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FORMULATION AND EVALUATION OF MEDICATED ANTIEMETIC CANDY LOZENGES

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Abstract: The goals of this study or project are to develop, prepare, and evaluate the medication and dosage form. Granisetron hydrochloride lozenges are administered to treat nausea and vomiting to. A particular antagonist for the 5-HT3 serotonin receptor. These prepared lozenge's advantage includes an increase in bioavailability, a reduction in stomach irritation due to first pass metabolism, and a quicker onset of action. Carboxymethyl cellulose (CMC), hydroxypropyl methyl cellulose (HPMC K4M), were employed as polymers in the preparation of the lozenges, that were made by heating and congealing a base of sucrose.It was found that the polymer or hydrocolloid-free formulation i.e. (B1) proved to be more optimized than the other formulations. By using industry-recognized pharmaceutical standard methodologies, all the produced formulations were evaluated for drug content uniformity, hardness, thickness, friability, diameter, weight variation, moisture content, and in-vitro dissolution. The resulting formulations were grit-free. IR Spectral analysis was done to check for potential drug-excipient interactions. Stability study investigation carried out in accordance with ICH criteria (zone IV) at 45 °C and 75 % relative humidity revealed no significant interactions between the drug, flavor, or color, and the created formulations were stable. The antiemetic lozenges are prescribed to patients who suffer emesis as an alternate formulation.

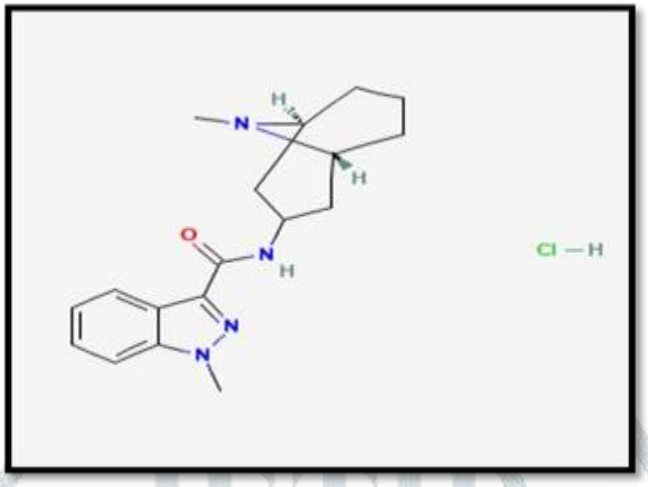
Keywords: Granisetron Hydrochloride, Mold, Lozenges, Emesis.

I. INTRODUCTION

Lozenges are solid preparations that comprise one or more drugs, generally in a flavored, sweetened base, and are meant to be sucked and held in the mouth to lubricate, and pacify irritated tissues of the throat. They are planned to be dissolved in the posterior surface of the tongue to deliver drugs locally to the mouth, tongue, and throat, and to relieve oropharyngeal symptoms. The dosage form can be implemented for local as well as systemic treatment.[1] Lozenges are utilized for juvenile and geriatric patients who are unable to swallow solid oral dose forms, as well as drugs that are designed to release quickly over time to maintain a steady amount of drug in the oral cavity.[2] Lozenges are a common and unique medication delivery technique, as well as a more inventive dosage form and oral confectionery goods.[3] It is most likely beneficial for administering medicine either locally or continuously through the mouth. The reasons for this preference include ease of administration for elderly and pediatric patients, as well as widespread patient acceptability. Development of novel drug delivery methods for current drugs that improve effectiveness, minimize first-pass hepatic metabolism, eliminate the requirement for water consumption, and boost bioavailability while lowering dosage frequency.[4] Lozenges are used for patients who cannot swallow solid oral dosage forms as well as for medications designed to be released effectively to yield a constant level of drug in the oral cavity or to bathe the throat tissues in a solution of the drug.[5] Lozenges are intended to relieve oropharyngeal symptoms, which are commonly caused by local infections and for systemic effect provided the drug is well absorbed through the buccal linings or when it is swallowed. Lozenges are used for patients who cannot swallow solid oral dosage forms. Drugs often incorporated into lozenges include analgesics, anesthetics, antiemetic, antimicrobials, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants, and demulcents. However, this is by no means an exhaustive list as many other drugs may lend themselves to delivery by a lozenge. As well, both single and multi-ingredient lozenges can be compounded, depending on the patient's needs. Oral drug delivery is the most favored route for the administration of various medications and tablets are the most widely accepted dosage form. Solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly patient compliance.[6] Vomiting is the reflex action of ejecting stomach contents via the mouth and occasionally through the nose, whereas nausea is the sensation of being about to vomit. Emesis and nausea can be caused by some factors, including medication consumption, stomach irritants, chemotherapy, radiation, and gastrointestinal infections.[7]

