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Formulation and Evaluation of Medicated Chewing Gum of Ondansetron by using Guava Leaves Extract as a Natural Excipient

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Abstract: *The main objective of the present study was formulation & evaluation of medicated chewing gum of Ondansetron by using guava leaves extract as a natural excipient. MCG of Ondansetronis an excellent drug delivery system for self medication as it is convenient. MCG were prepared by direct compression mold method. Ondansetron HCL, ascorbic acid, gum base(including PEG 400, PVP, elastomer), ginger, flavouring agent, calcium carbonate, dextrose, coloring agent, glycerine & guava leaves extract were used in the different concentration. In these formulation guava leaves extract was prepared by Maceration process & it was used as a natural excipient which overcomes the drawbacks of chewing gum & Ondansetron like diarrhea, dizziness, stomach pain, constipation etc. & ginger was used to reduce the nausea and vomiting. Medicated chewing gum is a cost-effective product & also showed better compliance.*

Keywords: Medicated Chewing Gum, Ondansetron Hydrochloride, Gum base, Mold

I. INTRODUCTION

"Medicated chewing gum is an excellent drug delivery system for self medication as it is convenient and can be administered solely without water. Medicated Chewing Gum is a single solid dosage form novel drug delivery system which is intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa.[1,2]
Medicated chewing gum contains masticatory gum base along with pharmacologically active ingredient which is intended to chew not to be swallowed.[3,4]After dissolution or dispersion of the active ingredient(s) in saliva, drugs released from the gum within the oral cavity can act locally, be absorbed via the buccal mucosa, or from the gastrointestinal tract (when swallowed with the saliva).[5,6]

1.1 Advantages

1. Increased rate of effectiveness rather than other oral delivery systems.[6,7]
2. Removal of gum at any time; therefore termination of drug delivery.[6,7]
3. Reduced risk of overdosing while it's whole swallowed.[6,7]
4. Requiring no water to drink.[7]
5. Both systemic and local drug delivery.[6,7]
6. High acceptance by children and teenagers.[7]
7. Low first-pass effect so reduced dose is formulated in chewing gum compared to other oral delivery systems.[7]
8. Good for rapid delivery.[6,7]
9. Reduced risk of intolerance to gastric mucosa.[6,7]
10. Good stability against light, oxygen, and moisture.[7]

1.2 Characteristic Features of Chewing Gum

- Chewing gum is a soft cohesive substance designed to chew without being swallowed.[6]
- Modern chewing gum is composed of gum base, sweeteners, softeners, plasticizers, flavors, colors and typically a hard or powdered polyol coating..[6]

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- Its texture is reminiscent of rubber because of the physical chemical properties of its polymer plasticizer and resin components which contributes to its elastic plastic, sticky, chewy characteristics.[6]

II. METHODS OF PREPARATION OF CHEWING GUM

- Conventional or traditional method
- Cooling, grinding and tableting method
- Direct compression method

2.1 Conventional or Traditional Method

Gum components →melted and placed in a kettle mixer→gum sent through a series of rollers→thin, wide ribbon formed During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. In a carefully controlled room, the gum is cooled for up to 48 hours. This allows the gum to set properly. Finally the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.[8]

2.2 Cooling, Grinding and Tabletting Method

Aim of the method-to lower the moisture content and alleviate the problems faced in conventional methods.

Cooling: The Chewing Gum composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. General temperature of the refrigerated mixture is -15oC or lower.[8]

Temperature which is required for cooling is determined by the composition of the Chewing Gum and empirically by observing the properties of the cooled chewing gum composition. Coolants used are liquid nitrogen, hydrocarbon slush, and carbon dioxide. Carbon dioxide is preferred as it can give temperatures as low as 78.50oC.[8]

The solid carbon dioxide sublimes readily on warming the mixture and is not absorbed by the chewing gum composition. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition.[8]

Grinding: Cooling of the grinding apparatus is done by keeping the grinding apparatus in contact with a coolant or by placing the grinding apparatus in a cooling jacket of liquid nitrogen or other cold liquid. For more efficient cooling, the chewing gum composition can be pre cooled prior to cooling to the refrigeration temperature.[8]

Tableting: Compression can be carried out by any conventional process like punching. Similar to the Conventional process even this process requires careful monitoring of humidity during the tabletting process.

