Formulation and Evaluation of Paracetamol Loaded Mucoadhesive Microspheres

Nethaji Ramalingam*1, Shahana Parvin1, Binulal C1, Manikandan Palanivelu1, N. Subramaniam Surendiran1, Babu Ganesan2

1Department of Pharmaceutics, Devaki Amma Memorial College of Pharmacy, Chelembra-673634, Malappuram, Kerala, India.
2Department of Pharmaceutical Chemistry, Devaki Amma Memorial College of Pharmacy, Chelembra-673634, Malappuram, Kerala, India.

*Corresponding author: Nethaji Ramalingam, Department of Pharmaceutics, Devaki Amma Memorial College of Pharmacy, Chelembra-673634, Malappuram, Kerala, India, E-mail: nethajijkncp32@gmail.com

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Abstract

Objective: The present work is to formulate the mucoadhesive microspheres loaded Paracetamol using two different natural gums with an aim to increase the GI retention time, enhance bioavailability over prolonged period of time in the stomach and upper GIT and decreased GI side effect.

Methods: Paracetamol mucoadhesive microspheres were formulated using sodium alginate, different concentration of Xanthan gum and Guar gum by ionic gelation technique. Six formulations were prepared and evaluated for relevant parameters.

Results: Percentage yield is found between 52.34 ± 0.58% to 84.21 ± 0.21% in all formulations. The surface morphology of microspheres was characterized by SEM; it was discrete, spherical in shape and showed free flowing properties. The mean particle size of microspheres significantly increases and it was the range between 37.05 ± 0.05 µm to 45.29 ± 0.06 µm. Among all the formulations, XG-III showed a high entrapment efficiency is 94.80 ± 0.54% and highest percentage sorption in distilled water is observed. The in-vitro drug release studies revealed that XG-III is controlled and found to be 77.04 ± 0.22% at the end of the dissolution studies. The mechanism of drug release was evaluated using the linear regression coefficient. Stability studies of selected mucoadhesive microspheres showed good results. It could be also concluding that the all the formulations were shown satisfactory results and suitable for potential therapeutic uses.

Keywords: Paracetamol, Mucoadhesive microspheres, Xanthan gum, Guar gum, In-vitro evaluation, Stability studies
Introduction

Development of oral controlled release formulations is an attempt to release drug slowly and control manner into gastro intestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for longer time. But several physiological difficulties such as inability to restrain and locate within the desired region of the GIT due to variable gastric emptying and motility are observed. Furthermore, due to short residence time through the major absorption zone, can results incomplete drug release lead to reduced therapeutic efficacy of an administered dose and eliminated quickly from the blood circulation therefore bioavailability of drug also suffers [1-3]. In order to avoid this variability, efforts have been made to increase and prolonged gastric retention time by using oral controlled drug delivery system with gastro retentive properties which remain at the absorption site for an extended period of time. It can be achieved by coupling mucoadhesion characteristics to microspheres which has efficient absorption and enhanced bioavailability of drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting to the absorption site results an improved therapeutic effect for gastric diseases, ex. liver damage and peptic ulceration [4]. Paracetamol is a mild “aniline” analgesic with weak COX enzyme inhibiting activity which used as analgesic and antipyretic. The onset of an action is approximately 11 min after oral administration, and the limitation is short biological half-life (2-3 h). It has rapidly absorbed from small intestine and fast metabolize and about 98% of the drug gets eliminated after a single oral dose (500 mg every 4-6 h), thus requiring a high frequency dosing (3-4 times/day) [5-8] for maintain the plasma level and an acute overdoses of paracetamol can cause potentially fatal liver damage [9]. Also, Paracetamol tablet gets rapidly absorbed from small intestine following an oral route and produce gastro intestinal toxicity following repeated dose administration. So, it’s necessary to develop mucoadhesive microspheres from naturally occurring polymers, which adhere to the mucosa, prolong gastric residence time, enhance bioavailability and maintain constant drug levels for extended period with decrease dosing frequency and reduces dose related toxicity such as peptic ulceration and liver damage compared than conventional oral dosage forms. The objective of the present work is to formulate the Paracetamol loaded mucoadhesive microspheres using two different natural gums with varying drug - polymer ratios and to evaluate the microspheres characterization.

