FORMULATION AND EVALUATION OF GLIPIZIDE MICROCAPSULES PREPARED BY NATURAL GUMS AND SYNTHETIC POLYMERS

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ABSTRACT

The GI tract is the most preferred and commonly used route for the delivery of drug. Microencapsulation is a useful method for prolonging drug release from dosage forms and drug targeting. Mucoadhesion has been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form at the site of absorption to improve and enhance the bioavailability of drugs. Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes. The main objective of the present study was to prepare and evaluate Glipizide Mucoadhesive microcapsules by Emulsification Gelation process. The microcapsules were evaluated for flow properties, Carr’s index, hausner ratio, micro encapsulation efficiency, drug release characteristics, and surface characteristics; compatibility studies and mucoadhesive properties. Sharp endothermic peaks were noticed from the microcapsules formulated 215°C indicating the compatibility between the drug and the polymer. In-vitro studies showed that Glipizide release from the Microcapsules was slow, spread over extended period of time which is depend on the coat:core ratio. Microcapsules prepared by 5:1 ratio were subjected to comparative studies. A significant difference in the permeability coefficient was observed between. In-vitro release studies shows the microcapsules prepared by Gum Kondagogu was in controlled manner when compare to other polymers used. In-vitro wash off test shows the microcapsules prepared by Gum Kondagogu had good mucoadhesive potency than the microcapsules prepared by other polymers used. Correlation coefficient (R) value was used to choose the best model to describe the drug release and it showed the R value was high in zero order models than other models. It indicates the microcapsules followed zero order kinetics. The drug release mechanism from the
microcapsules was Non fickian transport as n value is in between 0.69 to 1.12 This study clearly demonstrated that the microcapsules prepared by Gum Kondagogu are, thus, suitable for oral controlled release of glipizide.

**Keywords:** Emulsification Gelation process, Glipizide, Gum kondagogu, Gum Karaya, HPMC, Carbopol.

**INTRODUCTION**

The GI tract is the most preferred and commonly used route for the delivery of drug. Microencapsulation by various polymer and its applications are described in standard text books. It is a useful method for prolonging drug release from dosage forms and drug targeting. Micro particles are defined as spherical polymeric particles. These micro particles constitute an important part of this drug delivery system by virtue of their small size and efficient carrier characteristics. However the success of these micro particles is limited due to their short residence time at the site of absorption. Mucoadhesion has been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form at the site of absorption to improve and enhance the bioavailability of drugs. Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes. It is reported to have a short biological half-life (3.4±0.7 h) requiring it to be administered in 2 to 3 doses of 2.5 to 10 mg per day. Controlled release formulations that would maintain plasma levels of drug for 8 to 12 hrs might be sufficient for once a day dosing for Glipizide. Controlled release products are needed for Glipizide to prolong its duration of action and to improve patient compliance.

**MATERIALS AND METHODS**

Glipizide was obtained as gift sample from madras pharmaceuticals, carbopol and HPMC were obtained from central drug house, Mumbai, Gum Kondagogu, Gum Karaya were obtained from cooperative corporation ltd, Visakapatnam, all the other reagents used were analytical grade

**Preparation of mucoadhesive microcapsules by Emulsification Gelation process**

In Emulsification gelation process, sodium alginate (1gm) and the polymer (1gm) were dissolved in water (32ml). The drug (2gm) was added and mixed properly. The polymer dispersion was then added in a thin stream to 50ml of heavy liquid paraffin in a 250ml beaker, while stirring at 500rpm to emulsify the added dispersion as fine droplets. Then 20ml
of calcium chloride solution (15% w/v) was transferred into the emulsion while stirring at 500rpm for 15 min to produce spherical microcapsules. The microcapsules were collected by decantation and washed repeatedly with petroleum ether. Then the product was air dried to obtain discrete microcapsules. Different ratios of mucoadhesive microcapsules were prepared. [formulation code 1:1[MC1], 2:1[MC2],3:1 [MC3], 5:1 [MC4] were prepared by gum karaya, 1:1 [MC5], 2:1 [MC6], 3:1 [MC7],5:1 [MC8] were prepared by gum kondagogu, 1:1 [MC9], 2:1 [MC10], 3:1 [MC11], 5:1 [MC12] were prepared by HPMC and 1:1 [MC13], 2:1 [MC14], 3:1 [MC15],5:1 [MC16] were prepared by Carbopol]