Direct Compression Chewing Gum: Direct compression chewing gum can be directly compressed on a traditional tableting machine, thus enabling rapid and low-cost development of a gum delivery system. SPI Pharma has developed a compatible gum system known as Pharmagum. Pharmagum is a mixture of polyols and sugar with gum base.[8]

III. MATERIAL AND METHOD

Material: Ondansetron HCL obtained from S.G.Traders, Indore,India. Polyvinylpyrrolidone, polyvinyl alcohol, Polyethylene glycol 400, gumbase, dextrose, calcium carbonate, strawberry, ascorbic acid from S. K. Services and other reagents were of analytical grade.

Guava Leaves Extract: Guava leaves extract is prepared by the maceration process. Guava leaves are used as an antidiabetic, anti-bacterial,antioxidant etc.[9,10]

Procedure:

- Rinse the guava leaves by using water. Then dry the guava leaves in a hot air oven at 200°C temperature for 1 hour. After drying, crush the dry guava leaves.The methanol extract ofguava leaveswere prepared by placing a sample of 10 gm of guava leaves dry powder in 50 ml pure methanol (purity 99.8%), respectively, for 4 days at room temperature.
- Then filter it by using filter paper & collect the guava leaves extract.

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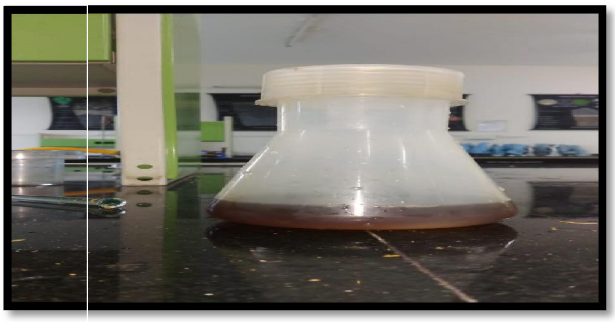

Figure 01: Guava leaves extract

Method: MCGs were prepared by direct compression mold method.

- In this method, each ingredient was weighed accurately and separately.
- Then the gum base was melted at a 115°C temperature by using a microwave.
- OHC, PVP, beeswax, dextrose, calcium carbonate, strawberry flavor essence, and ascorbic acid, glycerine, ginger, guava leaves extract, all ingredients were thoroughly mixed in ascending order of their weights in a mortar.
- After proper mixing, ingredients smoothly grounded in a mortar pestle and then previously weighed quantities of PEG-400 were added. Then, the whole mixture was again mixed thoroughly in pestle mortar.
- All mixed ingredients were added into the melted gum base & mixed well.
- After mixing and grinding, the mixture was subjected for compression into the desired molds and pressed to form medicated chewing gum.
- After removing from mold, formulated chewing gums were weighed and wrapped properly.

Formulation Code:

Table 1: Formulation codes

Ingredients	MCG 1	MCG 2	MCG 3
Ondansetron HCL	8.0 mg	8.0 mg	8.0 mg
Ascorbic acid	0.2 gm	0.2 gm	0.2gm
Gum base (Including PEG 400, PVP, elastomer)	2.40 gm	2.60 gm	2.80 gm
Ginger	0.2 gm	0.2 gm	0.2 gm
Strawberry flavor	2 ml	2 ml	2 ml
Calcium carbonate	0.5 gm	0.5 gm	0.5 gm
Dextrose	3.4 gm	3.6 gm	3.8 gm
Coloring agent	q. s.	q. s.	q. s.
Glycerine	2 ml	3 ml	4 ml
Guava leaves extract	2 ml	3 ml	4 ml
Netweight	12.7gm	15.10gm	17.5gm

Figure 02: Medicated chewing gum

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Preformulation Studies of Drug:

Organoleptic properties: Organoleptic properties are defined as being perceivable by the senses, such as smell, appearance, taste, & touch.[1]