II. DRUG PROFILE:

Granisetron is a medication used to prevent nausea and vomiting caused by motion sickness, overeating, chemotherapy, and radiation therapy, as well as after surgery. It belongs to a class of drugs called 5-HT3 receptor antagonists, which work by blocking the action of serotonin, a natural substance in the body that can cause nausea and vomiting. Granisetron lozenges should be typically taken prior to the occurring symptoms, and the dose and frequency will depend on the individual's condition and response to treatment. They are usually prescribed for people who have difficulty swallowing pills or who experience nausea and vomiting shortly after taking oral medications



2.1 Properties:

Table No:1 Drug Profile of Granisetron Hydrochloride.

Properties	Value
Drug Name	Granisetron Hydrochloride
IUPAC Name	1-Methyl-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)-1H-indazole-3-carboxamide
Class of Drug	5-HT3 receptor antagonists
Synonyms	Kytril, Sancuso, Granisol
Molecular Formula	C18H24N4O
Molar Mass	312.417 g/mol
Solubility	Water (70 mg/ml at 25° C), Ethanol (1 mg/ml at 25° C).
Melting Point	Above 270°C

2.2 PREFORMULATION STUDIES:

Preformulation is the stage of development during which the physicochemical properties of the drug substance are characterized and established.

2.2.1 Physical Properties:

What is called physical property?

Physical property is defined as a characteristic of matter that may be observed and measured without changing the chemical identity of a sample.

The Following are the physical properties of Granisetron Hydrochloride:

1. Color: White
2. Odour: Odourless
3. Taste: Bitter
4. Texture: Fine Powder

Solubility of Granisetron hydrochloride:

The maximum amount of solute that can dissolve in a known quantity of solvent at a certain temperature is its solubility. It was determined in following solvents buffers:

Preparation of Phosphate Buffer: Dissolve 28.80g of disodium hydrogen phosphate and11.45g of potassium dihydrogen phosphate in sufficient water to produce 1000ml.

Distilled water: Highly Soluble

Phosphate buffer, pH 6.8: Soluble

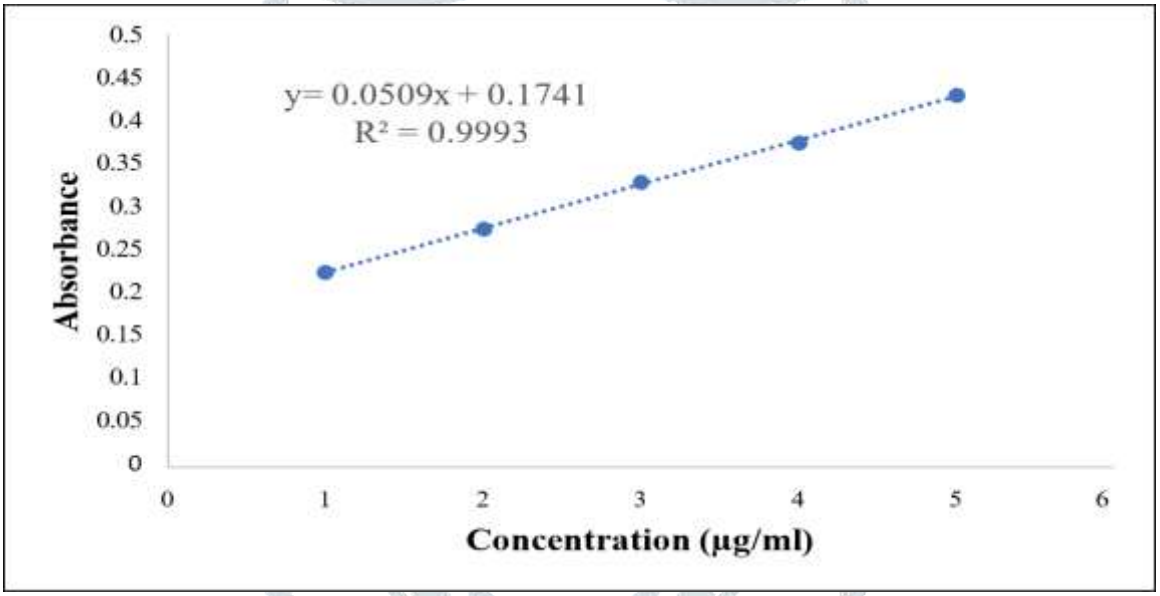
Preparation of Aliquot:

1. 10 mg of drug was weighed and dissolved in distilled water and phosphate buffer and later the volume was make up to 100 ml by distilled water and phosphate buffer respectively to get 1000 µg/ml stock solution.
2. Then 1ml was withdrawn from the stock solution and volume was make up to 10 ml by distilled water and phosphate buffer respectively to get 100 µg/ml solution.
3. Then 0.8 ml, 1.0 ml, 1.2 ml, 1.4 ml, 1.6 ml of aliquot were pipetted out from the above solution of 100µg/ml and volume was make up to 10ml by distilled water and phosphate buffer respectively. To get concentration of 8 µg/ml, 10 µg/ml, 12 µg/ml, 14 µg/ml, 16 µg/ml.

Absorbance of Granisetron in Distilled Water at 301nm Wavelength

Table No:2 Absorbance of Granisetron in Distilled Water.

Sr.No.	Concentration of Granisetron (µg/ml)	Absorbance
1.	8(µg/ml)	0.2247
2.	10(µg/ml)	0.2753
3.	12(µg/ml)	0.3295
4.	14(µg/ml)	0.3745
5.	16(µg/ml)	0.4295

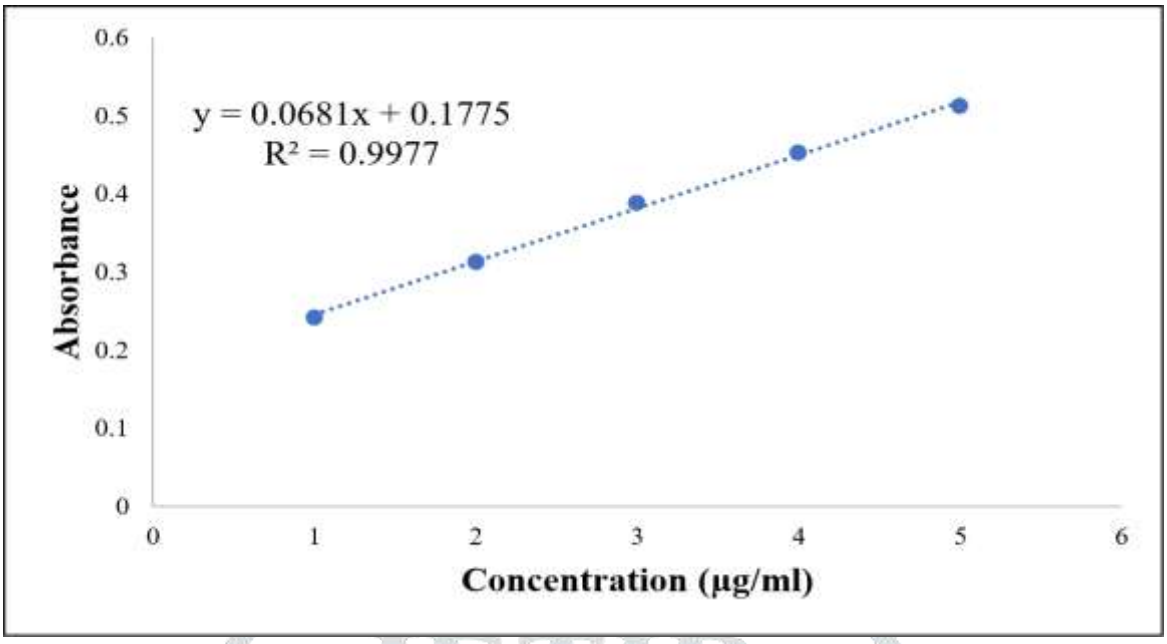


Absorbance of Granisetron in Distilled Water.

