanced research involved development and characterization of Cordia myxafruit gum based mucoadhesive novel tablet technology for gastroretantive delivery of Losartan potassium to overcome issues pertaining to shorter biological half-life of the drug [3]. Additionally, grafting of poly(acrylonitrile) on gum Cordia myxaenhanced the mucoadhesive gastroretentive characteristics in development of sustained release captopril tablet dosage form [4]. Also, recent publication revealed QBD based systematic development of once-a-day gastroretentive formulation of cefuroxime axetil employed rational blend of hydrophilic polymers for attaining controlled drug delivery [5].

In order to achieve a desired therapeutic concentration of Glibenclamide, various dosage forms and technologies are reported. Briefly, tablet dosage form of Glibenclamide was formulated, evaluated and compared with suppository system of the drug [6]; Extended release dosage form of Glibenclamide [7]; sustained release matrix tablets of Glibenclamide [8]. Other dosage forms were also formulated viz. chitosan and Eudragit buccal strips [9]; acrylate based transdermal drug delivery system [10], microcapsule [11], self-microemulsifying drug delivery systems [12]; floating microspheres using emulsification solvent diffusion.
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Glibenclamide has been chosen as candidate in formulating novel floating microbeads using high and low molecular weight HPMC, Ethyl cellulose, sodium alginate, calcium chloride, calcium and sodium carbonates. This study includes in depth comparison evaluation to access the potential of alternative approach in drug delivery potential with different polymers based on parameters viz. particle size, percentage buoyancy, drug entrapment efficiency, percentage yield and \textit{in vitro} drug release study using calcium carbonate and sodium bicarbonate. The oral absorption of Glibenclamide is 95 ± 5%, volume of distribution is reported as 0.151/kg and its plasma protein binding is 99%. However, its biological half-life in plasma is 4 to 5 hours due to which frequent dosing is required. One of the approaches to achieve controlled drug release of antidiabetic agent is through increase formulation’s gastric residence time. Hence, in present study the aim was to develop a straightforward, scalable, novel technology to reduce frequency of administration through controlled drug release of Glibenclamide.

II. Materials And Methods

2.1 Materials
Glibenclamide received as a gift sample from Zen Labs Chandigarh, India, HPMC 4K, ethyl cellulose, sodium alginate low or medium viscosity grade obtained from Sigma Aldrich, calcium chloride from Merck (Germany), calcium carbonate, sodium bicarbonate, acetic acid were provided by Hi-Media.

2.2 Methodology

2.2.1 Determination of solubility of Glibenclamide
Solubility of Glibenclamide was determined in various solvents such as phosphate buffer saline (PBS) pH 7.4, organic solvent such as acetone, methanol and dichloromethane. Briefly, an excess amount of drug was taken and transferred to 50 ml volumetric flasks containing 25 ml of solvent, flasks were securely capped and placed in the mechanical shaker water bath at 25°C for 24 hrs and then sonicated for 10 min. Thus, sufficient time was provided for contact to produce saturated solutions. Solutions were filtered by passing through a 0.45 µm membrane filter and concentration of drug was determined UV Spectrophotometrically at \( \lambda_{	ext{max}} = 229 \) nm.

2.2.2 Compatibility studies
Drug excipient interaction studies were carried out by FTIR spectroscopy of Glibenclamide, physical mixture of drug and sodium alginate using NaCl-press (spectra lab, India) spectrophotometer for compatibility studies. The pellets were prepared on NaCl-press (spectra lab, India). The spectra were recorded over the wave number range of 4000 to 500 cm\(^{-1}\).

2.2.3 Method of preparation of floating microbeads
The preparation methodology of microspheres was based on earlier studies conducted[16-17] with major modifications. In the present study formulation composition is designed with polymer including HPMC high MW grades, ethyl cellulose, sodium alginate and calcium chloride. Calcium carbonate and sodium bicarbonates were used as gas generating agents. Microspheres were prepared by uniformly dispersing sodium alginate in purified water by mechanical stirring. HPMC 4K and Ethyl cellulose wereincorporated into the above alginate dispersion in suitable proportion as mentioned in the Table 1 and the entire mixture was stirred. Glibenclamide was then added to the above dispersion then calcium chloride/sodium bicarbonate was added and stirred thoroughly to afford homogeneous dispersion. The dispersion was sonicated for 30 min. to remove any air bubble that may have been formed during the stirring process. Then resulting solution was dropped through a syringe needle into 5%(w/v) \( \text{CaCl}_2 \) solution which was prepared in water containing 10%(v/v) acetic acid. The droplets from the dispersion instantaneously gelled into discrete Glibenclamide-alginate matrices upon contact with the solution of cross-linking agent. The solution containing suspended microspheres was kept for 1.5h to improve the mechanical strength of the microspheres and allowed to complete the reaction to produce gas. On expiration of this period the solution of cross linking agent was decanted and the microspheres were washed with 3x50 ml volumes of deionized water.