Flow properties:

Bulk density & tapped density: Directly compressible blend was poured gently through a glass funnel into a graduated cylinder of bulk density apparatus. Then bulk density & tapped density were calculated.[1]

Bulk density = Weight of sample in gm / Final volume of sample contained in cylinder

Tapped density = Weight of sample in gm / Final volume after tapping in cylinder

Carr's index: Used to compare the bulk density & tapped density.
The compressibility index was calculated by the formula.[1]

Carr's index = (Tapped density - Bulk density) / Tapped density X 100

Hausner ratio: The flow properties of blend,granules or powder are measured by this ratio.

Hausner ratio = Tapped Density / Bulk density

Angle of repose: Angle of repose With care, dynamic angle of repose measurement can be replicated with relative standard deviation of approximately 2 % they are particularly sensitive to change in particle size distribution and to moisture content and they provide rapid means of monitoring significant batch differences in these respells.[1]

$$\theta = \tan^{-1} h/r$$

Where, θ - Angle of repose
H-Height of the pile
R-Radius of the base of the conical pile.

Angle of repose was determined by using a funnel method. Powder was paired from a funnel that can be raised vertically until a maximum cone height was obtained. Diameter of heap, d was measured.

Bulk characters:

Calibration of drug solubility by using UV Spectrophotometer method: Weighed accurately 100 mg pure ondansetron drug was taken and dissolved in 100ml of water. This made up to 100 mg/ ml solution. From this stock solution 0.5ml was taken and diluted with distilled water. The absorbance was measured at 310 nm using UV-spectrophotometer.[1]

Melting point: The melting point of the ondansetron was determined by the capillary method.
Take the capillary tube & fill with a sample. Capillary tube attached to the thermometer. Now attach both into the melting point apparatus & then adjust the temperature. Then, note the temperature on that was melted.[1]

Post-Formulation Test

Physical Evaluation: Physical properties such as size, shape, thickness, color, and odor must be evaluated. It is very important to investigate the MCGs physically, which plays a key role and these should not be disregarded, it is necessary for acceptance by individuals and even also in marketing.[11,12,13,14]

Weight variation Test: Weight variation plays an important role in evaluation parameters, it ensures that each of the medicated chewing gum contains the proper amount of drug. The test was carried out by weighing the 20 mediated chewing gum individually using analytical balance, then calculating the average weight, and comparing the individual medicated chewing gum to the average.[11,12,13,14]

Stickiness: On a plain surface, medicated chewing gum was placed, and it was subjected to colliding with a Teflon hammer with a mass of 250 g for a period of 10 min. Hammering frequency was 30/min. After specified time, the amount of mass stuck to the hammer was observed and reported.[12,13,14]

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Test for Hardness/Plasticity: There is no one reported method for the determination of hardness; hence, it was decided to use Pfizer type hardness tester for the determination of hardness/plasticity of all MCG formulations.[11,12,13,14]

Thickness & Diameter:-Thickness& diameter was measured using Vernier Calipers. It was determined by checking the thickness and diameter of 10 medicated chewing gum of formulation. The allowed limit of thickness variation is ±5% of the size of the chewing gum.[13]

IV. RESULT & DISCUSSION

In the present work, an attempt was made to develop medicated chewing gum containing OHC drug. Formulation for making medicated chewing gums, where Guava leaves extract was used as a antidiabetic, treatment of diarrhea & overcome the other side effects of Ondansetron HCL, Ascorbic acid was used as antioxidant, dextrose was used as sweetening agent as well as bulking agent, PVP as elastomer and gum, strawberry was used as a flavoring agent.

Formulation was physically evaluated having weight 1.6 g, shape was round having thickness 1.4 cm with light pinkish color and fruity odor. Weight variations study revealed that all formulations have weights in the normal range. All formulations showed negligible stickiness and hardness also found within range, as shown in Table.