Absorbance of Granisetron in Phosphate Buffer pH 6.8 at 301nm Wavelength.

Table No:3 Absorbance of Granisetron in Phosphate Buffer pH 6.8.

Sr.No.	Concentration of Granisetron (µg/ml)	Absorbance
1.	8(µg/ml)	0.2421
2.	10(µg/ml)	0.3125
3.	12(µg/ml)	0.3888
4.	14(µg/ml)	0.4531
5.	16(µg/ml)	0.5122



Absorbance of Granisetron in Phosphate Buffer pH 6.8.

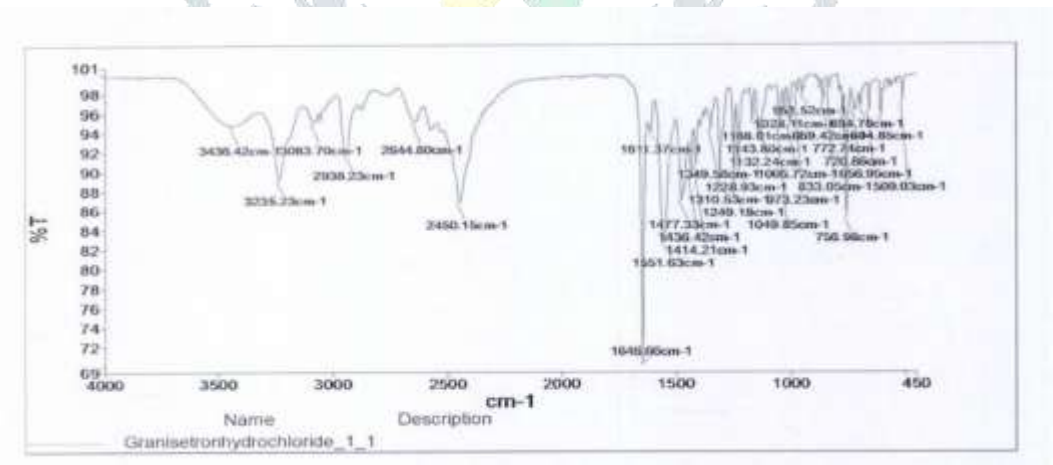
IR SPECTROSCOPY OF GRANISETRON

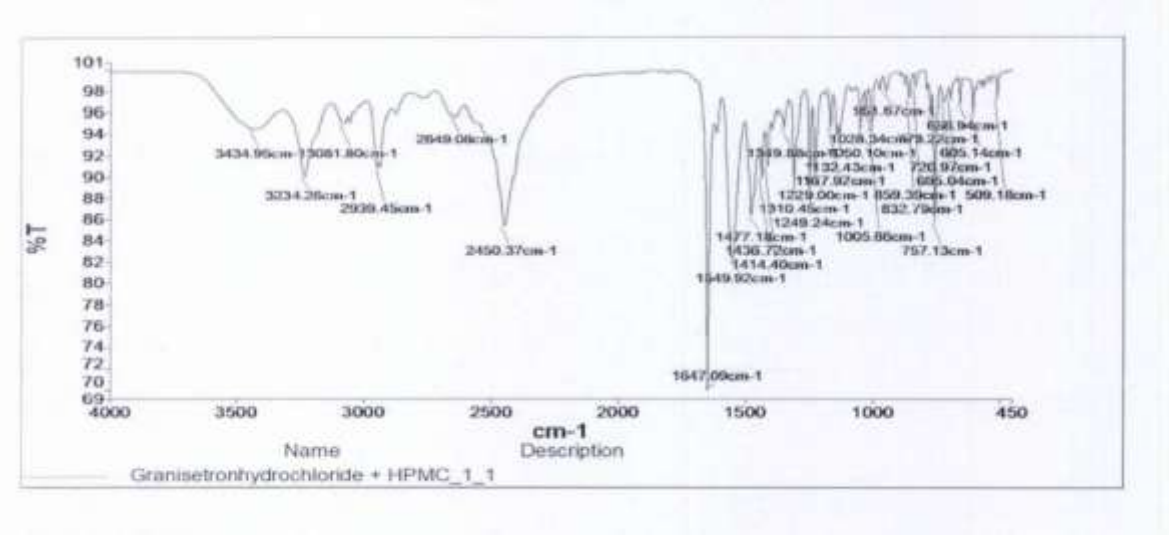
Fourier Transform Infrared Spectroscopy Test (FTIR) identifies chemical bonds in a molecule by producing an infrared absorption spectrum. The spectra produce the profile of the sample, a distinctive molecular fingerprint that can be used to screen and scan samples for many different components

The following samples were tested:

1. Granisetron Sample
2. Granisetron + Hydroxypropyl methylcellulose (HPMC)
3. Granisetron + Carboxymethyl cellulose (CMC)

FTIR of Granisetron hydrochloride





FTIR Of Granisetron + Carboxymethyl cellulose (CMC).