Materials and Methods

Materials

Paracetamol was obtained from Yarrow Chem Products, Mumbai, India. Sodium alginate and xanthan gum from Qualigens Fine Chem Pvt Ltd, Mumbai, India, Guar gum from Yarrow Chem Products, Mumbai, India, Calcium chloride from Flora Chemicals, India.

IR Spectral Analysis

FT-IR spectrum of Paracetamol and polymers was recorded using KBr mixing method on the FT-IR instrument (Schimadzu FTIR instrument). The drug alone and drug in combination with polymers in the ratio of 1:1 was taken and subjected to FT-IR studies [10].

Preparation of Mucoadhesive Microspheres of Paracetamol

The Microspheres were prepared according to the ionotropic gelation method by using different ratios of Paracetamol (PCT), sodium alginate, guar gum and xanthan gum. Sodium alginate was dissolved in deionized water to form a homogeneous solution (2% w/v). Guar gum and xanthan gum were dissolved separately with deionized water to get viscous and sticky solutions. The pure drug was dispersed in the solution of gum and then sodium alginate solution was added to it with vigorous stirring until formation of spheric rigid microspheres. They were collected by decantation, washed and dried at room.

temperature and subsequently stored in desiccators. Six formulations were prepared by different ratios of drug and polymer as given in Table 1 and were evaluated for relevant parameters [11].

Characterization of Mucoadhesive Microspheres

Micromeritic Properties

Mucoadhesive microspheres were characterized by their micromeritic properties like bulk density, tapped density, Carr’s index, Hausner’s ratio and angle of repose [12-15].

Percentage Yield

The prepared microspheres were collected, dried at room temperature and then weighed. The percentage yield of the microspheres was calculated by measured weight of prepared microspheres was divided by the total amount of all excipients and drug used [16]. Percentage yield (%) is estimated by:

\[
\text{Percentage yield} = \left( \frac{\text{Amount of microspheres obtained (g)}}{\text{Theoretical amount (g)}} \right) \times 100
\]

Determination of Particle Size

The prepared mucoadhesive microspheres were selected randomly and their size was measured by optical microscopy (Olympus, India) method [17-19].

Entrapment Efficiency

The calculated amount of the microspheres was taken and the drug was extracted from the microspheres by crushing the microspheres using mortar and pestle. 25 mg of this powder were added to the 100 ml phosphate buffer (pH 7.4) followed by stirring of the solution at 1000 rpm for 3 h. After that, the solution was filtered and the filtrate was analyzed spectrophotometrically at 249 nm [20]. The Percentage entrapment efficiency is calculated by:

\[
\text{Entrapment efficiency} = \left( \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \right) \times 100
\]

In-Vitro Drug Release Studies

It was carried in USP XXI paddle type dissolution test apparatus using phosphate buffer (pH 7.4) as dissolution medium, volume of dissolution medium was 900 ml and temperature was maintained at 37 ± 0.5°C throughout the study. Paddle speed was adjusted to 50 rpm. An interval of 30 minutes, 5 ml of sample was withdrawn with replacement of 5 ml fresh medium and analyzed for drug content by UV Visible spectrophotometer at 249 nm. All the experimental units were analyzed in triplicate and cumulative percentage drug release was calculated [21]. To understand the mechanism and kinetics of in-vitro drug release studies of all formulations was subjected to goodness of fit test by linear regression analysis, according to Zero order and First order kinetics equations, Higuchi’s and Korsmeyer-Peppa’s model [22-23].

