FABRICATION AND RELEASE KINETICS OF PIPERAZINE CITRATE TABLETS USING NATURAL GUM

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ABSTRACT

Objective: The objective of the present study was to formulate the piperazine citrate tablets using natural aloe vera gum as a binding agent and evaluate the tablets.

Methods: The extracted aloe vera gum was used for the preparation of piperazine citrate tablets, and the binding characteristics are compared with an equivalent amount of acacia and sodium carboxymethyl cellulose (NaCMC) in different formulations of piperazine citrate tablets. Three batches of piperazine citrate tablets were prepared using acacia (F1), NaCMC (F2), and aloe vera gum (F3) as binding agents. The assessment parameters that are used to evaluate the binding property were the hardness, friability, disintegration time, in vitro dissolution rate, and amount release study. The drug release kinetics of different formulations was determined.

Results: The granules were evaluated by determining the angle of repose $(25.39\pm0.13$ to $26.23^\circ\pm0.11^\circ)$, bulk density $(0.567\pm0.004$ to $0.596\pm0.006$ g/cm$^3$), tapped density $(0.672\pm0.006$ to $0.717\pm0.007$ g/cm$^3$), Hausner ratio $(1.185\pm0.03$ to $1.211\pm0.016$), and Carr’s index $(15.62\pm0.02$ to $17.48\pm0.099)$, which shows a satisfactory flow ability. The tablets were subjected to hardness $(3\pm0.63$ to $4\pm0.82$ kg/cm$^2$), friability $(0.57\pm0.01$ to $0.75\pm0.01)$ w/w, disintegration time $(14.78\pm0.23$ to $20.02\pm0.11$ min), and in vitro release studies. The drug release kinetics of different formulations was determined.

Conclusion: As per the results, aloe vera gum has good binding properties and can be preferred over other binders and might be found to be a suitable binder in fast dissolving tablets formulation.

Keyword: Aloe vera gum, Piperazine citrate, Binders.

INTRODUCTION

In recent years, there has been a lot of development in natural products which are used in different pharmaceutical formulations due to their diverse pharmaceutical applications, such as diluents, binders, disintegrates in tablet formulation, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels, and bases in suppositories. Natural products also have advantages over chemical products, and their efficacy, bioavailability, and applicability have been proven. Hence, natural products have been studied for their pharmaceutical application in different dosage forms [1].

Pharmaceutical excipients are inert substances other than active pharmaceutical ingredients that are included in pharmaceutical dosage forms, not for therapeutic action but to enhance stability, safety, and efficacy or for bioavailability or patient acceptability. The frequently used excipients in tablet formulation are – diluents, binding agents, disintegrants, lubricants, and glidants. Binding agents are the excipients that hold the ingredients of a formulation together by ensuring that tablets, powders, granules, and other can be formulated with the required mechanical strength and also give volume to low active doses tablets.

Natural gums are considered to be pathological products formed following injury to the plant or due to unfavorable conditions, such as drought by a breakdown of cell walls. Nowadays, these gums are widely used in tablet formulation due to their non-toxicity, less side effect, and they are cheap and easily available in the market.

Aloe vera is a dried leaf juice of *Aloe barbadensis* belonging to the family Liliaceae [4]. It has many medicinal properties [4] – burns and wound healing properties, purgative, and anti-inflammatory. It is also used in the treatment of pain, itching, and also to slow down ulceration. Aloe gel is used in skin cosmetics as a protective due to its anti-wrinkle property. It is also used as a binding agent [3] in various types of tablet formulations.

Therefore, the objective of the study was to determine the binding characteristics of aloe vera gum so that it can be used in tablet formulation since it is non-toxic, bio-degradable, and easily available.

METHODS

Chemicals and reagents

Piperazine citrate (Yarrow Chemie Pvt. Ltd.), acacia (Loba Chemie), sodium carboxymethyl cellulose (NaCMC) (Loba Chemie), magnesium stearate (Loba Chemie), microcrystalline cellulose (Merck Ltd.), lactose (Merck Ltd.), and talc (Loba Chemie) were used.

Method of extraction of aloe vera gum [5]

After recognizing a mature and healthy aloe vera plant, fresh leaves were collected 20 cm long. During the collection of leaves, a cut is given to the leaves near their bases. After cutting, washed out with tap water and allowed to dry. Then, a single incision is given for drawing out all the mucilage and then homogenized. Then, ethanol is added to precipitate the aloe gum. The aloe gum is then separated and used as a binder in the piperazine citrate tablet formulation.