2.2.4 Formulation Characterization

2.2.4.1 Particle Size
Particle size of microbeads was evaluated following earlier reported technology [18] with essential modifications by using optical microscopy. Briefly microbeads were uniformly spread on the slide and were carefully observed for estimation of particle size using a calibrated optical microscope. The particle size of the microbeads was measured along the longest axis and the shortest axis. Average of these two readings was given as mean diameter of particles. The diameter of a minimum number of 100 microbeads in each batch was calculated.
2.2.4.2 Shape and Surface Morphology

The shape and surface characteristics of the prepared microbeads were evaluated by means of scanning electron microscopy (SEM) LEO 435 VP. The samples for SEM were prepared by gently sprinkling the floating microbeads on a double adhesive tape, which is stuck to an aluminum stub. The stubs were then coated with gold using a stupper coater under high vacuum and high voltage to achieve a film thickness of 30nm. The samples were then imagined using a 20 kv electron beam [16-17].

**Table 1- Composition of floating microbeads of Glibenclamide**

<table>
<thead>
<tr>
<th>Formulation Codes</th>
<th>Drug (mg)</th>
<th>Sodium Alginate (w/v)</th>
<th>Drug:Polymers (HPMC 4K, Ethyl cellulose W/W)</th>
<th>CaCo$_3$ (gm)</th>
<th>NaHCo$_3$ (gm)</th>
<th>CaCl$_2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>100</td>
<td>5</td>
<td></td>
<td>0.5</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>F1</td>
<td>100</td>
<td>5</td>
<td>1:1</td>
<td>0.5</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>F2</td>
<td>100</td>
<td>5</td>
<td>1:2</td>
<td>0.5</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>F3</td>
<td>100</td>
<td>5</td>
<td>1:3</td>
<td>0.5</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>F4</td>
<td>100</td>
<td>5</td>
<td>1:4</td>
<td>0.5</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>F5</td>
<td>100</td>
<td>5</td>
<td>1:1</td>
<td>-</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>F6</td>
<td>100</td>
<td>5</td>
<td>1:2</td>
<td>-</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>F7</td>
<td>100</td>
<td>5</td>
<td>1:3</td>
<td>-</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>F8</td>
<td>100</td>
<td>5</td>
<td>1:4</td>
<td>-</td>
<td>0.5</td>
<td>5</td>
</tr>
</tbody>
</table>

2.2.4.3 Floating Potential

Floating behavior of microbeads was estimated following slight changes making earlier reports [18-20]. Briefly, 50 mg of the microbeads sample was placed in 100ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours the layer of buoyant microbeads was collected. Particles in the sinking particulate layer were separated by filtration using Millipore filter paper. Particles of both types were dried in desiccators until constant weight was achieved. Both the fractions of microbeads were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

\[
\text{Buoyancy} \% = \frac{\text{weight of the floating microbeads after specified time t}}{\text{initial weight of the microbeads}}
\]

2.2.4.4 Drug Entrapment Efficiency

Entrapment efficiency was evaluated according to the methodology reported earlier with slight modification [18-19]. Briefly, microbeads equivalent to 10 mg of Glibenclamide were crushed in a glass mortar and pestle and the powdered microbeads were suspended in 100ml of acidic buffer 0.1N HCl with pH 1.2. After 24 hours the solution was filtered, 1ml of the filtrate was sampled out and diluted sufficiently. The prepared samples were analyzed for the drug content using U.V visible spectrophotometer at absorption maxima of 229nm.

\[
\% \text{ Drug entrapment efficiency} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100
\]

2.2.4.5 Determination of Percentage Yield

The percent yield was evaluated following the reported method [21-23] with slight modification. The prepared microbeads collected were accurately weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microbeads.

\[
\% \text{ yield} = \frac{\text{total weight of the floating microbeads}}{\text{total weight of non volatile ingradients}}
\]

2.2.4.6 In Vitro Drug Release

In vitro drug release studies were carried out using six basket dissolution apparatus USP XXIII paddle type. The dissolution medium was 900ml of simulated gastric fluid (acid buffer, pH 1.2 without enzymes) at 37±0.5°C at 100 rpm. At specific time intervals, 5ml aliquots were withdrawn and analyzed by UV spectrophotometer at the respective $\lambda_{max}$ value 229 nm after suitable dilution against suitable blank. The withdrawn volume was replaced with an equal volume of fresh 1.2 pH buffer.

2.2.4.7 Release Kinetics

The result of in vitro release profiles obtained for the formulations were fitted into four models of data treatment as follows:

i) Zero order release equation: \[ Q = Q_0 - K_0 t \]
Q is the amount of drug released at time t, $K_0$ is zero-order release rate constant
A plot of fraction of drug released against time will be linear if the release obeys zero order release kinetics. This model represents an ideal release in order to achieve prolonged pharmacological action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets containing low soluble drugs.

ii) First order release equation: In Q = InQ0 – K0t

Q is the amount of drug released at time t, Q0 is the amount of drug remaining in the formulation. Thus a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics. The model is applicable to hydrolysis kinetics and to study the release profile of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

iii) Higuchi square root of time equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) on the surface root of time.

\[ Q/Q_0 = Kt^{1/2} \]

Kt is Higuchi square root of time release rate constant.

iv) Korsmeyer-peppas equation: Hixson – crowell equation:

\[ Q/Q_0 = Kt^n \]

Q/Q0 is fraction of drug released at time t and k is a constant and n is diffusion exponent indicating the mechanism of drug release.

v) Hixson – Crowell equation: (Fraction released)\(^{1/3}\) = 1 - kt

This equation applies to pharmaceutical dosage form like tablets where dissolution occurs in plane that are parallel to drug surface if the tablet dimensions diminish proportionally in such a manner that the initial geometric form keep constant all the time. When this model is used it is assumed that the release rate is limited by the drug particle dissolution rate and not by the diffusion that might occur through polymer matrix [16, 24-26].

2.2.5 Stability Study

Stability studies were carried out at 25°C±60% RH and for 2 months [21, 27-28]. Selected formulation was packed in their final (amber colored glass) containers and tightly closed with the cap. They were stored at 25°C±2%/60°C±2% RH for 60 days. Samples were analyzed after 2 months and for percentage drug entrapment in vitro drug release studies.

2.2.6 In Vivo Study

Albino rats of either sex were selected for in vivo experimental study with rats weighing between 250-300g. After 12hrs overnight fasting the experimental animals were rendered diabetic by single intera-peritonal administration of cold freshly prepared solution of Alloxan at a dose of 150 mg/kg dissolved in 2Mm citrate buffer (pH 3.0) after a week animal with fasting blood glucose of 250 mg/dl or more considered diabetic and employed in study (Etuk and E.U., 2010). The rats were divided randomly in 3 groups including one control, each containing 6 animals. The group one was treated as control group, rest groups were treated with developed formulations via oral route of administration. Blood samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 24 hours, by tail vein at predetermined time upto 24 h and blood glucose level was analyzed by glucose oxidase and peroxidase method using commercial glucose kit [29].

III. Results And Discussions

3.1 Pre-formulations study

Calibration plot of drug: A solution of 10µg/ml of Glibenclamide was scanned in the range of 200-360nm. The drug exhibited a \( \lambda_{max} \) at 229nm in 0.1 N HCl (pH 1.2) and displayed significant reproducibility. Correlation between the concentration and absorbance was found to be near to 1 with a slope of 0.0385 and intercept of 0.0034.

Solubility Determination: Solubility of drug was determined by dissolving the drug in different solvents such as PBS pH 7.4, methanol, acetone and dichloromethane. The solubility of Glibenclamide in dichloromethane was highest i.e. 216.24±1.4mg/ml whereas the lowest solubility (2.61±1.1mg/ml) was recorded in PBS 7.4. 80.23±1.2 mg/ml and 69.41±1.8mg/ml solubility of drug was recorded in acetone and methanol respectively.