Characterization and Evaluation of mucoadhesive microcapsules

A] Size distribution and size analysis
For size distribution analysis, different samples in batch were separated by sieving, using a range of standard sieves. The amount retained on different sieves was weighed and the mean particle size of microcapsules was calculated.

B] Flowability of microcapsules
The angle of repose was measured according to the fixed funnel and free standing cone method. The bulk density of the microcapsules was calculated by determining the hausner’s ratio and carr’s index from the pored and tapped bulk densities of a known weight of sample using a measuring cylinder.

C] Compatibility studies
Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent. It was scanned from 4000 to 400 cm\(^{-1}\) in a Shimadzu FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks.

D] Drug content evaluation
Glipizide content in the microcapsules was estimated by a UV spectrophotometric method based on the measurement of absorbance at (223nm) in phosphate buffer (pH 7.4)
E] Scanning electron microscopy (SEM)
The samples for the SEM analysis were prepared by sprinkling the gel beads on one side of double adhesive stub. The stub was then coated with fine gold dust. The gel beads were then observed with the scanning electron microscope.

F] Micro encapsulation efficiency
Micro encapsulation efficiency was calculated using the following formula.
Microencapsulation Efficiency = \[ \frac{\text{Estimated % drug content}}{\text{Theoretical % drug content}} \times 100 \]

G] Mucoadhesion evaluation
The Mucoadhesive property of the microcapsules was evaluated by an in vitro adhesion testing method known as the wash-off test.

H] Infrared spectroscopic studies
Compatibility between the drug and the different polymers were studied using Perkin Elmer 2000 FT-IR system.

I] In vitro release studies
Dissolution studies of microcapsules were performed according to USP XXIII 8-station dissolution rate test apparatus in phosphate buffer. The temperature was maintained at 37±1°C and the rotation speed was 50 rpm. The samples were withdrawn at various time intervals and analyzed spectrophotometrically.

J] Kinetic modeling
In order to understand the kinetics and mechanism of drug release, the result of in vitro drug release study of microcapsules were fitted with various kinetic equations like zero order (cumulative % release vs. time), first order (log % drug remaining Vs time), Higuchi’s model (cumulative % drug release vs. square root of time), Peppas plot (log of cumulative % drug release Vs. log time). r2 and k values were calculated from the linear curve obtained by regression analysis of the above plots (Saparia B, 2002).

K] Swelling Index
Pre weighed Glipizide microcapsules (w₀) of different batches were placed in phosphate buffer pH 7.4 at 37°C. The microcapsules were collected after 3rd hour and removed the excess of water and weighed (wₙ). The swelling index was calculated by using
Swelling index = \( \frac{W_t - W_o}{W_o} \times 100 \)

Where \( W_t \) = weight of microcapsules observed at 3\(^{rd} \) hour
\( W_o \) = initial weight of microcapsules

L] Permeability studies

Permeability constant was calculated by using

\[
P_m = \frac{H \cdot V \cdot H}{A \cdot C_s}
\]

\( V \) is the volume of the dissolution medium, \( H \) is the wall thickness of the micro capsules, \( A \) is the surface area of the microcapsules. \( C_s \) is the solubility of the core material in the dissolution medium and \( K \) is the release rate constant.

M] Stability studies

From each method the ideal formulations were selected for stability studies. They were subjected for long-term stability studies and accelerated stability studies. Long-term stability studies were carried out at 5\(^o\)C ± 3\(^o\)C and 30\(^o\)C ± 2\(^o\)C, 65% ± 5 % RH. The samples were stored at the above said condition for minimum 1 year and their drug content and \textit{in vitro} release was determined for every 3 months. Similarly an accelerated stability study was carried out by storing the selected preparation at 40\(^o\)C ± 2\(^o\)C, 75% ± 5 % RH for about 6 months. The drug content and in vitro release were determined for every 3 months (ICH Guidelines).

