Available online on 10.01.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research



Open Access Research Article

# Design, Development, Characterization and in-vitro Evaluation of Medicated Chewing Gum: Granisetron Hydrochloride

**Agrawal Ankit*, Sudhakar CK**

Chameli Devi Institute of Pharmacy, Indore (M.P.), India

## ABSTRACT

Medicated Chewing Gums are mobile drug delivery systems. It is a potentially useful means of administering drugs either locally or systemically via, the oral absorption. The medicated chewing gum has through the years gained increasing acceptance as a drug delivery system. e.g. Aspirin as an analgesic, Chlorhexidine as local disinfectant, Fluoride for prophylaxis of dental caries, Nicotine for smoking cessation, Caffeine as a stay alert preparation and Dimenhydrinate as antiemetic drugs etc. MCGs are solid, single dose preparations with a base consisting mainly of gums that are intended to be chewed but not swallowed. They contain one or more active substances which are released by chewing and are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa and improve the oral bioavailability of drugs undergoing first pass metabolism.

**Keywords:** Chewing gums, Mobile Drug Delivery System, Dental Caries, Emesis, Local Disinfectant, Mouth Diseases

**Article Info:** Received 25 Sep 2018; Review Completed 28 Nov 2018; Accepted 12 Dec 2018; Available online 10 Jan 2019

Agrawal A, Sudhakar CK, Design, Development, Characterization and in-vitro Evaluation of Medicated Chewing Gum: Granisetron Hydrochloride, Journal of Drug Delivery and Therapeutics. 2018; 8(6-A):43-47

***Address for Correspondence:**

Agrawal Ankit, Chameli Devi Institute of Pharmacy, Indore (M.P.), India

## INTRODUCTION

Nausea means feeling "sick to the stomach", a sensation that is associated with the urge to vomit. Vomiting, the forceful discharge of gastric contents may be a protective physiologic mechanism that prevents entry of potentially harmful substances into the gastrointestinal tract. Persistent vomiting can lead to dehydration, severe alkalosis, bleeding and rarely esophageal perforation -- irrespective of the cause of vomiting[1-2].

Vomiting is to be differentiated from retching, regurgitation or rumination. Retching or dry heaves involves the same physiological mechanisms as vomiting, but occurs against a closed glottis; there is no expulsion of gastric contents. Regurgitation is the return of small amounts of food or secretions to the hypo pharynx in the context of mechanical obstruction of the esophagus, gastro esophageal reflux disease or esophageal motility disorders[3-7].

Medicated Chewing Gum (MCG) is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. The introduction and subsequent success of nicotine chewing gum in the 1980s paved the way for a more general acceptance of chewing gum as a drug delivery system[8-12]. Chewing gum delivery system is convenient, easy to administer anywhere, anytime and is pleasantly tasting making it patient acceptable. Medicated chewing gum offers a wide range of advantages that make it an excellent alternative.

The medicated gums are dosage forms given orally for both local and therapeutic effect. It also offers the possibility of rapidly absorbing the drug through the oral mucosa leading to fast onset of action and bioavailability[13-16]. Also, it has superior sensorial properties compared with other dosage forms; it has a more attractive appeal and offers the patient an active control over the treatment. Drug absorbed directly via the buccal membrane avoids metabolism in the GI tract and the first-pass effect of the liver; it might therefore be to administer a reduce dose in chewing gum Compared to other oral delivery system.

The dosage form offers many advantages like:

- Convenient – promoting higher compliance.
- Administration without water can be taken anywhere.
- Advantageous for patients with difficulty in swallowing tablets.
- Pleasant taste.
- Counteracts dry mouth: Through stimulation of the salivary secretion thereby preventing Candidacies and

caries.

- Highly acceptable by children.

Active substances are released from medical chewing gum during chewing and are dissolved in saliva. The release rate can be carefully controlled through the formulation of the chewing gum allowing extended exposure in the oral cavity.

Consequently, a lower dosage of substance may be therapeutically sufficient, possibly resulting in a fewer side effects, and promote fast absorption. Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets, Stimulates flow of saliva in the mouth, Helps whiten teeth by reducing and preventing stains. The approach of this study was to design a chewing gum where the complete release of the drug dose from the formulation can be detected from an organoleptic change of the gum (in this case, the loss of a color) independently of the different chewing times and chewing frequency of the patients. Here, synthetic polymer is used as a base for chewing gum with different plasticizer, sweetener, colorants, fillers etc. for that we have to study some evaluation parameters like, release of drug in saliva, urinary excretion profile of drug, buccal absorption test. The main aim of this study is to reduce the vomiting frequency by enhancing its bioavailability and to by-pass its hepatic first pass metabolism.

### Granisetron hydrochloride

Granisetron hydrochloride is a potent, selective antagonist of 5- $HT_3$ receptors. The antiemetic activity of the drug is brought about through the inhibition of 5-HT3 receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract) [19-20].

## MATERIALS AND METHODS

### Materials

Granisetron hydrochloride was received as a gift sample from. Sorbitol, Di-butyl phthalate, Glycerin, Talc, Sucrose and Peppermint flavor were of pharma grade and synthetic gum base from kamco chew foods and all other materials used were of the best possible Laboratory Reagent (LR) grade.

### Method of preparation

Each gradient weighed accurately. Synthetic gum base and wax was melted to this molten mass , previously weighed quantity of plasticizer was added and then mixed thoroughly, the melting carried out in a porcelain dish at about 85-90°C on steam bath. This mixture allowed to cool at temperature of 35-45° C then the physical homogenous mixture of granisetron hydrochloride, talc and sucrose was added with continuous stirring so that to ensure even distribution of drug. Then add flavor and color at the end of mixing. Then the mass was allowed to cool at room temperature in plastic moulds and weighed pieces are removed and wrapped properly (Table I)

**Table I: Different formulations and their ratios of ingredients**

| S. No | Ingredients | Percentage | | | |
|---|---|---|---|---|---|
| | | MCG I | MCG II | MCG III | MCG IV |
| 1 | Synthetic gum base | 25 | 35 | 45 | 55 |
| 2 | Drug | 1% | 1% | 1% | 1% |
| 3 | Sorbitol | 14.6 | 14.6 | 14.6 | 14.6 |
| 4 | Sucrose | 1% | -- | -- | 1% |
| 5 | Flavor | 0.6 | 0.6 | 0.6 | 0.6 |
| 6 | Magnesium stearate | 0.2 | 0.2 | 0.2 | 0.2 |
| 7 | Talc | 2.364 | 2.364 | 2.364 | 2.364 |
| 8 | Color | Q.S | Q.S | Q.S | Q.S |

### Evaluation Parameters:

**Physical evaluation** of synthetic gum base: The results of various test carried out for studying the properties of synthetic gum base and formulations are reported on the basis of their color, softening characters, relative humidity, moisture absorption, solubility studies in different solvents.

**Weight variation**: weight of the ten chewing gums is taken in a one batch then average weight is calculated from that standard deviation is calculated.

**Hardness / Plasticity**: Due to absence of any reported method, it was decided to use the Monsanto type hardness tester for determination of hardness / plasticity of all MCG formulations.

**In-vitro drug release**: All the formulation was studied for in- vitro drug release and the cumulative % of drug release was calculated. In-vitro release of drug was done by method described in experimental work.

**Stickiness:** The MCG placed on the plain surface, mass of 250 gm Teflon hammer collide on it for period of ten minute. The frequency of hammering was about 30 / minute. After 10 minutes, sticking of mass to the hammered surface was observed and reported.

**Stability studies** of synthetic gum base: 10 gm of synthetic gum base was stored in bottle at 50º C for 30 days. After 30 days the gum was examined for natural ageing and physical nature.

**Release of drug in saliva**:

The drug release process from medicated chewing gum is quite different compared to a conventional oral drug delivery system, in fact; in this case, not only the dosage form but also the chewing activity of the patient may influence drug delivery. Gums are not intended to dissolve/disintegrate by themselves but a mechanical treatment of the dosage form is required to cause the drug to be delivered. For these reasons, the European Pharmacopoeia guidelines suggest the employment of a specific apparatus for gum formulations which simulates human chewing behavior. To overcome all these difficulties, alternative solutions have been proposed19, 20, 21 the most accessible and obvious approach is to ask to a panel volunteers to chew the drug delivery device for a certain

period of time and to assess the remaining quantity of active substance in the residual gum. In this way, the gums are really chewed and the formulation is subjected not only to the mechanical stresses of an artificial machine but it also undergo all the phenomena involved in this process (increase of salivary secretion, saliva pH variation, swallowing and absorption by the oral mucosa, etc.) which can strongly influence the performance of the dosage form and the amount and rate of drug release.

Optimized formulation with good consistency was selected for the release of drug in saliva. Four human volunteers were selected (two male and two female). Volunteers were instructed to rinse their mouth with distilled water and allowed to chewing the medicated granisetron hydrochloride chewing gum for 15 minutes, so that it's maximum release has to be taken. Sample of saliva was taken after the 5 minutes and then intervals were 2, 4, 6, 8, 10, 12, 14, 15 min. The saliva sample was made diluted in the phosphate buffer pH 6.8 and absorbance was analyzed at 301 nm by UV spectrophotometric method against reagent blank.

Buccal absorption test: It was done by introducing 25 ml of drug solution of concentration about 5 mg / ml at different pH value of 1.2, 5, 6, 6.5, 7, 7.5, 7.8, 8, in the oral cavity of human volunteer who swirled it for 15 min and then expelled out. The expelled saliva was analyzed at 301 nm by UV spectrophotometric method against blank reagent.

## RESULTS AND DISCUSSION

Melting point: The melting point of the granisetron hydrochloride was found to be in the range of 290- 292 °C. It means the drug used is a pure one. Identification test: The λ max for granisetron hydrochloride was found to be 301 nm in the medium in the phosphate buffer having pH 6.8. Physicochemical properties of synthetic gum: Softening range of synthetic gum base is suitable for formulation of medicated chewing gum. Moisture absorption studies of synthetic gum: Synthetic gum base absorbs very less % of moisture means gum base is stable during shelf life. Solubility studies of synthetic gum: Solubility study of synthetic gum shows the sample of gum shows 1% solubility in alcohol. As the synthetic gum shows very minor amount soluble in phosphate buffer this value was as negligible so that taken in account so that synthetic gum was to be found to be best suited as chewing gum base in the formulation of MCGs. The synthetic gum shows insoluble nature in which gain boost for use in MCGs and confirms the insoluble nature of gum base. Stickiness of the all formulations was found negligible and hardness was found within the limit. Weight variations of all formulations were also found satisfactory. Drug content uniformity was between 93 to 96% that is within the normal range. Weight variations were also within the normal range. In-vitro drug release: From the study it was found that drug release of all formulations after 15 minute were more than 55 %. These findings proposed a longer oral presence of granisetron hydrochloride in oral cavity. The graph shows the comparative drug study of all formulations in 20 minute. From the above study it was found that formulation "B" shows better release than other formulation. It concluded that formulation "B "was selected as best batch and carried out for his stability study. Drug release in saliva: From study it was found that drug release from all formulation after 14 minute was more than 40 %. In this study the drug release was depends upon the chewing frequency of the volunteer. From the study it was found that formulation "B" which we select as a best batch shows better release than other formulation in 14 minute.

Stability studies of synthetic gum base: The stability study of synthetic gum base confirms the stability of gum during the process of ageing. There was no change in physical appearance and color of stored sample of synthetic gum base. There was change in the softening point of gum which confirms stability of synthetic gum base.

**Table 2: Physicochemical Properties of Synthetic Gum Base after Stability Studies**

| S. No. | Properties | Observation |
|---|---|---|
| 1 | Color (before ageing) | Off white- pale yellow |
| 2 | Color (after ageing) | Off white- pale yellow |
| 3 | Softening range (before ageing) | 85-90°C |
| 4 | Softening range (after ageing) | 85-90°C |

**Table 3: Texture Analysis data of Medicated Chewing Gum of Granisetron HCl**

| S. No. | Formulation Code | Texture Analysis Data | | |
|---|---|---|---|---|
| | | Hardness (Mean Max Force) (g) | Firmness (Mean Max Force) (g) | Springiness Mean Ratio (%) |
| **1** | MCG I | 3.515±0.24 | 966.3±0.81 | 7.414±0.12 |
| **2** | MCG II | 2.163±0.07 | 931.6±0.66 | 7.332±0.14 |
| **3** | MCG III | 2.095±0.04 | 787.8±0.20 | 7.123±0.23 |
| **4** | MCG IV | 1.676±0.34 | 684.6±0.87 | 7.014±0.34 |

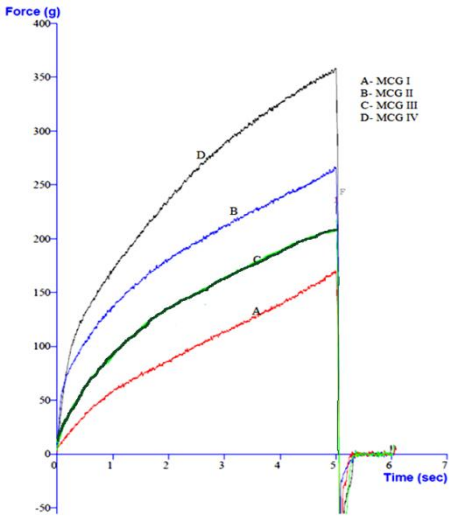
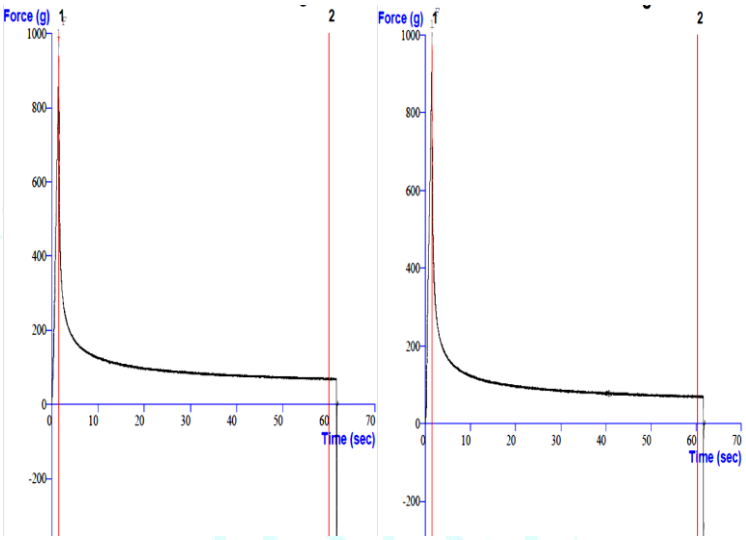
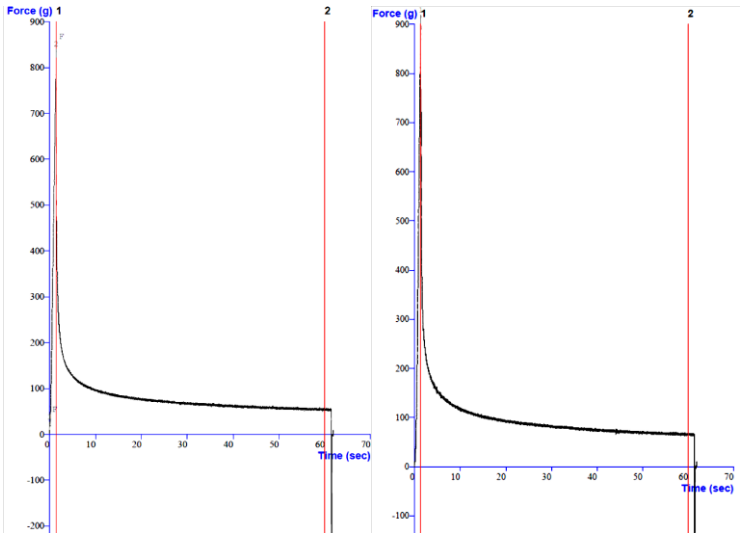