3.2 Compatibility studies

Drug-excipient compatibility study was performed using Fourier transform infra-red spectroscopy (FTIR) to establish any possible interaction of drug, Glibenclamide with the polymeric excipient used in the formulation. The FTIR spectra of the formulations were compared with the FTIR spectra of the pure drug kept...
at RT (25°C) on 15th day. The results indicated that the characteristic absorption peaks due to pure Glibenclamide have appeared in the samples without noticeable change in their positions indicating no chemical interaction between Glibenclamide and polymers (Fig. 1a,1b).

**Figure 1.** FTIR spectra of (a) Glibenclamide and (b) Glibenclamide and sodium alginate mixture.

### 3.3 Evaluation of Floating Microbeads
#### 3.3.1 Particle size
Floating microbeads of Glibenclamide using HPMC with calcium carbonate, exhibit a size range between 660.50 μm to 765.61 μm and microbeads of Glibenclamide using HPMC with sodium bicarbonate between 809.42 μm to 895.38 μm. The particle size as well as percentage drug entrapment of the microbeads increased with increase in polymer concentration (Fig. 2). It was observed that particle size of floating microbeads obtained from calcium carbonate were smaller than sodium bicarbonate probably because calcium carbonate is a less effective gas forming agent than sodium bicarbonate. However, CaCl2 displayed superior floating beads with favorable control of drug release rate [30].

#### 3.3.2 Shape and surface morphology
Morphology of the microbeads was investigated by Scanning electron microscopy, LEO 435VP. The results of SEM (Fig 3 a, b, c) revealed that the microbeads using sodium alginate alone were discrete and with cracks on a rough outer surface, which might be due to cross-linking of the polymer with Calcium chloride. Microbeads using HPMC 4K and ethyl cellulose were spherical and their surface was smooth and devoid of cracks giving them a smooth textured appearance. Further pores can be observed from figures 3a-3c which suggests the role of polymers in the formulation.

#### 3.3.3 Floating potential
Results of floating tendency of developed drug carriers indicated formulations containing HPMC 4K with sodium bicarbonate (F5-F8) shows better floating tendency than the formulation containing HPMC 4K with calcium carbonate (F1-F4) due to low density of the polymer sodium bicarbonate then calcium carbonate (Fig. 4).

**Figure 2.** Relative particle size of different formulations containing calcium carbonate and sodium bicarbonate.
3.3.4 Drug entrapment efficiency

Percent drug entrapment efficiency of Glibenclamide using HPMC 4K with calcium carbonate was found to be 77.35% to 86.41% and 74.04% to 82.72% for floating microbeads using HPMC 4K with sodium bicarbonate (Table 2). The drug entrapment efficiency of the prepared microbeads increased progressively with increase in proportion of the respective polymer (HPMC 4K). It was observed that the drug entrapment efficiency increased progressively with increase in the concentration of polymer (HPMC 4K) with calcium carbonate which formed the carrier system resulting in formation of microbeads entrapping the higher content of drug, as compared to sodium bicarbonate.
3.3.5 Determination of percentage yield

It was observed that as the polymer ratio (HPMC 4K, Ethyl cellulose) in the formulation increases, the product yield slightly decreases. This phenomenon might be due to high viscosity of the solution. The percentage yield was found to be of 91.42% for microbeads of Glibenclamide in FA (formulation without polymer). However, for microbeads of Glibenclamide using HPMC 4K with calcium carbonate was found to show percentage yield in range of 83.67 to 89.88% and 80.86 to 88.95% for microbeads of Glibenclamide using HPMC 4K with sodium bicarbonate (Table 2).

Table 2- Drug entrapment efficiency and percentage yield of the various formulations

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Entrapment Efficiency (%)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>77.35±0.26</td>
<td>89.88±0.08</td>
</tr>
<tr>
<td>F2</td>
<td>79.82±0.44</td>
<td>88.17±0.10</td>
</tr>
<tr>
<td>F3</td>
<td>84.01±0.12</td>
<td>85.86±0.14</td>
</tr>
<tr>
<td>F4</td>
<td>86.42±0.15</td>
<td>83.67±0.18</td>
</tr>
<tr>
<td>F5</td>
<td>74.08±0.62</td>
<td>89.95±0.12</td>
</tr>
<tr>
<td>F6</td>
<td>76.96±0.42</td>
<td>85.96±0.16</td>
</tr>
<tr>
<td>F7</td>
<td>81.14±0.22</td>
<td>83.35±0.26</td>
</tr>
<tr>
<td>F8</td>
<td>82.73±0.34</td>
<td>80.86±0.22</td>
</tr>
</tbody>
</table>

