Formulation of Sustained Release Matrix Tablets Using Plant Gum

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ABSTRACT

Natural polymers such as, sugars, gums, mucilages are widely used in the pharmaceutical as excipients and additives due to their disintegrant, filler, sustain release as well as environment-benign, biodegradable, easy availability and cost-effective behavior. The objective of this study is to investigate the binding property of Calotropis gigantea gum based matrix tablets and to evaluate sustained release of water soluble drug Amoxicillin. In-vitro drug release mechanism was elucidated for different formulation of gum tablets at various gastrointestinal tract (GIT) pH. All the formulations exhibited significant results in pre-compression and post-compression experiments. Drug release rate increased with the decrease of plant gum amount. The release of drug is pH sensitive. The formulation T5 sustained, the release of drug with 96.26% at pH 7.4 and 84.77% at pH 1.2. Because of swelling property increased the drug release profile to some extent due to change in swelling at the tablet surface. The results of the tablet evaluation and sustained release profile of the drug reveal the potentiality of C. gigantea gum as better excipient.
INTRODUCTION

Sustained release system implies to the pharmaceutical dosage form formulated for retardation of release of therapeutic agent such that its appearance in the systemic circulation was delayed or prolonged and its plasma profile was sustained in duration. The main objective in designing sustained delivery system is to reduce dosing frequency and thereby increasing the action\(^1\). The effectiveness of this system depends on the excipients. Excipients are additives used to convert the active pharmaceutical ingredients into dosage forms suitable for administration to patient\(^2\). Excipients of natural origin are of particular interest to us for reasons of reliability, sustainability and avoiding reliance upon materials derived from fossil fuels\(^3\). Natural gums obtained from plants have diverse applications in drug delivery as disintegrant, emulsifying, suspending agents and as binders. They have also been found useful in formulating immediate and sustained release preparations\(^4\)\(^-\)\(^8\). Gums generally polysaccharides which are polymeric in nature of natural substance obtained from woody and non woody plant parts such as bark, seeds, sap, roots, rhizomes, fruit, leaves and plant gums are widely used in formulation of pharmaceutical dosage forms. The major application of gum is as binding agent in tablet\(^9\)\(^,\)\(^10\).

*Calotropis gigantea* R.Br (Asclepiadaceae) is a xerophytic, erect shrub, growing widely throughout the tropical and subtropical regions of Asia and Africa. This plant is popularly known because it produces large quantity of latex\(^11\). Leaves, roots, stem, flowers and latex of *Calotropis gigantea* are used in traditional medicinal system to cure several diseases and medicinal potential of the *Calotropis gigantea* proved scientifically. The flowers of the *Calotropis gigantea* are used in stomachic, backache, anti-asthmatic, analgesic activity\(^12\). The main objective of the current study is to exploit the use of gum *Calotropis gigantea* as natural binding agent in development of matrix tablet formulations taking Amoxicillin as model drug.

MATERIALS AND METHODS

Plant materials

The fresh sample of gum from *Calotropis gigantea* was authenticated by Dr. Arvind, Ph.D., National Institute of Siddha, Medicinal plants of research unit, Tambaram, Chennai-600045. Other reagents used were of analytical grade and were used without further purification.
Isolation and Purification of *Calotropis gigantea* gum

Fresh gum of *Calotropis gigantea* was collected (Figure 1) and washed with water to remove dirt and debris. Following this, acetone was added to precipitate the gum. The gum was separated, dried in an oven at a temperature less than 50˚C, and the dried powder gum was passed through a sieve no. 80 and stored in a desiccator until required\textsuperscript{13}.

![Figure 1: Calotropis gigantea fresh gum (a) and after processing (b)](image)

Preparation of tablets by using wet granulation methods

Five different batches of tablets were prepared using wet granulation technique. The composition of single tablet per batch is given in Table 1. Each polymer was used separately. Calculated amount, which was required to prepare 100 mg Amoxicillin tablets containing drug and binder was mixed uniformly. A sufficient amount of distilled water was added slowly to prepare wet mass. Dried granules were stored in desiccators until compression of tablets. The compressed tablets of each batch were stored in air tight container.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug (mg)</td>
<td>T1 T2 T3 T4 T5</td>
</tr>
<tr>
<td>5</td>
<td>10 15 20 25</td>
</tr>
<tr>
<td>Natural polymers</td>
<td>95 90 85 80 75</td>
</tr>
<tr>
<td>(mg)</td>
<td></td>
</tr>
</tbody>
</table>

Evaluation of the formulation:

The prepared formulations were evaluated for the following parameters\textsuperscript{14-17}:
Pre-compression evaluation:

**Bulk Density**

Bulk density ($D_b$) was determined by measuring the volume ($V_b$) of known weighed quantity ($W$) of granules using bulk density test apparatus and can be calculated by using the formula:

$$D_b = \frac{W}{V_b}$$

**Tapped Density**

Tapped density ($D_t$) was determined by measuring the volume ($V_t$) of known weighed quantity ($W$) of granules using bulk density test apparatus and can be calculated by using the formula:

$$D_t = \frac{W}{V_t}$$

**Carr’s Index**

The Carr’s index (% compressibility) of the granules was calculated from the difference between the Tapped and Bulk densities divided by the Tapped density and the ratio expressed as a percentage.

$$\text{Carr’s Index} \% = \frac{D_t - D_b}{D_t} \times 100$$

Where, $D_t$ is the Tapped density and $D_b$ is the Bulk density.

**Hausner’s ratio**

The Hausner’s ratio was calculated by dividing the Tapped density by the Bulk density of the granules.

$$\text{Hausner’s index} = \frac{D_t}{D_b}$$

Where, $D_t$ is the Tapped density and $D_b$ is the Bulk density.
Angle of Repose

The accurately weight granules were taken in the funnel. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation:

\[ \tan \theta = \frac{h}{r} \text{ or } \theta = \tan^{-1}\left(\frac{h}{r}\right) \]

Where; \( \theta = \text{Angle of repose} \), \( h = \text{Height of the cone} \), and \( r = \text{Radius of the cone base} \)

Post-compression evaluation:

Tablet Thickness

The thickness of the tablets was determined by using screw gauge. Five tablets were used, and average values were calculated.

Weight Variation

To study weight variation twenty tablets of the formulation were weighed using a digital balance (Acculab ALC2104) and the test was performed according to the official method. Twenty tablets were selected randomly and weighed individually to check weight variation.

Content Uniformity

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in acetone, the drug content was determined by measuring the absorbance at 230 nm after suitable dilution using UV-visible double beam spectrophotometer (Shimadzu, UV-1800). The drug content was estimated from the standard curve of Amoxicillin.

Swelling Behavior of Formulations

The swelling index of all the tablet formulations was studied. The extent of swelling was measured in terms of percent weight gain by the tablet. To study the swelling behavior, one tablet from each formulation was kept in a Petri dish containing 20 ml phosphate buffer pH 7.4.
and 1.2. At the end of 1 h, the tablet was withdrawn, kept on tissue paper and weighed. The process was continued for every 1 h.

The % weight gain by the tablet was calculated by formula:

\[ S.I. = \left( \frac{M_t - M_0}{M_0} \right) \times 100 \]

Where,
- S.I. = Swelling index
- \( M_t \) = Weight of tablet at the time (t)
- \( M_0 \) = Weight of tablet at time 0.

**In-vitro drug release study**

The in-vitro drug release test was carried out at a constant temperature of 37±0.05 °C using a rotating basket apparatus method rotated at 100 rpm. About 300 ml of phosphate buffer solution (pH 7.4 and 1.2) was used as the dissolution media to simulate gastrointestinal tract (GIT) conditions. 2 ml aliquot was used each time for analyzing the Amoxicillin content at a fixed time interval (1 h). The amount of Amoxicillin released was analyzed using a UV spectrophotometer at the \( \lambda \)- max 230 nm and the percent drug release was calculated using calibration curve of Amoxicillin.

**RESULTS AND DISCUSSION**

Binders are agents used to impart cohesive qualities to the powdered material during the production of tablets. Here gum from *Calotropis gigantea* was used as natural polymers. Here tablets were prepared and verified by several pre-compression and post-compression methods.

**Evaluation of formulation variables:**

**Pre-compression parameters**

The prepared formulations were evaluated for pre-compression parameters and their results were given in Table 2. The powder blend of gum from *Calotropis gigantea* was evaluated for various parameters like bulk density, tapped density, Carr’s index and Hausner’s index, angle of repose. Bulk density and tapped density are used to identify, the interparticulate interaction that
influence the bulking properties of powder and also the interactions that interfere with powder flow. It is therefore possible to gain information about the relative importance of these interactions in a given powder by comparing the bulk and tapped densities, and such a comparison can be used to index the ability of the powder to flow. The result of bulk density and tapped density ranges from 0.8 to 0.11 g/cm³ and 0.10 to 0.13 g/cm³ respectively. The Carr’s index and Hausner’s ratio can be used as an index for the flowability of a powder because the densification occurring during tapped density measurement is influenced by the same interparticulate interactions which are affecting the flow of powders\textsuperscript{18}. The values of compressibility indices, including Carr’s index and Hausner’s ratio ranged from 8.33 % to 30.76 % and 1.09 to 1.44 respectively. Angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to interparticulate friction or resistance to movement between particles. The value of angle of repose of all formulations ranges between 23.19 ° to 35.75 ° which shows very good powder flow property.

