Formulation and Development of Medicated Chewing Gum Containing Ondansetron and Domperidone

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ABSTRACT

This study aimed to determine the feasibility of combining ondansetron and domperidone into a single medicated gum. Molded Chewing Gum (MCG) was developed via direct compression. Our medicated chewing gum was designed with diabetics in mind, and Stevia was selected for the research because it does not increase blood glucose levels. Direct compression was used in the development of medicated gum. Each formulation's permissible flow characteristics and pre-compression parameters, including bulk density, tapered density, Carr's compressibility index, and Hausner ratio, were shown. After compression, it was determined that all of the parameters were within acceptable limits, including changes in weight, thickness, appearance, and in vitro drug release. There is no indication of drug-excipient interactions based on physical testing or TLC analysis. Two plasticizers only when comparing glycerol with coconut oil, the latter proved to be the superior plasticizer. Formulation F6 was chosen as the best option since all of the attributes fall within the expected range. The results of the F6 formulation were analyzed for their thickness, weight fluctuation, appearance, and in vitro drug release. Coconut oil shown to be the superior plasticizer for making MCG after testing and evaluation. Probably because the concentration is optimized for releasing the drug from the formulation, the fact that F6 includes 24 mg of coconut oil makes it a more effective formulation.

Keywords: Chewing Gum, Ondansetron, Domperidone, Direct Compression, Antiemetic.

INTRODUCTION

Chewing gum with active pharmaceutical ingredients (APIs) added to it is a novel method of administering medication that allows the medicine to be absorbed systemically through the oral mucosa or used topically to treat oral conditions.[1] Advantages of Medicated chewing gums:

Because the included medicinal chemicals are shielded from oxygen and light and the water product stability is good, chewing gum can be utilized anytime, anywhere. Compatible with patients who have trouble swallowing, Outstanding for acute medicine, reduces dry mouth, avoids cavities and candidiasis, swift and quick start to activity, increased bioavailability, a tasty flavour, enhances the bioavailability of medicines by avoiding first-pass metabolism, able can be used.

The most frequent symptoms of the majority of pathophysiological disorders, including motion, cancer, pregnancy, and postoperative conditions, are nausea and vomiting. A sense of impending vomiting is referred to as nausea. Vomiting is the term used to describe the forceful ejection of stomach and proximal small intestine contents. Gum chewing also increases blood flow to the brain, which promotes mental clarity and increased alertness. When compared to conventional distribution methods, this formulation's resistance to moisture, oxygen, light, and high temperatures eliminates the need for more maintenance.[2]
Chewing gums use several different excipients in their creation, such as elastomers, elastomer solvents, bulking agents, softening agents, sweetening agents, flavoring agents, antioxidants, and glidants. The creation of medicated chewing gums can be done in a variety of ways, including the conventional/traditional, direct compression, and grinding processes.\[3\]

Domperidone and ondansetron are only weakly soluble in water. It effectively absorbs through the mouth cavity. Ondansetron and Domperidone chewing gum was created after research and analysis of the medicine and dosage form. Polyvinylpyrrolidine was used to determine the chewing gum's composition for Ondansetron and Domperidone. As a plasticizer, glycerol and coconut oil were employed to give the formulation chewability and a gummy texture.\[4\]

MATERIALS AND METHODS
Modern labs PvtLtd, Indore, offered a gift sample of ondansetron and dopamidole. Elastomers made of polyvinylpyrrolidone are synthetic. As a plasticizer, glycerol and coconut oil were utilised. Peppermint was employed as a flavouring agent, calcium carbonate served as filler, and stevia served as the sweetener.

Method
First The following ingredients are weighed individually and combined in increasing sequence in a mortar: polyvinylpyrrolidine, bees wax, stevia sugar, calcium carbonate, peppermint, glycerol, coconut oil, ascorbic acid, and medication. The required quantity of Polyvinylpyrrolidine was added after the components were well mixed in a mortar and pestle. The mixture was then well mixed and mashed in a pestle and mortar. The combination was blended and mashed to create the therapeutic chewing gum before being compacted with a rotary tablet press.\[5\]

Incompatibility study
For four weeks, the sample was physically observed visually once a week to look for any changes in the sample mixture.\[6\]

Discoloration
The discolouration research followed participants using a combination of ondansetron and domperidone for 4 weeks.

Table1: Formula of Medicated Chewing Gum

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Domperidone</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Polyvinylpyrrolidine</td>
<td>290</td>
<td>290</td>
<td>290</td>
<td>290</td>
<td>290</td>
<td>290</td>
</tr>
<tr>
<td>Glycerol</td>
<td>16</td>
<td>20</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Bees wax</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Stevia</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Peppermint</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>26</td>
<td>22</td>
<td>18</td>
<td>26</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Raspberry red</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Total (mg)</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Mobile phase preparation
For mobile phase, Methanol: Dichloromethan: Ammonia taken in the ratio of 80:20:0.5.\[7\]

Drug – Excipients interaction study
For four weeks, the sample was physically observed visually once a week to look for any changes in the sample mixture.
Discoloration

For discoloration study, drug was mixed with all the excipients and observed for any discoloration for 4 weeks.