Sorption Studies

The calculated quantity of dried microspheres from each batch was placed in two different media such as distilled water and 0.1N HCl (100 ml each) and it was kept at room temperature. At end of 48 h, measured the increase in weight and find percent water sorption by the following formula [24]. Percent water sorption is determined by:

\[
\text{Percent water sorption} = \left( \frac{W_s - W_d}{W_d} \right) \times 100
\]

Stability Studies

Best formulations were placed in borosilicate screw capped glass containers and stored in room temperature (27 ± 2°C, 60 ± 5% RH) and stability chamber (45 ± 2°C, 70 ± 5% RH) which was maintained at 90 days under ICH and WHO guidelines to assess their stability. At the end of specified day’s period, samples were withdrawn and are analyzed for their drug content [25].

Morphological Studies

Surface morphology of the selected mucoadhesive microspheres of paracetamol were determined by using Scanning Electron Microscopy (JEOL, JSM-6701 F, JAPAN) operating at 15 KV [26].
Results and Discussion

IR Spectral Analysis

FT-IR spectra of prepared sample were taken in the wavelength region was 400-4000 cm\(^{-1}\) at ambient temperature and the resolution was 4 cm\(^{-1}\) and compared the position and relative intensity of absorption band of physical admixtures (PSX & PSG) and pure drug was shown in Figure 1, Figure 2 and Figure 3. From the results, IR spectrum of pure drug was found to be similar to the standard IR spectrum which indicates that the obtained sample was pure Paracetamol. The IR spectra of all the pure samples and Paracetamol physical admixtures of suitable proportion of polymers were subjected to the study. From the results, it has been observed that the characteristic C-H stretching, C=O stretching, C=C stretching, NH bending, C-OH stretching of pure Paracetamol drug was unchanged in the spectra of Paracetamol physical admixtures and indicated that there was no significant difference in the IR spectra of pure drug compare with physical admixtures and with no changes in the peak shape and no shift of peaks. It is concluded that the characteristics bands of Paracetamol were not affected after loading polymer microspheres and the drug was compatible with the polymers and were expected to stable during the encapsulation process because there were no significant interactions between the drug and polymers in the physical admixtures.

Micromeritic Properties

From Table 2 stated that the bulk density and tapped density lies in between 0.6150 to 0.7709 and 0.6486 to 0.8578 g/cm\(^3\) indicate good packing of the microspheres. The Carr’s index was lies between 5.18 % to 10.13% indicating excellent flow characteristics. The Hausner’s ratio was lies between 0.898 to 0.948 indicate good flow. Also, it was observed that the angle of repose is found to be less than 40° indicate free and good flow properties of microspheres.

Percentage Yield, Particle Size and Drug Entrapment

From Table 3, the percentage yield is found between 52.34% to 84.21% in all formulations and it was observed that, the concentration of polymer increased, the percentage yield of the mucoadhesive microspheres was also slightly increased. The average particle size found in between 37.05 ± 0.05 to 45.29 ± 0.06 µm. As the drug to polymer ratio was increased the mean particle size of microspheres were also increased. The significant increase in particle size may be because of the increase in the viscosity of droplets which formed larger droplets and consequently larger microspheres due to increase in concentration of polymer solution. From the results, the entrapment efficiency was found to be in the range 44.28% to 94.80%. A maximum of 94.8% of drug entrapped in XG-III mucoadhesive microsphere which was prepared by xanthan gum batches. It was observed that the entrapment efficiency increase with increasing the polymer concentration. Also, the particle size increases more drug will be bound in the microspheres leading to increased entrapment efficiency.