RESULT AND DISCUSSION

Mucoadhesive Microcapsules of Glipizide were prepared by \textit{Emulsification Gelation process} and the prepared microcapsules were found to be discrete spherical and free flowing. The microcapsules were in the size range of 850\(\mu\) shown in Table 1. The SEM photograph indicates that the microcapsules were spherical and completely covered with the polymer which is shown in Fig 1. Low coefficient of variation [<2.0%] in percentage drug content indicated uniformity of drug content in each batch of microcapsules. IR studies showed that there is no chemical incompatibility between the drug and the polymer. Glipizide release from the microcapsules was slow and spread over extended period of time, and the release was depended on the coat: core ratio. The microspheres prepared by 5:1 coat: core ratio was found to be more sustained release as it yield slow release of drugs. Based on the \textit{in-vitro} studies, Microcapsules prepared by 5:1 ratio of all polymers were subjected to comparative
studies. A significant difference in the permeability coefficient was observed. In-vitro studies show the microcapsules prepared by Gum Kondagogu offered much slower permeability of glipizide fig.2. In-vitro wash off test shows mucoadhesive potency of the microcapsules prepared by Gum Kondagogu was relatively high when compared to other polymers used Table.2. R value was higher in Zero Order than that of other models which indicates the drug release from the microcapsules followed Zero Order Kinetics. Based on the n - value it indicates the drug release mechanism from the microcapsules was Non.Fickian transport. Stability studies showed that the prepared microcapsules will be stable in 50 ± 30 C and 300 ± 20 C, 65% ± 5%RH.

Table 1: Physical properties of microcapsules prepared by Emulsification Gelation method