Interaction

Using the Thin Layer Chromatography (TLC) technique, it was determined whether different excipients and drugs were compatible. Ondansetron (10 mg) and Domperidone (10 mg) were completely combined with excipient in a ratio of 1:5 and placed in tightly closed glass vials for the study. For four weeks, all the vials were maintained at 400°C. Before and after storage, the sample was examined physically and using TLC.[7]

Mobile phase preparation: For mobile phase, Methanol: Dichloromethan: Ammonia take in the ratio of 80:20:0.5

Fig. 2: Physical Compatibility of Ondansetron, Domperidone and Excipients

Evaluation of Prepared formulation

Bulk density

Using a bulk density instrument, the drug's bulk density was assessed. It was given by and expressed in gm/ml.

\[
Bulk\ Density(\rho_b) = \frac{\text{Mass of the powder (m)}}{\text{Volume of the bulk powder (Vb)}}
\]

Tapped density

It represents the ratio of the total mass of the powder to the volume obtained after tapping. The tapped volume was determined by tapping the powder to a predetermined volume. The value is expressed as a number of grams per milliliter.

\[
Tapped\ Density = \frac{\text{Mass of the powder (m)}}{\text{Tapped volume of the powder (Vt)}}
\]

Compressibility Index or car’s index

It is inextricably linked to particle size, cohesiveness, and relative flow rate. It is an easy, well-liked, and quick way of forecasting powder flow properties. The % compressibility of the bulk medication was calculated using the following formula based on the apparent bulk density and the tapped density.[8]

\[
\text{Car’s Index} = \frac{\text{Tapped density} – \text{Bulk density}}{\text{Tapped density}} \times 100
\]

Hausner’s ratio

Measures the inter-particle friction present in a moving powder mass.

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

Angle of repose

Angle of repose is the angle formed by a powder pile's slope and a horizontal surface.

\[
\tan \theta = \frac{h}{r}
\]

Where, h = height of pile, r = radius of the pile base.

Evaluation of Physicochemical Properties of MCG (Medicated Chewing Gum)

Thickness

Each batch of medicated chewing gums had a random sample's thickness tested in millimeters using a Screw gauge.

Uniformity of weight

The average weight of 20 different types of medicated gum was calculated by first weighing each gum individually using an electronic scale.

Color

It was possible to clearly compare the finished colors of the various types of medicated chewing gums.
Stickiness
Adhering of the mass to the hammered surface was observed when the produced medicated chewing gums were subjected to a Teflon hammer weight of 250 gram colloid for 10 minutes on a plain surface.\(^9\)

Uniformity of drug content
The equivalent of 10 mg of medicine was extracted from five medicated chewing gums and placed in a 100 mL conical flask with a stopper. For one hour at 100 rpm on a mechanical shaker, 40 mL of distilled water was used to extract the medicine. Using a UV spectrophotometer, absorbance at a specific wavelength was measured against a blank after heating on a water bath for 30 minutes with intermittent shaking, filtering into a 50 mL volumetric flask, and then diluting.

Method development of dissolution apparatus for studying the release of drug from Chewing Gums
The disintegration equipment needed just minor adjustments after the thorough literature analysis. The principal stand of the device doubles as both the bottom and upper chewing surfaces, and is constructed from a beaker with a 1000 mL capacity, two rods, and two plates that are welded together. Chewing gum was put on the bottom surface of the rod to guarantee maximal drug release from the formulation, and the top side of the rod is designed to travel in an upward and downward motion at a chewing frequency of 60 strokes per minute. After 30 minutes of watching the drug's release in a 6.8 pH phosphate buffer, the experiment ends.

In vitro drug release study
An adjusted dissolving equipment was used to dissolve the sample in 500 mL of phosphate buffer pH 6.8 in a 37 0.5 °C beaker. The gadget is loaded with produced chewing gums. 5 mL of the sample was taken away and replaced with fresh medium every 5 minutes for the first 5, 10, 15, 20, 25, and 30 minutes. Each experiment was repeated three times, and the average of the results was recorded. Samples were diluted at a certain wavelength, filtered using 0.25 M membrane filter paper, and then analyzed with a UV-Visible spectrophotometer to find out how concentrated the drugs were.\(^{10}\)

**Fig. 3: Modified in vitro dissolution apparatus**

Stability Studies
The ICH recommendations were followed in the stability investigations. For six months, the finished medicated gums were stored in a stability chamber at 25 degrees Celsius and 60% relative humidity (RH). After 6 months, samples were taken to examine their outward appearance and to determine the percentage of medication release.\(^9\)

RESULT AND DISCUSSION

Incompatibility study

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Description</th>
<th>Room Temperature in days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Ondansetron + Domperidone + PVP</td>
<td>White powder</td>
<td>NC</td>
</tr>
<tr>
<td>Ondansetron + Domperidone + Glycerol</td>
<td>White color</td>
<td>NC</td>
</tr>
</tbody>
</table>
Table 3: Physical Compatibility of Ondansetron, Domperidone and Excipients

<table>
<thead>
<tr>
<th>Drugs + Excipients</th>
<th>Room Temperature in days</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>15th</td>
</tr>
<tr>
<td>Ondansetron+ Domperidone+ Coconut oil</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>Ondansetron+ Domperidone+ Bees wax</td>
<td>0.74</td>
<td>0.73</td>
</tr>
<tr>
<td>Ondansetron+ Domperidone+ Stevia</td>
<td>0.76</td>
<td>0.77</td>
</tr>
<tr>
<td>Ondansetron+ Domperidone+ Peppermint oil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron+ Domperidone+ CaCO₃</td>
<td>0.74</td>
<td>0.73</td>
</tr>
<tr>
<td>Ondansetron+ Domperidone+ Raspberry red</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NC = Not Change

Table 4: Powder Blend Pre-compression Evaluation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk Density (g/ml)</th>
<th>Tapped Density (g/ml)</th>
<th>Haussner's Ratio</th>
<th>Carr's Index</th>
<th>Angle of Repose (θ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.582±0.12</td>
<td>0.623±0.061</td>
<td>1.07±0.06</td>
<td>6.58±0.032</td>
<td>28°85'±0.025</td>
</tr>
<tr>
<td>F2</td>
<td>0.591±0.24</td>
<td>0.631±0.043</td>
<td>1.06±0.13</td>
<td>6.33±0.014</td>
<td>29°93'±0.041</td>
</tr>
</tbody>
</table>

*NC = Not Change
Table 5: Post-Compression parameters of directly compressed chewing gum

<table>
<thead>
<tr>
<th>Batch</th>
<th>Thickness (mm)</th>
<th>Weight variation (mg)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.58±0.12</td>
<td>389.2±0.21</td>
<td>95.34±0.56</td>
</tr>
<tr>
<td>F2</td>
<td>3.60±0.25</td>
<td>393.5±0.44</td>
<td>93.51±0.32</td>
</tr>
<tr>
<td>F3</td>
<td>3.59±0.20</td>
<td>397.6±0.31</td>
<td>94.51±0.32</td>
</tr>
<tr>
<td>F4</td>
<td>3.50±0.10</td>
<td>390.4±0.64</td>
<td>95.52±0.12</td>
</tr>
<tr>
<td>F5</td>
<td>3.58±0.06</td>
<td>399.6±0.14</td>
<td>96.87±0.34</td>
</tr>
<tr>
<td>F6</td>
<td>3.59±0.15</td>
<td>399.2±0.34</td>
<td>94.54±0.71</td>
</tr>
</tbody>
</table>

F1, F2, F3, F4, F5, F6

The formulations from F1 to F6 were tested for weight variation and drug content using various gum base and plasticizer concentrations. The findings are shown in table 6. The values of weight variation are found to be 389–399 mg. The presence of drugs in the formulations was then assessed. Different formulations’ drug contents are within acceptable bounds. The high drug content demonstrated that the method and formulation chosen are appropriate for creating Ondansetron and Domperidone MCG formulations.

Fig. 4: In-vitro Release Profile of Ondansetron from various formulations

By means of a modified dissolution equipment, ondansetron and domperidone formulations made with glycerol and coconut oil as a plasticizer are released into the body in vitro. Figures 4 and 5 depict the cumulative medication release graph in
percentage terms. Because of the soft quality that glycerol lends to the formulation, the drug release rises as the concentration of glycerol and coconut oil increases. In each of these formulations, F6 demonstrated a 90 & 91% drug release within 30 minutes. This formulation was determined to be an optimised combination of ondansetron and domperidone utilising coconut oil as a plasticizer and manufactured using the direct compression method since the highest drug release was seen while employing it.

CONCLUSION

By using the direct compression technique, medicated chewing gum containing Ondansetron and Domperidone was successfully created. MCG is a desirable delivery form due to its potential for buccal distribution, quick commencement of action, and prospect for product-line extension. Just two plasticizers The composition includes glycerol and coconut oil, with coconut oil serving as the best plasticizer. Because all the characteristics are within a standard range, formulation F6 was determined to be the optimal formulation. Thickness, Weight variation, appearance, and in vitro drug release are the outcomes of F6 formulation. Based on analysis, it is determined that coconut oil proved to be the more efficient plasticizer for making MCG. The combination of F6 with 24 mg of coconut oil is more successful, which is likely due to the concentration's optimal release rate.

Conflicts of Interest: The authors declare no conflict of interest.

ACKNOWLEDGEMENT

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REFERENCES