Table 2: Pre-compression properties of granules

<table>
<thead>
<tr>
<th>Properties</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
</tr>
<tr>
<td>Bulk density (g/cm³)</td>
<td>0.08</td>
</tr>
<tr>
<td>Tapped density (g/cm³)</td>
<td>0.10</td>
</tr>
<tr>
<td>Carr’s index (%)</td>
<td>20</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.25</td>
</tr>
<tr>
<td>Angle of repose (degree)</td>
<td>34.65</td>
</tr>
</tbody>
</table>

Among all formulations, T4 batch showed excellent flow property with high compressibility index or Carr’s index (8.33 %), Hausner’s index (1.09) and significant angle of repose (23.19 °).

Post-compression parameters

The prepared tablets were evaluated for post-compression parameters such as weight variation, thickness, swelling behavior, content uniformity and in-vitro drug release profile characteristics. Results of the evaluation tests of weight variation, tablet thickness, content uniformity are shown in Table 3. All the formulations of tablets made with gum of Calotropis gigantea showed very
Slight weight variation and it ranged between 0.09 mg to 0.11 mg. Thickness values, which were obtained within limits ranges from 1.21 mm to 1.86 mm and content uniformity obtained at the absorbance rate of 230 nm was between 0.155 - 0.648.

Table 3: Post-compression parameters of tablets with mucilage from *Calotropis gigantea*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight variation (mg)</td>
<td>0.09</td>
<td>0.10</td>
<td>0.11</td>
<td>0.10</td>
<td>0.11</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>1.25</td>
<td>1.86</td>
<td>1.21</td>
<td>1.65</td>
<td>1.63</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>0.155</td>
<td>0.316</td>
<td>0.359</td>
<td>0.452</td>
<td>0.648</td>
</tr>
</tbody>
</table>

**Swelling behavior**

The swelling index or swelling behavior of all the tablet formulations was studied. The extent of swelling was measured in terms of percent weight gain by the tablet. The swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration up to certain limit. Swelling capacity of a substance reflects the increase in volume of that substance following water absorption. In addition, the higher swelling capacity values that were observed with gum of *Calotropis gigantea* could possibly be due to the higher powder porosity of the gum of *Calotropis gigantea* extract. Figure 2 shows the formulation of T5 exhibits more swelling index than other tablet formulation.

![Swelling behavior of tablet prepared using gum from *Calotropis gigantea* as binder](image)

**Fig. 2: Swelling behavior of tablet prepared using gum from *Calotropis gigantea* as binder**
In-vitro drug release profile:

In-vitro release profile of the drug from tablets was major governing criteria to decide whether the natural binder or the commercially used binder is good binding agent. The release profile for the drug was taken for a period of five hours which can best be depicted by graph between percentage drug release and time. Phosphate buffer solution (pH 7.4 and 1.2) was used as the dissolution media or drug release study to simulate gastrointestinal tract (GIT) conditions.

The in-vitro dissolution profiles of the prepared formulations with gum of Calotropis gigantea were shown in Figure 3 (pH 7.4) and 4 (pH 1.2). T5 formulation showed maximum release of 96.26 % at pH 7.4, and 84.77 % at pH 1.2. The swelling property increased the drug release profile to a small extent due to change in swelling at the tablet surface. The drug was released in the dissolution media slowly with the time; this sustained effect caused prolonged treatment by the drug.

![Graph showing drug release profile](image)

**Fig. 3: In-vitro drug release profile of different formulations prepared using gum from Calotropis gigantea at pH 7.4**
Fig. 4: *In-vitro* drug release profile of different formulations prepared using gum from *Calotropis gigantea* at pH 1.2

The drug release was inversely proportional to the concentration of the gum. These tablets have shown reduced diffusion of drug which was due to the formation of viscous gel in the form of thick sticky film on the surface of tablets. This may be the reason for the reduced dissolution of the drug with increased gum concentration.

**CONCLUSION**

The present study elucidated the physical, mechanical and functional properties of tablets formulated with *Calotropis gigantea* gum and Amoxicillin as drug. All characterized parameters of plant gum were found to be within the satisfactory limit and it has excellent binding capacity. *In-vitro* drug release profile followed the sustained release pattern. The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased. It was also found that gum of *Calotropis gigantea* is pH sensitive, so it can be used to develop drugs for efficient gastrointestinal delivery system.

**REFERENCES**