**Figure 1: Hardness test graph of various Medicated Chewing Gum formulation of Granisetron Hydrochloride MCG I (A), MCG II (B), MCG III (C), MCG IV (D)**




**A** **B**

**Figure 2: Firmness and Springiness of Medicated Chewing Gum of Granisetron Hydrochloride: MCG I (A), MCG II (B)**




**A** **B**

**Figure 3: Firmness and Springiness of Medicated Chewing Gum of Granisetron Hydrochloride: MCG III (A), MCG IV (B)**

**Table 4: Content Uniformity of Formulation**

| S. No. | Formulation | % Purity |
|---|---|---|
| 1 | A | 95.68 |
| 2 | B | 97.85 |
| 3 | C | 93.65 |
| 4 | D | 92.45 |

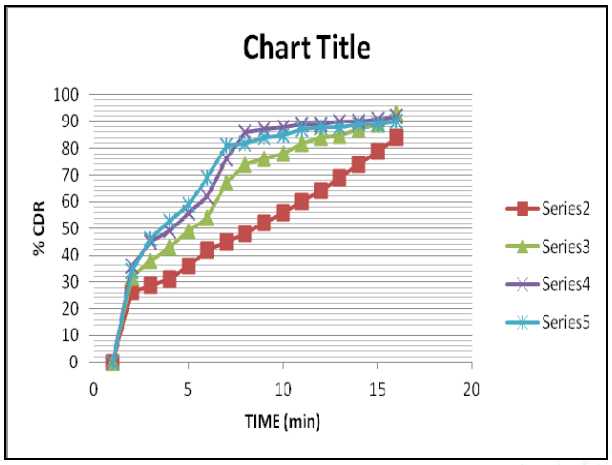



**Figure 4: % cumulative drug release for different MCGs formulations**

## CONCLUSION

Results of in-vitro release profile indicated that formulation "B" was the most promising formulation as the extent and steady release of drug from formulation was high as compare to other formulations. Infra-red spectroscopy shows the characteristics of the drug. Stability study conducted on medicated chewing gum for best formulation "B" under stress conditions for one month. Medicated chewing gum were evaluated for physical parameter as in-vitro release after stability study, shows no significant changes were found in the parameters studied thus it could be concluded that formulation was fairly stable. A modified in-vitro drug release apparatus has been fabricated by modification of the IP disintegration test apparatus. Various Gum formulations with different composition were used to demonstrate the versatility of the chewing apparatus during study. When the in-vitro and in- vitro drug release results were compared, the drug release patterns in-vitro were fairly steady as compared to in-vitro and also less amount of drug has been released in equivalent time in vivo salivary drug release case. The vitro clinching apparatus needs bit further modifications for steady and relatively similar drug release match up to vivo drug release pattern. It can be concluded that in concentration of 50% synthetic gum base give promising results with the water soluble drug Granisetron Hydrochloride for steady drug release coupled with adequate release properties from medicated chewing gum. Some of the promising agents may incorporate in medicated chewing gum for improving the drug release from medicated chewing gum. The dissolution curves for the release of Granisetron Hydrochloride from the medicated chewing gum formulations are showed a satisfactory release rate. An explanation for this can be proposed by examining the drug release profiles of the gums. Synthetic gum formulations are similar marketed medicated chewing gum in appearance. Since synthetic gum base has 50% gum base used to formulate MCG compared to market medicated chewing gum this should provide a more pleasant mouth feel and it was expected that this would result in a steady and controlled release of drug.