3.3.6 In vitro drug release

The dissolution studies were conducted by using dissolution media 0.1N HCl pH 1.2. The formulations F1, F2, F3 and F4 containing HPMC 4K, ethyl cellulose and calcium carbonate showed a release between 85-91% after 24 hours. This shows that sustained release was observed with the increase in polymer ratio. The formulations F5, F6, F7 and F8 containing sodium alginate along with HPMC 4K, ethyl cellulose and sodium bicarbonate showed a release between 90-95% respectively after 24 hours. This shows that the HPMC 4K with calcium carbonate formulation showed lesser content of drug release with time as compared to formulation containing HPMC 4K with sodium bicarbonate. As the polymer to the drug ratio was increased the extent of drug release was found to decreased (Fig. 5a and 5b).

Figure 5. In vitro drug release profile of formulation containing (a) calcium carbonate (b) sodium bicarbonate.
3.3.7 Release Kinetic

For understanding the mechanism of drug release and release rate kinetics of drug from dosage form, the *in vitro* drug diffusion data obtained was fitted to various mathematical models such as zero order, first order, Higuchi matrix, Krosmeyer-peppas model and Hixon-crowell model. The drug release was found to follow matrix diffusion kinetics and the plot revealed linearity. Hence it was concluded that diffusion was the main mechanism of drug release from the floating alginate microbeads (Fig. 6a, b, c, d and e, and Table 3).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi model</th>
<th>Krosmeyer-peppas equation</th>
<th>Hixon-crowell model</th>
</tr>
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<tr>
<td>Slope</td>
<td>2.979</td>
<td>0.050</td>
<td>17.633</td>
<td>0.521</td>
<td>-0.107</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.954</td>
<td>0.982</td>
<td>0.994</td>
<td>0.986</td>
<td>0.993</td>
</tr>
</tbody>
</table>

3.3.4 Stability study

Stability study was conducted at 25°±2°C/60±2%RH for 60 days as shown in Table 4. Two formulations F2 and F6 were chosen for stability studies based on their percentage yield, percentage drug entrapment efficiency and *in vitro* drug release characteristics. The stability data showed that there was no change in the appearance of the formulations indicating that their stability at room conditions to which they were exposed. No significant change in drug content and *in vitro* drug release study was observed in formulations kept at condition as mentioned at the end of 2 months. The formulation was found to be stable with the shelf life for 60 days (estimated period) under standard conditions.

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>F2 Initial</th>
<th>F2 Final (after 60 days)</th>
<th>F6 Initial</th>
<th>F6 Final (after 60 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrapment efficiency (%)</td>
<td>79.82±0.44</td>
<td>78.31±0.22</td>
<td>76.96±0.42</td>
<td>76.12±0.24</td>
</tr>
<tr>
<td><em>In vitro</em> drug release (%)</td>
<td>87.97±0.24</td>
<td>88.61±0.34</td>
<td>91.97±0.64</td>
<td>91.12±0.14</td>
</tr>
</tbody>
</table>

![Graphs showing drug release kinetics](image-url)
3.3.5 *In vivo* Study

It was observed from the data shown in fig 7 that appreciable reduction in blood glucose level was observed in 1h in case of pure drug. On the other hands significant reduction in blood glucose level was observed upto 8h in case of floating microbeads. Thus, it was observed that the reduction in blood glucose level with floating microbeads for longer period as compared to pure drug (Fig.7).

![Figure 6. In vitro drug release kinetics](image)

![Figure 7. Comparison of in vivo plasma glucose level in alloxan-induced diabetic albino rat following oral administration of pure drug and Glibenclamide floating microbeads.](image)

**IV. Conclusions**

The results of the present investigation indicated that ionic cross-linking technique ionotropic gelation method can successfully be employed to fabricate Glibenclamide loaded floating microbeads. The technique provides characteristic advantage over conventional microbeads method, which involves an “all aqueous” system, avoids residual solvents in microbeads. Other method utilizes larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution and toxicity and present difficulty to remove traces of organic solvent completely. It was observed from the pharmacodynamic data that blood glucose level sustained below 200mg/dl from 4\textsuperscript{th} h to 24\textsuperscript{th} h unlike plain drug. This emphasizes importance of gastro-retentive carrier propose in present study.

**Acknowledgement**

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**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.
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