In-Vitro Drug Release Studies

The in-vitro drug release profile of all batches of microspheres was studies using Phosphate buffer (pH 7.4). The comparative in-vitro drug release curve was found in Figure 4 and Figure 5 and shows that the drug release from XG-III formulation is found 77.04%; similarly, GG-III formulation was 80.28% at the end of dissolution studies. From the results, it was observed that, the in-vitro performance of mucoadhesive microspheres show prolonged and controlled release of paracetamol due to the increasing the level of polymer concentration leads to increased density of polymer matrix into the microspheres which results in increased diffusional path length. This may decrease the drug release from the polymer matrix and exhibit prolonged time. In order to understand the mechanism and kinetics of in-vitro drug release studies of all formulations are given in Table 4 and coefficient of correlation (r) values were computed. From the results, zero order kinetics was found to be 0.9901, 0.9952, 0.9908, & 0.9911, 0.9916, 0.9948 respectively. So, the co-efficient of determination indicated that the release data was best fitted with zero order kinetics. When the drug release data was put in to Higuchi’s equation, good correlation coefficient (r) values 0.9789 to 0.9899 were obtained, indicating the drug release was diffusion controlled release mechanism. The release data obtained were

also put in Korsmeyer–Peppas model in order to find out n values, which describe the drug release mechanism. From the kinetics result data, the ‘n’ values of mucoadhesive microspheres were found in the range of 0.8675 to 1.0567 with correlation coefficient values ranging from 0.9502 to 0.9972, indicating good linearity. Hence, the above observations, the release of drug from mucoadhesive microspheres provide a controlled release for a period of sufficient hours and the kinetics study shows that ‘r’ values of all formulated batches indicate compliance with Higuchi’s plot and reveals that the drug release follows non-Fickian diffusion mechanism.

**Sorption Studies**

From Table 5 the percentage water sorption behavior of best formulations (XG-III and GG-III) was determined in distilled water and 0.1N HCl. The percentage water sorption of mucoadhesive microspheres is found in distilled water ranges from 18.20% to 84.80% and 17.04% to 72.40% in 0.1N HCl at the end of 48 h. From the results, it was observed that sorption behavior indicates that the microspheres exhibit excellent sorption in distilled water which may be attributed to the pores and cavities present in them. Formulation GG-I showed least percentage sorption in both media and XG-III which shows highest sorption in distilled water (84.80%) and in 0.1N HCl (72.40%). The fundamentals that increase in degree of sorption depends on polymer concentration in formulations. From the results, it was observed that the xanthan gum formulations showed greater percentage of sorption than guar gum batches.

**Stability Studies**

Best formulation of Paracetamol microspheres (XG-III) based upon in-vitro drug release studies was taken and stored at room temperature and in stability chamber and analyzed for their drug content and illustrated in Table 6. From the results shows that there is about 64.28% to 65.98% of drug present in XG-III formulation with no observable physical changes occur during the storage period for three months.

**Morphological Studies**

The surface morphology was determined by SEM for the characterization of shape and size of mucoadhesive microspheres. Figure 6 and Figure 7 shows that the prepared microspheres is completely covered with the mucoadhesive polymer and were a good specificity, spherical, uniform in shape and exhibited smooth surface. The surface smoothness of prepared microspheres was decreased by increasing the amount of gum which confirmed by SEM.

**Conclusion**

Mucoadhesive microspheres loaded Paracetamol is obtained by using suitable ratios of Xanthan gum and Guar gum and the formulated microspheres might be better practical approach to achieve the retarded effect and continuously releasing the medication over extended period of time in the stomach and upper GIT with decreased GI side effect due to the less frequently of administration and all the result data were found to be satisfactory. Hence, it’s concluded that the prepared mucoadhesive microspheres can be selected for the development of gastro retentive drug delivery system for potential therapeutic uses, thereby enhance bioavailability and improve the patient compliance.

**Conflict of Interest**

The authors declare no conflict of interest.

**Acknowledgements**

The authors are thankful to the Management, Devaki Amma Memorial College of Pharmacy, Chelembra, Malapuram District, Kerala, for providing support and necessary facilities to carry out this research work.

