Modified *Terminalia randii* gum as a binder in metronidazole tablet formulation


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**ABSTRACT:** The aim of this work is to acetylate *Terminalia randii* gum and evaluate its effectiveness as a binder in metronidazole tablet formulations. The gum was extracted using standard methods. The extracted gum was acetylated and used at varying concentrations (1%-5%w/w) as a binder in metronidazole tablets and compared with a standard binder, polyvinylpyrrolidone (PVP) using wet granulation. The granule properties were assessed using bulk and tapped densities, Carr’s index, Hausner’s ratio, angle of repose and flow rate. The mechanical properties of tablets were assessed using friability, crushing strength and crushing strength friability ratio while the release properties were evaluated using disintegration time and dissolution time for 50% and 80% of the drug (t50 and t80 respectively). Statistical analysis using ANOVA was carried out with computer software graph pad prism (Graph pad software INC, San Diego, USA). At 95% confidence intervals, *p* value less than or equal to 0.05 were considered significant.

There was no significant difference (P>0.05) in the granule properties. Formulations prepared with acetylated gum (ATR) had significantly lower (*p*<0.05) mechanical properties which were still within Pharmacopeia limits. There was no significance difference (*p*>0.05) in the release properties of the formulations.

ATR could be substituted for PVP as a binder in pharmaceutical formulations.

**KEYWORDS**- Acetylation, Metronidazole, Release properties, Tablet, *Terminalia randii* gum

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**I. INTRODUCTION**

Gums are natural polysaccharides consisting of multiple sugar units linked together to form large molecule. Gums may be classified as natural, semi synthetic or modified and synthetic gums [1]. These natural gums have found great use in the pharmaceutical industries due to their non-toxicity, ready availability and they are biodegradable. They have been explored as emulsifier, suspending agent, adhesives and binding agents [2], [3]. Most natural gums are safe for oral use in the food and pharmaceutical industries [4]. However, the use of these gums could be associated with certain problems such as pH dependent solubility, uncontrollable swelling, change in viscosity on storage and possibly microbial contamination [4]. Chemical modifications of these gums can be carried out to minimize these problems.

Carboxymethylation of gums has been shown to increase the hydrophilicity thus, making them more soluble in aqueous systems [5]. Grafting of acrylic acid on gums has been shown to modify the swelling characteristics and drug release properties of gums [6], [7].

In this present study, *Terminalia randii* gum has been modified by acetylation and its binding properties in metronidazole tablet was compared with a standard binder polyvinyl pyrrolidone.

**II. MATERIALS AND METHODS**

**Materials**

The materials used were metronidazole (gift from Bond chemicals, Awe, Nigeria), Lactose BP (Ind-Swift Labs Ltd, Parwanoo, India), Corn starch powder BP (BDH, England). Magnesium Stearate (LobaChemie PVT Ltd, Mumbai India), Polyvinylpyrrolidone USP K29/32 (molecular weight: 58,000) (ISP Technologies, IncWayne, USA). *Terminalia randii* gum obtained from Olabisi Onabanjo University, Nigeria. All other materials were analytical grade.

2.1 Gum Extraction

*Terminalia randii* gum was extracted using the method described by Bamiro et al. [8]. The gum was hydrated in chloroform water double strength for 5 days with intermittent stirring, and extraneous materials were removed by straining through a calico cloth. The gum was then precipitated from solution using absolute...
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ethanol. The precipitated gum was filtered washed with diethyl ether and then dried in a hot air oven at 40 °C for 24 hours. The purified gum was then pulverized and packed in an airtight container.

2.2 Acetylation of Terminalia randii gum
Extracted gum (10g) was dispersed in 100ml of distilled water with constant stirring for 30mins. The slurry was adjusted to pH 8.0 with NaOH. 1.2g of acetic anhydride was added to the slurry and the reaction was allowed to proceed for another 5 minutes. The pH of the slurry was adjusted to 4.5 with 0.5M HCL and then filtered through Whatman filter 1 paper. The residue was thoroughly washed with distilled water to completely remove some acid that may be present in the product and finally air dried at room temperature. The acetylated gum was characterised using Fourier Transform Infrared Spectroscopy (FTIR).

2.3 FTIR of acetylated and natural Terminalia gum
The FTIR spectrum of the gum was recorded with a Perkin Elmer RXI spectrophotometer (Connecticut, USA). The dry gum powder was mixed with potassium bromide (KBr) and pressed into pellets. The spectrum was obtained by scanning between 4000 and 500 cm⁻¹.

2.4 Tablet Preparation
100g batch sizes were prepared containing 60 % w/w metronidazole (drug), 30 % w/w lactose (diluent) and 10% w/w corn starch (disintegrant). Metronidazole granules were prepared using wet granulation method. Acetylated Terminalia gum (ATR) was used as a binder at different concentrations (1-5 % w/w), while PVP was used as a standard. The granule properties of the granules were evaluated using USP 2007 methods. The granules were compressed on a Carvier hydraulic machine (Model C, Carver Inc., Menomonee Falls, WI) with predetermined load for 30 seconds. The tablets were stored in air tight containers for 24 hours to allow for elastic recovery.

2.5 Tablet properties
Friability was determined with a DBK friabilator test apparatus (Mumbai, India) set to rotate at 25 rpm for 4 minutes. Determinations were done in triplicate.

Crushing strength was determined with a DBK Instrument Tablet Hardness Tester MODEL EH 01. Five tablets were taken from each batch and the results were given as mean ±SD.

Disintegration test was carried out in distilled water at a temperature of 37±0.5°C in a DBK Tablet Disintegration test apparatus (Mumbai, India). Determinations were done in quadruplicates.

The in vitro dissolution test was carried out in 900ml of 0.1M HCL at a constant temperature of 37 ±0.05°C using a rotating basket apparatus method rotated at 100 rpm. 5 mL samples were withdrawn at different time intervals and replaced with fresh samples. The amount of metronidazole released in each sample was determined using a UV spectrophotometer (Cecil CT 2041200 series) at a wavelength of 277nm. Determinations were done in triplicates.

Statistical analysis was carried out using ANOVA (analysis of variance) with computer software graph pad prism 4 (Graph pad software Inc. San Diego, USA). At 95% confidence interval, p ≤ 0.05 were considered significant.

III. RESULTS AND DISCUSSION
The FTIR of Terminalia randii gum and acetylated Terminalia randii gum are presented in Figs. 1 and 2. The peak at 1749 cm⁻¹ is a C=O stretching which indicates esterification which is brought about by the presence of an acetyl group.

The granule properties are presented in Table 1. The mean granule size was observed to increase with increase in binder concentration. This could be attributed to strengthening of bonds between particles as there would be more binder per bond as the concentration is increased [9], [10]. The bulk densities generally decreased with increase in binder concentration. The flowability of a material is an important parameter in the production of tablets. The flow properties were determined by evaluating the angle of repose, Hausner’s ratio, Carr’s index and the flow rate. Angle of repose less than 25° indicates very good flow, 25° to less than 50° indicates good flow while greater than 50° is poor flow. Granules produced by the two binders exhibited good flow property. The Carr’s index is a measure of the flow-ability and compressibility of a material. All the granule formulations had Carr’s index of less than 15° which indicates good flow properties. Hausner’s ratio less than 1.2 indicates good flow. All the formulations had less than 1.2, indicating good flow [11].
The tablet properties are presented in Table 2. The mechanical properties of a pharmaceutical tablet are quantified by crushing strength and friability. These are ability of the tablets to withstand the rigors of transportation, dispensing and handling [12]. The friability was observed to decrease as concentration of binder increased, while crushing strength increased with increase in concentration of binder. This could be due to the heat produced during the compression of the tablets which caused melting of binding agent, which on cooling solidify to form strong solid bonds between the particles. All the formulations passed the friability test by showing friability values of less than 1% w/w [13]. The mechanical properties of formulations containing ATR were significantly lower (p<0.05) than those of formulations containing PVP. Crushing strength-friability ratio (CSFR) has also been used to measure mechanical strength of tablets [14]. High CSFR values indicates stronger tablet. Formulations containing ATR has significantly lower (p<0.05) CSFR.

Figure 1: FTIR of Acetylated Terminalia randii gum

Figure 2: FTIR of Terminalia randii gum
Modified terminalia randii gum as a binder in metronidazole tablet formulation

Table 1: Micromeritic Properties of Granules

<table>
<thead>
<tr>
<th>Binder</th>
<th>Conc of binder (% w/w)</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Flow rate (g/sec)</th>
<th>Angle of repose (°)</th>
<th>Carr’s index (O/O)</th>
<th>Hausner ratio</th>
<th>Mean granule size μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.00</td>
<td>0.48±±0.00</td>
<td>0.52±±0.01</td>
<td>3.95±±0.44</td>
<td>35.24±±0.21</td>
<td>7.62±±1.77</td>
<td>1.07±±0.01</td>
<td>445</td>
</tr>
<tr>
<td>PVP</td>
<td>1.00</td>
<td>0.41±±0.20</td>
<td>0.45±±0.00</td>
<td>4.74±±0.52</td>
<td>36.74±±0.56</td>
<td>7.41±±1.28</td>
<td>1.08±±0.01</td>
<td>485</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
<td>0.39±±0.18</td>
<td>0.43±±0.00</td>
<td>5.90±±0.56</td>
<td>37.55±±0.21</td>
<td>7.53±±1.33</td>
<td>1.08±±0.01</td>
<td>515</td>
</tr>
<tr>
<td></td>
<td>3.00</td>
<td>0.41±±0.19</td>
<td>0.43±±0.00</td>
<td>6.63±±0.57</td>
<td>36.62±±0.21</td>
<td>3.10±±1.33</td>
<td>1.03±±0.01</td>
<td>585</td>
</tr>
<tr>
<td></td>
<td>5.00</td>
<td>0.41±±0.18</td>
<td>0.45±±0.00</td>
<td>7.88±±0.60</td>
<td>36.00±±0.21</td>
<td>9.54±±1.13</td>
<td>1.10±±0.01</td>
<td>710</td>
</tr>
<tr>
<td>ATR</td>
<td>1.00</td>
<td>0.42±±0.00</td>
<td>0.43±±0.00</td>
<td>5.20±±0.41</td>
<td>48.86±±0.56</td>
<td>1.55±±1.34</td>
<td>1.01±±0.01</td>
<td>755</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
<td>0.41±±0.00</td>
<td>0.43±±0.00</td>
<td>5.73±±0.31</td>
<td>48.57±±0.52</td>
<td>4.65±±0.00</td>
<td>1.05±±0.00</td>
<td>765</td>
</tr>
<tr>
<td></td>
<td>3.00</td>
<td>0.40±±0.01</td>
<td>0.44±±0.01</td>
<td>7.22±±0.29</td>
<td>49.63±±0.14</td>
<td>9.09±±0.20</td>
<td>1.09±±0.00</td>
<td>770</td>
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<tr>
<td></td>
<td>5.00</td>
<td>0.40±±0.00</td>
<td>0.41±±0.01</td>
<td>9.78±±0.47</td>
<td>49.22±±0.42</td>
<td>2.32±±4.02</td>
<td>1.02±±0.04</td>
<td>860</td>
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</table>