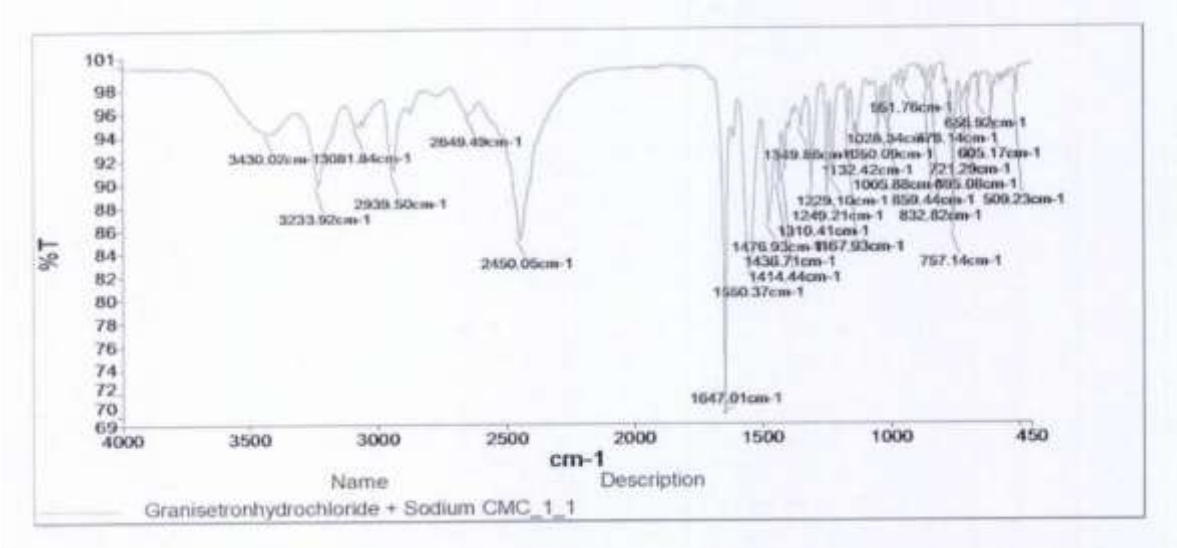


Table No. 4 FTIR Test Readings:

Sr. No	Functional Group	Standard Frequency Range (cm^{-1})	Observed frequency Range (cm^{-1})
1.	Secondary Amines (N-H)	3500-3100	3436.42
2.	Aromatic Alkyne (C-H)	3150-3050	3083.70
3.	Aliphatic Alkyne (C-H)	ca.3300	2938.23
4.	Aromatic Alkene (C=C)	1600-1475	1477.33

III. Method of Preparation:

1. Desired Quantity of Sugar was Dissolved in Water by Heating and Stirring in Porcelain dish and then Corn syrup was added when temperature reached 110ºC .
2. Then Addition of Polymer was done into the Candy Matrix.
3. After that Addition of Drug was done into the Polymer Candy Matrix.

4. Later then other Excipients were added such as Coloring and Flavoring agents.
5. Pour the mixture into mold of Desired Size and Shape and then allow it to cool at room temperature for the formation of lozenges

Different Trial Batches Containing Different Concentration of Polymers

Table No:5 Preparation of Different Trial Batches.