**References**


Table 1: Composition of Paracetamol mucoadhesive microspheres

<table>
<thead>
<tr>
<th>Formulations Code</th>
<th>Paracetamol (mg)</th>
<th>Sodium Alginate (% w/v)</th>
<th>Guar Gum ( % w/v)</th>
<th>Xanthan Gum (% w/v)</th>
<th>Calcium Chloride (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XG-I</td>
<td>500</td>
<td>10</td>
<td>-</td>
<td>1.25</td>
<td>50</td>
</tr>
<tr>
<td>XG-II</td>
<td>500</td>
<td>10</td>
<td>-</td>
<td>2.5</td>
<td>50</td>
</tr>
<tr>
<td>XG-III</td>
<td>500</td>
<td>10</td>
<td>-</td>
<td>3.75</td>
<td>50</td>
</tr>
<tr>
<td>GG-I</td>
<td>500</td>
<td>10</td>
<td>1.25</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>GG-II</td>
<td>500</td>
<td>10</td>
<td>2.5</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>GG-III</td>
<td>500</td>
<td>10</td>
<td>3.75</td>
<td>-</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 2: Micromeritic properties data of Paracetamol mucoadhesive microspheres

<table>
<thead>
<tr>
<th>Formulations Code</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 (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XG-I</td>
<td>0.6150 ± 0.02</td>
<td>0.6486 ± 0.07</td>
<td>5.18 ± 0.05</td>
<td>0.948 ± 0.09</td>
<td>29°.85 ± 0.45</td>
</tr>
<tr>
<td>XG-II</td>
<td>0.6228 ± 0.07</td>
<td>0.6774 ± 0.09</td>
<td>8.06 ± 0.11</td>
<td>0.920 ± 0.04</td>
<td>30°.20' ± 0.29</td>
</tr>
<tr>
<td>XG-III</td>
<td>0.6499 ± 0.03</td>
<td>0.7185 ± 0.05</td>
<td>9.54 ± 0.09</td>
<td>0.899 ± 0.31</td>
<td>32°.64’ ± 0.38</td>
</tr>
<tr>
<td>GG-I</td>
<td>0.7225 ± 0.05</td>
<td>0.7724 ± 0.03</td>
<td>6.46 ± 0.07</td>
<td>0.935 ± 0.11</td>
<td>28°.32’ ± 0.42</td>
</tr>
<tr>
<td>GG-II</td>
<td>0.7685 ± 0.04</td>
<td>0.8461 ± 0.01</td>
<td>9.17 ± 0.33</td>
<td>0.908 ± 0.42</td>
<td>30°.80’ ± 0.35</td>
</tr>
<tr>
<td>GG-III</td>
<td>0.7709 ± 0.07</td>
<td>0.8578 ± 0.09</td>
<td>10.13 ± 0.12</td>
<td>0.898 ± 0.15</td>
<td>31°.37’ ± 0.23</td>
</tr>
</tbody>
</table>

Results are mean ± SD of three trials (n=3)

Table 3: Percentage yield, Particle size and Drug entrapment of Paracetamol mucoadhesive microspheres

<table>
<thead>
<tr>
<th>Formulations Code</th>
<th>Percentage Yield (%)</th>
<th>Particle Size (µm)</th>
<th>Drug Entrapment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XG-I</td>
<td>68.48 ± 0.83</td>
<td>38.23 ± 0.05</td>
<td>51.34 ± 0.25</td>
</tr>
<tr>
<td>XG-II</td>
<td>76.61 ± 0.64</td>
<td>42.35 ± 0.09</td>
<td>68.98 ± 0.56</td>
</tr>
<tr>
<td>XG-III</td>
<td>84.21 ± 0.21</td>
<td>45.29 ± 0.06</td>
<td>94.80 ± 0.54</td>
</tr>
<tr>
<td>GG-I</td>
<td>52.34 ± 0.58</td>
<td>37.05 ± 0.05</td>
<td>44.28 ± 0.21</td>
</tr>
<tr>
<td>GG-II</td>
<td>74.61 ± 0.90</td>
<td>41.17 ± 0.07</td>
<td>62.15 ± 0.67</td>
</tr>
<tr>
<td>GG-III</td>
<td>82.05 ± 0.42</td>
<td>43.52 ± 0.09</td>
<td>86.24 ± 0.19</td>
</tr>
</tbody>
</table>

