INTRODUCTION
The novel design of an oral controlled drug delivery system should primarily be aimed at achieving more predictable and increased bioavailability of drugs. The drug delivery system should deliver a drug at a rate dictated by the needs of the body over a specified period of treatment. These preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. Diabetes is a chronic metabolic disease characterized by hyperglycemia i.e. high blood sugar levels in the blood. Metformin, a glucose-lowering drug, is one of the most widely prescribed drugs for type-2 (adult-onset) diabetes. It is a white to off-white crystalline compound with a molecular formula of C$_4$H$_5$N$_4$ •HCl and a molecular weight of 165.63. It is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK$_a$ of metformin is 12.4. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It has a short half-life (1.5-4 hrs) and is absorbed from upper intestine within 6 hrs, repeated administration is required to maintain effective plasma concentration.

Chitosan is widely used as a carrier for many novel dosage forms. The pH-dependant solubility of chitosan is a function of the amino groups in the molecule and is a drawback for oral delivery in that chitosan microspheres formed by electrostatic interaction between a polyelectrolyte and counterions become unstable in gastric fluid. This problem can be countered by irreversible chemical crosslinking. It has been demonstrated that drug diffusion from chitosan microspheres can be controlled by crosslinking with a dialdehyde such as glutaraldehyde.

MATERIALS AND METHODS
Metformin HCl was obtained as a gift sample from Zydis Cadila healthcare Ltd., Ahmedabad. Chitosan (medium viscosity grade) was obtained from Central Institute of Fisheries Technology, Cochin, glutaraldehyde from Spectrochem Pvt. Ltd (Mumbai). All other reagents used in experiment were of analytical grade and purchased from their respective commercial sources.

Preparation of Metformin hydrochloride microspheres
Chitosan loaded metformin microspheres were prepared by emulsification cross linking method. To a 100 ml beaker, chitosan dissolved in 5 ml of 4% acetic acid, 0.5 ml of tween 80 and metformin hydrochloride was added. 100 ml of liquid paraffin and 2.5 ml of tween 80 is added in another 500 ml beaker. This solution was stirred on a magnetic stirrer for 30 minutes, until a smooth emulsion is formed. To the above solution drop by drop of drug-chitosan mixture was added and stirred for 60 mins, finally glutaraldehyde was added as a cross linking agent. It was then filtered to remove the excess of liquid paraffin, and lastly the obtained microspheres were washed with acetone, dried at room temperature and stored in a dessicator.

Characterization of microspheres
FT-IR Studies
FTIR study of Metformin and polymers was carried out to find out any possible interaction between the drug and the polymers used in the formulations. FTIR spectra of pure drug and drug-polymer mixture were obtained in KBr pellets using IR-affinity-I, Shimadzu Auto-00518 spectrometer.

Surface morphology
The surface morphology and structure were visualized by scanning electron microscopy (SEM). The samples were prepared by lightly sprinkling the microspheres powder on a double side adhesive tape which already shucked to on aluminum stubs. The stubs were then placed into fine coat ion sputter for gold coating. After gold coating samples were randomly scanned for particle size and surface morphology.

Microsphere size determination
Microsphere size was determined using an optical microscope under regular polarized light. The mean
microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.  

**Micromeritic properties**

**Angle of repose:** The angle of repose of each powder blend was determined by glass funnel method, using following equation:

$$\theta = \tan^{-1} \frac{h}{r}$$

Where,

- $\theta$ = angle of repose
- $h$ = height of the pile and
- $r$ = radius of the powder cone

**Bulk density**

Bulk density of formulated microspheres was determined by taking a known mass of microspheres in a 5 ml graduated measuring cylinder. The cylinder was dropped three times from a height of one inch at an interval of two seconds. The bulk density was calculated by following equation.

$$\text{Bulk density} = \frac{\text{Weight of microsphere in grams}}{\text{Bulk volume of microsphere in cm}^3}$$

**Tapped density**

Tapped density is the volume of powder determined by tapping using measuring cylinder containing weighed amount of sample. Tapped density of microspheres was calculated by following equation.

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

**Carr’s compressibility index**

This is an important property in maintaining uniform weight. It is calculated using following equation,

$$\% \text{ Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

**Determination of % yield of microspheres:** The dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formulae given below.

$$\text{Percentage yield} = \frac{\text{microspheres obtained}}{\text{Total weight of drug and polymer}} \times 100$$

**Determination of drug content**

Microspheres (equivalent to 50 mg of the drug) were taken for evaluation. The amount of drug loaded and entrapped efficiency was estimated by crushing the microspheres and extracting with aliquots of 0.1 N Hcl, repeatedly. The extract was diluted to 100 ml in a volumetric flask using 0.1 N Hcl. The solution was filtered and the absorbance measured at 233 nm against appropriate blank.

**In-vitro release study**

100 mg equivalent weight of the Metformin HCl was taken in a dialysis tube and placed in 500 ml of phosphate buffer. The medium was stirred by using the magnetic stirrer and the temperature was maintained at 37±0.5°C. Periodically 1 ml of the samples were withdrawn and diluted to 10 ml by using 7.4 phosphate buffer. After each withdrawal the same quantity of the fresh medium was replaced immediately. Then the samples were assayed spectrophotometrically, Systronics UV spectrophotometer 116 at 233nm using medium as blank.