The release properties of the tablets were assessed using disintegration and dissolution times (t50 and t80 i.e. time required for 50% and 80% of the drug to be released respectively). The disintegration time of tablets is the rate limiting step in dissolution and consequently absorption of the active ingredient. The British Pharmacopoeia [13], states that uncoated tablets must disintegrate within 15 minutes. All the formulations disintegrated in less than 15 minutes. The result of the release properties are presented in Table 2. The disintegration time was observed to increase with increase in concentration of binder. Formulations containing ATR at 5 % w/w had significantly lower (p<0.05) disintegration time when compared with formulations containing PVP. This could be due to increase in interlocking bonds formed which led to reduction in the amount of water penetrating into the tablets. The dissolution profile of metronidazole formulation containing 5 % w/w binder is presented in Fig. 3. All the formulations released 80% of their drug content within 30 minutes as specified in the British Pharmacopoeia [13]. T50 and T80 increased with increase in binder concentration. There was no significant difference (p>0.05) in the dissolution time.

Table 2: Tablet Properties

<table>
<thead>
<tr>
<th>Binder</th>
<th>Concentration (% w/w)</th>
<th>Friability (%)</th>
<th>Crushing strength (N)</th>
<th>CSFR</th>
<th>Disintegration time (Min)</th>
<th>T50 (min)</th>
<th>T80 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVP</td>
<td>0.00</td>
<td>0.36±±0.01</td>
<td>18.58±±2.97</td>
<td>51.61</td>
<td>0.03±±0.00</td>
<td>2.35</td>
<td>4.45</td>
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<td></td>
<td>1.00</td>
<td>0.53±±0.03</td>
<td>27.46±±3.80</td>
<td>51.81</td>
<td>0.07±±0.01</td>
<td>2.35</td>
<td>4.50</td>
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<tr>
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<td>2.00</td>
<td>0.48±±0.01</td>
<td>59.54±±3.45</td>
<td>124.04</td>
<td>0.14±±0.01</td>
<td>2.52</td>
<td>4.75</td>
</tr>
<tr>
<td></td>
<td>3.00</td>
<td>0.44±±0.01</td>
<td>96.68±±3.88</td>
<td>219.72</td>
<td>0.38±±0.06</td>
<td>2.75</td>
<td>5.25</td>
</tr>
<tr>
<td></td>
<td>5.00</td>
<td>0.45±±0.04</td>
<td>104.88±±3.57</td>
<td>233.07</td>
<td>0.79±±0.02</td>
<td>2.80</td>
<td>5.75</td>
</tr>
<tr>
<td>ATR</td>
<td>1.00</td>
<td>0.69±±0.02</td>
<td>22.56±±2.86</td>
<td>32.70</td>
<td>0.07±±0.02</td>
<td>2.25</td>
<td>5.25</td>
</tr>
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<td>2.00</td>
<td>0.40±±0.01</td>
<td>26.58±±2.78</td>
<td>66.45</td>
<td>0.22±±0.01</td>
<td>1.85</td>
<td>3.75</td>
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<tr>
<td></td>
<td>3.00</td>
<td>0.30±±0.02</td>
<td>39.56±±3.00</td>
<td>131.87</td>
<td>0.31±±0.00</td>
<td>2.35</td>
<td>5.35</td>
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<tr>
<td></td>
<td>5.00</td>
<td>0.36±±0.02</td>
<td>31.72±±3.45</td>
<td>88.11</td>
<td>0.38±±0.05</td>
<td>2.55</td>
<td>5.75</td>
</tr>
</tbody>
</table>
**CONCLUSION**

The data obtained from this study indicates that acetylated *Terminalia randii* gum could be substituted for polyvinyl pyrrolidone as a binder in tablet formulations, especially where a tablet that is not “too strong” but with similar release property is required.

**REFERENCES**