Preparation of piperazine citrate tablets [6-8]

Three batches of piperazine citrate tablets, each tablet containing 500 mg of piperazine citrate, were formulated using three binders, namely, acacia,
quantities of powder were triturated together in a mortar pestle to form a homogeneous mixture. A weighed amount of each binder was mixed with 5 ml water to form a solution and added to the powder mix to form a damp coherent mass. The damp mass was sieved in granules using a 1.7 mm sieve. Moist granules were dried at 45°–50° in a hot air oven for 30 min. The dried granules were passed through a 1.0 mm sieve to obtain uniform-sized granules. Then, the different batches of the granules were then mixed with a calculated amount of lubricants. Then, the granules were compressed into tablets under constant pressure with a single punch tableting machine after adjusting the punch size and volume to obtain the required tablet size and weight (Table 1).

**Evaluation of granules flow characteristics**

**Bulk density**

The bulk density of a drug is defined as the ratio of the mass of the powder to bulk volume. Bulk volume is the volume occupied by the determined mass of powder when added into a measuring cylinder. Bulk density is obtained by transferring a known amount of powder to a measuring cylinder. The bulk density is given in g/ml.
Table 2: Precompression results of granules

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Properties</th>
<th>F1 (acacia)</th>
<th>F2 (NaCMC)</th>
<th>F3 (aloe vera)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bulk density (g/mL)</td>
<td>0.59±0.006</td>
<td>0.56±0.004</td>
<td>0.57±0.002</td>
</tr>
<tr>
<td>2</td>
<td>Tapped density (g/mL)</td>
<td>0.71±0.007</td>
<td>0.67±0.006</td>
<td>0.69±0.003</td>
</tr>
<tr>
<td>3</td>
<td>Carr's index (%)</td>
<td>16.87±0.11</td>
<td>15.62±0.21</td>
<td>17.48±0.009</td>
</tr>
<tr>
<td>4</td>
<td>Hausner ratio</td>
<td>1.20±0.017</td>
<td>1.18±0.030</td>
<td>1.21±0.016</td>
</tr>
<tr>
<td>5</td>
<td>Angle of repose (°)</td>
<td>25.39±0.13</td>
<td>25.97±0.17</td>
<td>26.23±0.11</td>
</tr>
</tbody>
</table>

*All values are expressed in means±(txSEM), n=3. SEM: Standard error of mean, NaCMC: Sodium carboxymethyl cellulose

Tapped density
Tapped density is the ratio of the mass of powder to the tapped volume. Tapped volume is the volume occupied by a certain mass of the powder after a standard number of tapping. Tapped density is obtained by mechanically tapping a measuring cylinder containing the sample until a little further volume change is observed.

\[
\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{tapped volume}}
\]

Compressibility index or Carr's index and Hausner ratio
The compressibility index is a measure of the volume changed in a powder sample after applying stress. The Hausner ratio measures the friction condition in a moving powder mass (interparticle friction). In a free-flowing powder, interparticulate interactions are less, and bulk and tapped densities will be closer in value, and for poorly flowing powder, there are greater interparticulate interactions, and a greater difference is observed between the bulk and tapped density.

\[
\text{Compressibility Index} = \left( \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \right) \times 100
\]

\[
\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

Angle of repose
The angle of repose is defined as the maximum angle possible between the free-standing surface of a powder heap and the horizontal plane, a simple practical technique for measuring resistance to particle movement.

To determine the angle of repose, a clean and dry funnel was taken and attached to a burette stand. A white paper was placed below the tip of the funnel. The sample was then poured into the funnel. The height of the heap was measured, and a circle was drawn around the tip of the powder, and the radius of the circle was measured.

\[
\text{Angle of repose (θ)} = \tan^{-1} \left( \frac{h}{r} \right)
\]

where, \(h\) = height of the heap
\(r\) = radius of the heap

Evaluation tests for piperazine citrate tablets

1. Hardness test: Monsanto hardness tester was used to find the hardness of the tablets
2. Friability test: Friability of the tablets was determined by Roche friabilator
3. Disintegration time: The U.S.P device is used to test disintegration time
4. In vitro release study: The rate of drug release from the dosage form was determined using U.S.P Dissolution Apparatus 2. 900 ml of distilled water was placed in the vessel of the apparatus. The apparatus was assembled, and the medium was equilibrated to 37±1°C. The tablet was placed in the vessel. Immediately, the apparatus was operated at 50 rpm. Within 5-min intervals, 5 ml samples were withdrawn with the help of a pipette. For each, 5 ml of fresh distilled water was replaced. Then, adequate dilutions were made, and the absorbance of the samples was determined at 344 nm using an array spectrophotometer
5. Drug release kinetics: The mathematical representation of drug release from the dosage form. The data obtained from the in vitro release study were further calculated using the following equations:

- **Zero-order release kinetics:**
  \[ M = k \cdot t \]
  where, \(M\) = the amount of drug release at time \(t\)
  \(K_0\) = zero-order release constant

- **First-order release kinetics:**
  \[ \log M = \log M_0 - \frac{kt}{2.303} \]
where, \(M\) = the amount of drug release at time \(t\) 
\(M_0\) = the initial concentration of the drug 
\(K\) = First-order release constant 
\(T\) = time

- Hixson-Crowell release model
  \[M^{1/2} = \frac{M_0^{1/2}}{K} \cdot t\]

- Higuchi model:
  \[M = R^{1/2}\]

- Korsmeyer-Peppas Model:
  \[\frac{M}{M_0} = k \cdot t^n\]

where, \(M/M_0\) is the fraction of drug release at time \(t\) 
\(n\) = the release exponent, indicates the mechanism of drug transport through a polymer. 
\(K\) is the rate constant.

RESULTS AND DISCUSSION

Three batches of piperazine citrate tablets were prepared by wet granulation method to compare the properties of the tablets formulated using aloe vera gum with the tablets formulated using acacia and NaCMC.

The bulk density of the granules of different formulations (F1–F3) was found within 0.567–0.596 g/ml, tapped density range between 0.672 and 0.717 g/ml, Carr’s index in between 15.62% and 17.48%, Hausner ratio within 1.185–1.211, and the angle of repose within 25.39–26.23, which are shown in Table 2. All the data were in triplicate and expressed as mean ± standard error of the mean. The above pre-compression results show that the prepared granules of all three batches have a good flow property.

The post-compression results show that the hardness ranged from 3 to 4 kg/cm², friability between 1.029% and 1.321%, and disintegration time between 14.78 and 20.02 min, which are shown in Table 3. These also give satisfactory results.

The drug release obtained from different formulations (F1–F3) of piperazine citrate is mentioned in Fig. 1, and the percentage of drug release after 60 min for F1–F3 was 77.5%, 89.7%, and 97.8%, respectively.

In general, the rate of dissolution and disintegration of any tablet is depending on the concentration of the binding agent in the tablet formulation. If the binder concentration increased, the amount of drug release decreased. Because an increase in binder concentration results in more strength between the particle which gives more hardness to the tablet, the rate of dissolution and disintegration decreased.

Hence, from the above release study, we can summarize that the % drug release is – aloe vera-NaCMC-acacia. Among all the binders, aloe vera has a faster onset of drug release. Hence, this shows that aloe vera gum is a better binder than acacia and NaCMC in fast-released tablets [2].

The drug release data of all formulations (F1–F3) were fitted to the different drug release kinetics models (zero-order kinetics, first-order kinetics, Hixson-Crowell release model, Higuchi model, and Korsmeyer-Peppas release model), and the correlation coefficient value \((R^2)\) was determined [11]. The model that best fitted was evaluated by the coefficient value \((R^2)\). Coefficient values \((R^2)\) for all formulations (F1–F3) in various models are mentioned in Table 4. After comparing the average of the \(R^2\) values of the entire formulations, the Korsmeyer-Peppas model showed the best-fitting of \(R^2\) value that is 0.9948. The above release data as per different kinetic models indicate that drug release from piperazine citrate tablet is best fitted toward the Korsmeyer-Peppas model, indicating that two or more mechanisms for drug release are involved (Figs 2–6).

CONCLUSION

Piperazine citrate tablets were formulated using different binding agents such as acacia, NaCMC, and aloe vera. Then, the evaluations of the prepared tablets were done by various physicochemical parameters and percentage drug release studies. The tablets formulated using aloe vera gum as a binding agent have sufficient hardness, low friability, desirable disintegration time, and better percentage of drug release compared to other tablets formulated using acacia and NaCMC. Hence, as per the research, aloe vera gum can be preferred over other binders and might be found to be a suitable binder in fast dissolving tablets formulation. This study further assures us the chance and possibility of further development and optimization of the drug taken as a candidate for further investigation.

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AUTHORS’ CONTRIBUTIONS

Research work and preparation of the manuscript were done by Sudipta Das and Pinki Biswas. Partial help with manuscript preparation was done by Chandrima Dutta and Diptendu Sekhar Biswas.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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