## REFERENCES


1. Gupta V, Wakhloo R, Mehta A, Gupta SD. Prophylactic Antiemetic Therapy with Ondansetron, Granisetron and Metoclopramide in Patients Undergoing Laparoscopic Cholecystectomy under GA, Journal of Medical Education & Research. 2008; 2:74-77.
2. Golding JF. Motion Sickness Susceptibility, Autonomic Neuroscience: Basic and Clinical. 2006; 129:67-76.
3. Minton NA. Volunteer Models for Predicting Antiemetic Activity of 5-HT3 Receptor Antagonists, British Journal of Clinical Pharmacology 1994; 37:525-530.
4. Ezhumlai K, Rajalakshmi AN, Ilavarasan P, Sathiyaraj U, Murali R. Medicated Chewing Gum- A Novel Drug Delivery Technique For Systemic and Targeted Drug Delivery, International Journal of Pharmacy & Technology2011; 3:725-744.
5. Patel VP. Medicated Chewing Gum: A Review, International Journal of Universal Pharmacy and Life Sciences2011; 1:111-128.
6. Kumar D, Rathi L, Tripathi A, Maddheshiya YP.A Review on Oral Mucosal Drug Delivery System, International Journal of Pharmaceutical Science and Research. 2010; 1:50-56.
7. Surana AS. Chewing Gum: A Friendly Oral Mucosal Drug Delivery System, International Journal of Pharmaceutical Science Review and Research. 2010; 4:68-71.
8. Jain H, Shah M, Shah B, Pasha TY. Medicated Chewing Gum: A Novel Oral Drug Delivery, International Journal of Drug Formulation & Research 2010; 1:80-96.
9. Mateti UV, Adla N, Rajakannan T, Valakkathala R. Insulin Chewing Gum: Need of the day for Diabetic patients, International Journal of Pharmaceutical Investigation. 2011; 1:31-134.
10. Naik H, Gupta S.Medicated Chewing Gum- Updated Review, International Journal of Pharma Research & Development 2010, 2: 66-76.
11. Pandey S, Goyani M, Devmurari V. Development, In-Vitro Evaluation and Physical Characterization of Medicated Chewing Gum: Chlorohexidine Gluconate, Scholars Research Library 2009; 2:286-292.
12. Gajendran J, Kraemer J, Knudsen SR. Product Performance Test for Medicated Chewing Gums, Pharmacopeial Forum 2008; 34:843-847.
13. Kvist LC, Andersson SBR, Berglund J, Bo Wennergren, Susan MF. Equipment For Drug Release Testing of Medicated Chewing Gums, Journal of Pharmaceutical and Biomedical Analysis 2000; 22:405-411.
14. Gavaskar B, Ramana VD, Madhusudan Rao Y. Medicated Chewing Gum – A Novel Approach to Improve Patient Compliance, International Journal of Research in Pharmaceutical and Biomedical Sciences 2011; 2:23-32.
15. Madan N, Rathnam A. Chewing Gum for Optimal Health, Chronicles of Young Scientist 2011; 2:7-10.
16. Patel Y, Shukla A, Saini V, Shrimal N, Sharma P. Chewing Gum as a Drug Delivery System, International Journal of Pharmaceutical Sciences and Research 2010; 2:748-757.
17. Adams VR, Valley AW. Granisetron: The Second Serotonin-Receptor Antagonist. and Pharmacother 1995; 29:1240-51.
18. Addelman M, Erlichman C, Fine S. Phase I/II trial of Granisetron: A Novel 5-HT3 Antagonist for The Prevention of Chemotherapy- Induced Nausea and Vomiting. Journal of Clinical Oncology 1995; 8:337-341.