Results are mean ± SD of three trials (n=3)

Table 4: Kinetic analysis data of Paracetamol mucoadhesive microspheres

<table>
<thead>
<tr>
<th>Formulations Code</th>
<th>Release model</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi’s Model</th>
<th>Korsmeyer and Peppa’s Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XG-I</td>
<td></td>
<td>0.9901</td>
<td>8.9480</td>
<td>0.9474</td>
<td>-0.0991</td>
</tr>
<tr>
<td>XG-II</td>
<td></td>
<td>0.9952</td>
<td>8.6372</td>
<td>0.9616</td>
<td>-0.0786</td>
</tr>
<tr>
<td>XG-III</td>
<td></td>
<td>0.9908</td>
<td>8.3495</td>
<td>0.9648</td>
<td>-0.0661</td>
</tr>
<tr>
<td>GG-I</td>
<td></td>
<td>0.9911</td>
<td>9.1155</td>
<td>0.9164</td>
<td>-0.1086</td>
</tr>
<tr>
<td>GG-II</td>
<td></td>
<td>0.9916</td>
<td>8.7716</td>
<td>0.9640</td>
<td>-0.0847</td>
</tr>
<tr>
<td>GG-III</td>
<td></td>
<td>0.9948</td>
<td>8.5377</td>
<td>0.9645</td>
<td>-0.0720</td>
</tr>
</tbody>
</table>

Table 5: Sorption ability of Paracetamol mucoadhesive microspheres

<table>
<thead>
<tr>
<th>Formulations Code</th>
<th>In Distilled Water (%)</th>
<th>In 0.1 HCl (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XG-I</td>
<td>36.60 ± 0.04</td>
<td>24.80 ± 0.03</td>
</tr>
<tr>
<td>XG-II</td>
<td>49.20 ± 0.02</td>
<td>30.20 ± 0.02</td>
</tr>
<tr>
<td>XG-III</td>
<td>84.80 ± 0.03</td>
<td>72.40 ± 0.06</td>
</tr>
<tr>
<td>GG-I</td>
<td>18.20 ± 0.06</td>
<td>17.04 ± 0.01</td>
</tr>
<tr>
<td>GG-II</td>
<td>32.40 ± 0.08</td>
<td>24.40 ± 0.05</td>
</tr>
<tr>
<td>GG-III</td>
<td>52.80 ± 0.02</td>
<td>42.01 ± 0.02</td>
</tr>
</tbody>
</table>

Results are mean ± SD of three trials (n=3)

Table 6: Stability studies data of Paracetamol mucoadhesive microspheres (XG III)

<table>
<thead>
<tr>
<th>At the end (in days)</th>
<th>Physical Appearance</th>
<th>Percentage Drug Content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>27 ± 2°C, 60 ± 5% RH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 ± 2°C, 70 ± 5% RH</td>
</tr>
<tr>
<td>30</td>
<td>No change</td>
<td>65.98 ± 0.13</td>
</tr>
<tr>
<td>60</td>
<td>No change</td>
<td>65.34 ± 0.17</td>
</tr>
<tr>
<td>90</td>
<td>No change</td>
<td>64.80 ± 0.12</td>
</tr>
</tbody>
</table>

Figure 1: IR spectra of pure Paracetamol

Figure 2: IR spectra studies of physical admixtures of Paracetamol, sodium alginate and xanthan gum (PSX)

Figure 3: IR spectra studies of physical admixtures of Paracetamol, sodium alginate and guar gum (PSG)

Figure 4: Comparative in-vitro drug release plot of Paracetamol mucoadhesive microspheres (XG-I to XG-III)
Figure 5: Comparative in-vitro drug release plot of Paracetamol mucoadhesive microspheres (GG-I to GG-III)

Figure 6: SEM image of Paracetamol mucoadhesive microspheres (XG-III)

Figure 7: SEM image of Paracetamol mucoadhesive microspheres (GG-III)
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