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose</th>
<th>Bulk Density</th>
<th>Carr’s Index</th>
<th>Hausner Ratio</th>
<th>Average particle size</th>
<th>%Encapsulation Efficiency</th>
<th>% Drug Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC1</td>
<td>22.06±0.08</td>
<td>0.43±0.05</td>
<td>19.45±0.24</td>
<td>1.22±0.08</td>
<td>826.93</td>
<td>90.87</td>
<td>45.08</td>
</tr>
<tr>
<td>MC2</td>
<td>23.08±0.12</td>
<td>0.47±0.06</td>
<td>18.79±0.26</td>
<td>1.16±0.07</td>
<td>840.15</td>
<td>92.40</td>
<td>36.28</td>
</tr>
<tr>
<td>MC3</td>
<td>24.14±0.11</td>
<td>0.58±0.03</td>
<td>17.84±0.32</td>
<td>1.06±0.10</td>
<td>855.78</td>
<td>94.40</td>
<td>31.08</td>
</tr>
<tr>
<td>MC4</td>
<td>25.16±0.17</td>
<td>0.68±0.13</td>
<td>16.74±0.32</td>
<td>1.02±0.08</td>
<td>865.98</td>
<td>95.46</td>
<td>28.08</td>
</tr>
<tr>
<td>MC5</td>
<td>22.13±0.09</td>
<td>0.42±0.08</td>
<td>19.65±0.18</td>
<td>1.20±0.06</td>
<td>828.35</td>
<td>90.77</td>
<td>46.06</td>
</tr>
<tr>
<td>MC6</td>
<td>23.23±0.11</td>
<td>0.49±0.05</td>
<td>17.76±0.22</td>
<td>1.18±0.09</td>
<td>852.12</td>
<td>91.65</td>
<td>36.58</td>
</tr>
<tr>
<td>MC7</td>
<td>25.54±0.13</td>
<td>0.57±0.05</td>
<td>16.35±0.18</td>
<td>1.12±0.08</td>
<td>876.48</td>
<td>93.09</td>
<td>31.28</td>
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<tr>
<td>MC8</td>
<td>26.04±0.16</td>
<td>0.62±0.05</td>
<td>15.35±0.08</td>
<td>1.02±0.08</td>
<td>878.48</td>
<td>95.09</td>
<td>28.28</td>
</tr>
<tr>
<td>MC9</td>
<td>21.06±0.07</td>
<td>0.48±0.08</td>
<td>13.85±0.23</td>
<td>1.12±0.06</td>
<td>828.76</td>
<td>91.66</td>
<td>44.02</td>
</tr>
<tr>
<td>MC10</td>
<td>22.68±0.18</td>
<td>0.58±0.04</td>
<td>12.69±0.18</td>
<td>1.08±0.08</td>
<td>846.66</td>
<td>92.88</td>
<td>35.96</td>
</tr>
<tr>
<td>MC11</td>
<td>23.86±0.09</td>
<td>0.63±0.07</td>
<td>12.24±0.20</td>
<td>1.02±0.10</td>
<td>865.56</td>
<td>95.06</td>
<td>30.60</td>
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<tr>
<td>MC12</td>
<td>24.86±0.19</td>
<td>0.65±0.07</td>
<td>11.24±0.20</td>
<td>1.00±0.10</td>
<td>869.56</td>
<td>95.66</td>
<td>28.60</td>
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<tr>
<td>MC13</td>
<td>21.75±0.14</td>
<td>0.46±0.05</td>
<td>19.15±0.22</td>
<td>1.22±0.04</td>
<td>822.34</td>
<td>91.28</td>
<td>44.98</td>
</tr>
<tr>
<td>MC14</td>
<td>23.29±0.12</td>
<td>0.54±0.05</td>
<td>16.76±0.26</td>
<td>1.14±0.06</td>
<td>845.22</td>
<td>92.68</td>
<td>36.20</td>
</tr>
<tr>
<td>MC15</td>
<td>24.98±0.08</td>
<td>0.60±0.06</td>
<td>16.45±0.24</td>
<td>1.06±0.10</td>
<td>864.58</td>
<td>94.88</td>
<td>30.98</td>
</tr>
<tr>
<td>MC16</td>
<td>25.98±0.08</td>
<td>0.66±0.06</td>
<td>15.45±0.24</td>
<td>1.02±0.10</td>
<td>868.58</td>
<td>95.88</td>
<td>28.98</td>
</tr>
</tbody>
</table>
Fig.1. Dissolution Profiles of the drug release from the mucoadhesive microcapsules of glipizide.

Table 2: *In vitro* wash-off test

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Percentage of alginate beads adhering to tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1N HCL, pH1.2</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>MC4</td>
<td>95</td>
</tr>
<tr>
<td>MC8</td>
<td>99</td>
</tr>
<tr>
<td>MC12</td>
<td>90</td>
</tr>
<tr>
<td>MC16</td>
<td>92</td>
</tr>
</tbody>
</table>

Fig 2. SEM photograph of glipizide microcapsules formulated with gum Kondagogu [5:1] by Emulsification Gelation technique.
CONCLUSION
The Glipizide mucoadhesive microcapsules with coat consisting of alginate and mucoadhesive polymers were prepared by Emulsification Gelation process. The microcapsules exhibited good mucoadhesive properties in an in-vitro wash off test and the in-vitro release studies of Glipizide microcapsules shows significant difference in their release rate. The microcapsules prepared by mucoadhesive polymer Alginate-Gum Kondagogu [5:1 ratio] showed slow and controlled release over extended period of time when compared to other mucoadhesive polymer. And the Drug release was diffusion controlled and followed zero-order kinetics. These bioadhesive microcapsules are, thus, suitable for oral controlled release of glipizide.

ACKNOWLEDGEMENT
The authors are wished to acknowledge the encouragement given by the Dr.Adlin Jose, principal and all the Teaching & Non Teaching staff of Maheshwara Institute of pharmacy, Hyderabad. They are also thankful to C. Jose Gnana Babu & Dr.Parthiban for their help rendered throughout the work.

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