Preformulation studies of powder:-

Organoleptic properties:

Table 2: Organoleptic properties of powder

S. No.	Parameters	Result
1	Colour	Off - White
2	Odour	Odourless
3	Taste	Bitter

Flow properties:

Table 3: Flow properties of powder

Flow properties	**Result**
Bulk density (g/cm^3)	0.133
Tapped density (g/cm^3)	0.153
Carr's compressibility index (%)	13.06
Hausner's ratio	0.86
Angle of repose	29.98°C

Bulk characters:-

Calibration of drug solubility:-

Table 4: Absorbance Of Drug

S. No.	**Concentration in (µg/mL)**	**Absorbance at 310 nm**
1	5	0.2096
2	10	0.4352
3	15	0.6148
4	20	0.8412
5	25	1.2001

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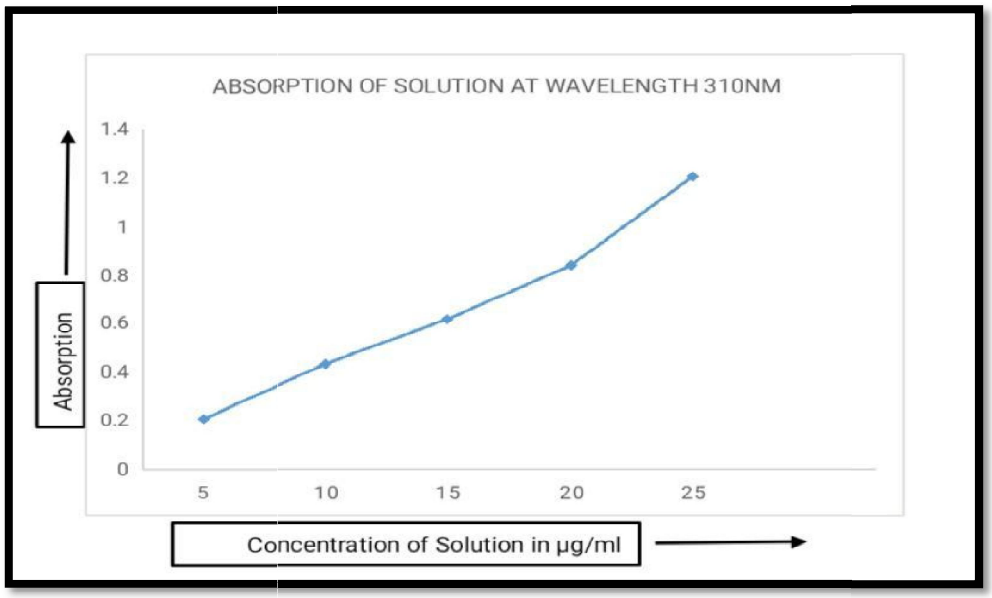

Figure 3: Calibration of drug solubility

Melting point:-231-232°C

Post formulation evaluation of MCG:-

Table 5: Post formulation test

Formulation	Colour	Odor	Smell	Taste	Weight variation (gm)	Hardness (g/cm^3)	Stickness	Thickness (mm)	Diameter (mm)
MCG 1	Light pink	Fruity	Strawberry	Sweet	1.4±0.3	2.21±0.11	Passable	4.7	12.6
MCG 2	Light pink	Fruity	Strawberry	Sweet	1.6±0.0	1.21±0.10	Passable	4.8	12.5
MCG 3	Light pink	Fruity	Strawberry	Sweet	1.4±0.2	1.0±0.08	Passable	4.7	12.6

IV. CONCLUSION

Medicated chewing gum OHC was successfully prepared. OHC is a potent and highly selective 5-HT3 receptor antagonist having important antiemetic activity and good tolerability. It is a cost-effective formulation and has better patient compliance and bioavailability.

In these Formulation guava leaves extract was used as a natural excipient which decreases the chances of side effects of Ondansetron & Ginger was used to reduce the nausea & vomiting.OHC is completely absorbed by GIT which makes this as a choice of drug in preparing medicated chewing gum of OHC. All the parameters found to be satisfactory; hence, the therapeutic dose of OHC can be given in medicated chewing gum with optimized formula, i.e., MCG 2. This study concluded that it is possible to make medicated chewing of OHC for prevention and treatment of vomiting for instant relief.

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