Sr. No	INGREDIENTS	B1	B2	B3	B4	B5	B6	B7
1.	Invert Sugar (grams)	27.4	27.4	27.4	27.4	27.4	27.4	27.4
2.	Corn Syrup (grams)	11.6	11.6	11.6	11.6	11.6	11.6	11.6
3.	Drug (grams)	0.08	0.08	0.08	0.08	0.08	0.08	0.08
4.	Hydroxypropyl methylcellulose (grams)	-	0.4	0.8	0.12	-	-	-
5.	Carboxymethyl cellulose (grams)	-	-	-	-	0.4	0.8	0.12
6.	Citric Acid (grams)	1	1	1	1	1	1	1
7.	Flavoring agent (grams)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
8.	Coloring agent (grams)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
9.	Water (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
10.	Number of Lozenges	20	20	20	20	20	20	20
11.	Total Weight (grams)	40	40	40	40	40	40	40

- **Each Lozenges Contains 4 mg of Drug.**
- **Average weight of each Lozenges is 2 grams.**

IV. EVALUATION PARAMETER:

WEIGHT VARIATION: The weight of the lozenges being made was routinely determined to ensure that a lozenge contains the proper amount of drug. The USP weight variation test is done by weighing 20 lozenges individually, calculating the average weight and comparing the individual weights to the average. The lozenges met the USP specification that no more than 2 lozenges are outside the percentage limits and no lozenges differs by more than 2 times the percentage limit

HARDNESS: The hardness of each batch of lozenges was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 lozenges were chosen randomly and tested for hardness

THICKNESS AND DIAMETER: Thickness and diameter was measured using Vernier Caliper. It was determined by checking the thickness and diameter of 3 lozenges of each formulation. The extent to which the thickness of each lozenge deviated from ± 5% of the standard value was determined.

FRIABILITY TEST: The friability of the 10 lozenges from each batch was tested by a Friabilator. At a speed of 25 rpm for 4 minutes. The lozenges were then dedusted, reweighed and percentage weight loss was calculated by the equation.

% Friability = (initial weight – weight after friability) × 100/ initial weight

MOISTURE CONTENT: The sample was weighed and crushed in a mortar. From this, one gram of the sample was weighed and placed in a desiccator for 24 hours. After 24 hours the sample is weighed. The moisture content is determined by abstracting the final weight from initial weight of lozenges.

% Moisture Content = (initial weight – final weight) × 100/ initial weight.

DETERMINATION OF DRUG CONTENT: Twenty lozenges were finely powdered; quantities of the powder equivalent to 80 mg (each lozenges contain 4 mg of Granisetron) of Granisetron were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml of distilled water and allowed to stand for 30 min with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to desired volume with distilled water. The solution was suitably diluted and the absorption was determined by UV- Visible spectrophotometer at λmax of 301nm. The drug concentration was calculated from the standard curve

IN-VITRO STUDIES: The rate of the drug absorption was determined by the rate of drug dissolution from the lozenges. Thus, the rate of dissolution and bioavailability may be directly related to the efficacy of the lozenges. The boat shaped paddle was used and the dissolution medium pH 6.8 phosphate buffer, 500 ml was placed in the beaker containing the lozenges and stirred at 100 rpm. 5 ml aliquot samples were withdrawn at 2 min. interval and replaced immediately with an equal volume of fresh fluid i.e., simulated salivary fluid. Each aliquot was diluted and they were analyzed at 301 nm, by UV Visible spectrophotometer

PHYSICAL APPEARANCE OF LOZENGES:

4.1 EVALUATION OF TRIAL BATCHES:

Table No:6 Evaluation of Trial Batches

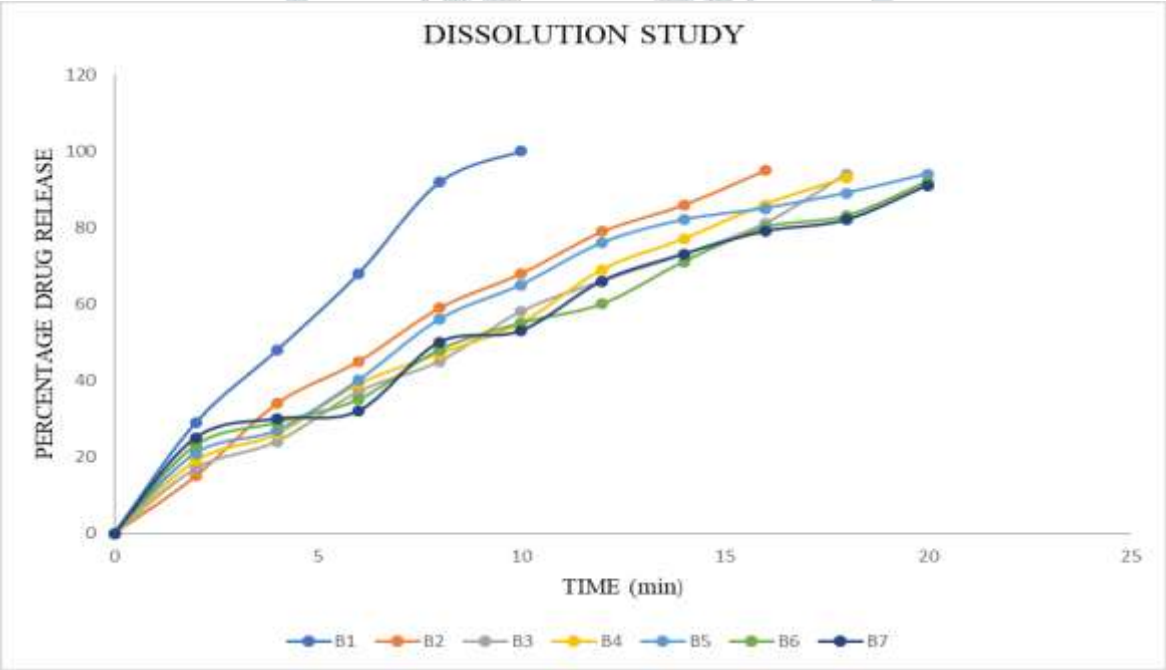
Parameter	B1	B2	B3	B4	B5	B6	B7
Weight Variation (grams)	2.00±0.01	2.05±0.02	2.09±0.02	2.10±0.01	2.07±0.01	2.20±0.01	2.27±0.01
Hardness Test (Kg/cm^2)	8.00±0.05	8.40±0.05	8.50±0.05	8.50±0.05	9.05±0.05	9.10±0.05	9.10±0.05
Thickness (mm)	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Diameter (mm)	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Friability Test (%)	0.3%	2.0%	2.2%	2.0%	0.5%	0.5%	0.6%

Moisture Content (%)	0.8%	1.4%	1.2%	1.0%	1.6%	1.4%	1.5%
Content Uniformity	99.65	98.23	99.12	98.44	99.23	98.63	99.61

4.2 IN-VITRO DRUG RELEASE STUDY:

- Dissolution conditions:
- Apparatus: USP I apparatus
- Dissolution Medium: 5 ml of pH Phosphate buffer
- Temperature: 37±0.5ºC
- Rotating speed of the paddle: 25 rpm
- Sample time intervals: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, minutes
- Detection; UV-VIS spectrophotometer at λmax 301nm

The samples were withdrawn at predetermined time points, diluted appropriately, and were analyzed spectrophotometrically at 301nm



The percentage drug release of each batch is shown in the above graph **Fig-26,** from which we can conclude that batch (**B1**) shows rapid drug release compared to other batches which includes polymer with different concentrations.

V. DISCUSSION:

All the formulation showed good physical appearance. The absorption maxima of granisetron hydrochloride when observed under UV absorption spectrophotometer were found under 301nm wavelength. The Prepared lozenges were of Strawberry and pineapple flavor and had average weight of 2 grams. The diameter of all the formulation was found to be 15.00 mm. The thickness was in the range of 5.00 mm. All the Formulations had good hardness and passed drug content uniformity. Thus, it can be concluded that all the formulations passed physicochemical evaluation. The details of physicochemical properties are given in Table-7. The Moisture content of all the formulation was found to be below 2%. This is due to less uptake of water by the polymers. The in-vitro dissolution studies of the batches B1-B7 shows that Batch (B1) has better drug release than compared to other batches.

VI. CONCLUSION:

Sucrose based medicated hard-candy lozenges of granisetron hydrochloride will be an alternative dosage form for emesis patients. These will have additional advantages of patient compliance, convenience and comfort for efficient treatment including low dose, immediate onset of action, reduced dosage regimen and economy.

The physicochemical characterization revealed that all the formulations were found to show acceptable thickness, weight, and hardness.

The content uniformity estimation showed uniform content in all the formulations.

The moisture content test reveals that the prepared formulations were within the limits.

From all the above result and discussion, we conclude that the product without polymer showed optimized results i.e., B1 batch.

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