**RESULTS AND DISCUSSION**

Drug polymer compatibility studies were conducted by FTIR spectroscopy and the results are presented in figure 1 and figure 2. The results indicated that there was no interaction between the drug and the polymers. SEM image of optimized formulation F-3 is depicted in figure no 3. The particles appear to be spherical and smooth surfaced.

![Figure 1: IR graph of chitosan and metformin hydrochloride](image-url)
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Figure 2: IR graph of metformin hydrochloride

Figure 3: SEM image of F-3 formulation

Table 2: Micromeritics properties of metformin loaded chitosan microspheres

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Average particle size(μm)</th>
<th>Bulk density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
<th>Angle of repose (º)</th>
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<tbody>
<tr>
<td>F1</td>
<td>642.53±12.24</td>
<td>0.402±0.03</td>
<td>0.462±0.03</td>
<td>14.19±2.1</td>
<td>1.14±0.3</td>
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<tr>
<td>F2</td>
<td>533.22±11.12</td>
<td>0.342±0.02</td>
<td>0.532±0.02</td>
<td>12.22±3.2</td>
<td>1.12±0.3</td>
<td>27°20’</td>
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<tr>
<td>F3</td>
<td>505.56±9.55</td>
<td>0.356±0.03</td>
<td>0.367±0.03</td>
<td>11.21±2.2</td>
<td>1.13±0.2</td>
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<tr>
<td>F4</td>
<td>623.71±11.22</td>
<td>0.354±0.02</td>
<td>0.412±0.02</td>
<td>15.13±2.1</td>
<td>1.11±0.3</td>
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<tr>
<td>F5</td>
<td>572.30±11.19</td>
<td>0.323±0.02</td>
<td>0.345±0.03</td>
<td>13.11±0.3</td>
<td>1.15±0.3</td>
<td>23°25’</td>
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<tr>
<td>F6</td>
<td>682.43±13.14</td>
<td>0.403±0.03</td>
<td>0.531±0.02</td>
<td>15.22±2.4</td>
<td>1.15±0.3</td>
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Table 3: Percentage yield

<table>
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<tr>
<th>Formulation code</th>
<th>Percentage yield (%)</th>
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<tr>
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<tr>
<td>F6</td>
<td>80.43</td>
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**Figure 4:** In vitro release and zero order graph of metformin hydrochloride microspheres

**Figure 5:** First order kinetics profile

**Table 4:** Kinetic data for Higuchi and Korsmeyer Peppas model

<table>
<thead>
<tr>
<th>FORMULATION CODE</th>
<th>HIGUCHI</th>
<th>KORSMEYER</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Slope(n)</td>
<td>Regression coefficient(R)</td>
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<tr>
<td>F-1</td>
<td>0.078</td>
<td>0.691</td>
</tr>
<tr>
<td>F-2</td>
<td>0.074</td>
<td>0.677</td>
</tr>
<tr>
<td>F-3</td>
<td>0.078</td>
<td>0.668</td>
</tr>
<tr>
<td>F-4</td>
<td>0.073</td>
<td>0.678</td>
</tr>
<tr>
<td>F-5</td>
<td>0.077</td>
<td>0.692</td>
</tr>
</tbody>
</table>
Chitosan loaded microspheres were prepared by using 5 different concentrations of chitosan. Mean particles size of formulated microspheres was found to be in the range of 533.50 ±10.62 to 700.36±10.33μm. The mean particle size of microsphere was found to increase with the polymer concentration, due to increase in viscosity of the polymer solution which increased the droplet size. The value of angle of repose determined ranges between 21° to 27°, bulk density and tapped density of formulated microspheres was found to be in range of 0.324±0.05 to 0.456±0.40 and 0.345±0.02 to 0.524±0.05 respectively. The Carr’s index and Hausner’s ratio was found to be in range of 11 to 15, 1.12±0.02 to 1.15±0.02 respectively as mentioned in table no 2. Percentage yield ranges from 80.43 to 90.32 as tabulated in table no 3. In vitro release profile was studied for all the formulations (F-1 to F-5) for 12 hrs and the results are given in figure 3. The release of drug depended on the concentration of polymer used. Drug release went on increasing with the increase in polymer concentration for the 3 formulations F-1, F-2 and F-3 (1:1, 1:2 and 1:4), further increase in polymer concentration decreased the release rate as seen in formulation F-4 and F-5. At 12th hour the drug release of the formulations (F-1 to F-5) were 70.56%, 74.77%, 78.78%, 69.88% and 65.12 % respectively. From the data it was concluded that F-3 showed best drug release in a controlled manner. Kinetic studies were conducted for all the formulations and the data for zero order and first order is presented in figure 3 and 4 and kinetic data for Higuchi and Peppas is tabulated in table 4. Regression co efficient values indicated that the formulations followed first order kinetics and n value was less than 1 which proves that formulation followed Peppas model with non Fickian diffusion.

CONCLUSION

Metformin loaded chitosan microspheres were promptly prepared by emulsification cross linking method. All the studies bulk density, Carr’s index, Hausner’s ratio, angle of repose, Percentage yield and in vitro drug release indicated that chitosan microspheres in the ratio 1: 4 (F-3) showed best results. Thus it can be concluded that formulation F-3 is best in the treatment of diabetes with reduced dosing frequency and better treatment in a controlled manner.

REFERENCES: