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FORMULATION AND EVALUATION OF MEDICATED CHOCOLATE OF ONDASETRON FOR PEDIATRICS

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ABSTRACT

Oral drug delivery is one of the most commonroute of drug administration due to its patient compliance and ease of usage. But this route is an immense challenge for the drug delivery to the pediatric patients. Our present research work emphasizes on the solution to this problem. The present research work deals with the formulation and evaluation of a medicated chocolate of ondansetron, which is one of the most common medicines used for pediatrics for the treatment of emesis. Chocolate is a range of products derived from cocoa which is mixed with cocoa butter and finely powdered sugar to produce a solid confectionery. Chocolates were formulated (F1-F6) with cocoa powder, cocoa butter, soya lecithin, sucrose and milk powder. The created chocolate formulas were put to the test in terms of general appearance, hardness, melting point, dimension, moisture content, weight variation, drug content, *In vitro* drug release, moisture content, blooming test and stability test. Within 60 minutes, the F1 formulation releases the entire medication. The results show that the formulation has no drug-excipient interactions and that the drug has not degraded throughout the manufacture of the chocolate formulation.

Keywords: Ondansetron, Medicated chocolate, Pediatrics, *In vitro* drug release

INTRODUCTION

For decades, oral drug delivery has been recognized as the most extensively used route of administration among all the methods that have been used for systemic

drug delivery via various pharmaceutical products in various dose forms. The oral route's success can be ascribed in part to its ease of administration. A method for long-term drug delivery via the mouth is called an oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Drug release in the absorption zone can be hampered by rapid GI transit and reduce the efficacy of the administered dose **[1]**. Oral drug delivery system can be very challenging for pediatrics, throughout continuous growth period. The innovative medicine delivery mechanism is intended to prevent issues related to physiological impairment and swallowing difficulties. Evolution of oral drug delivery system is extremely challenging for the wide range of pharmaceuticals and clinical aspects regarding quality, safety, efficacy of developed formulation. The demands, needs, and unique qualities of pediatrics formulation make it difficult to develop **[2]**. The pharmacokinetic and pharmacodynamic characteristics of an oral medication change as a result of a variety of factors. Pediatric growth stages necessitate dosage flexibility that encompasses all age groups. Dosing requirements for children. Oral formulations are cost-effective and convenient for patients. Introspectively, all points of view reveal that pediatric formulations take a variety of methods to new technology, design, and development, as a result of the quickest innovation.

The European Medicines Agency (EMA) is anticipated to develop The European Pediatric Formulation Initiative (EPFI) is a project that aims to improve World Health Organization (WHO) in 2007 (WHO) started a global project called "Make Medicines Child Size" to encourage the development of new medicines for children dose form for children **[3]**. Due to distinct requirements and limits, developing pediatric formulations can be fairly difficult from a scientific standpoint. Diversity of children, Taste masking, Stability – physical, chemical, microbiological, achieving global regulatory acceptance, providing quick patient access, and accelerated development timelines are some of the issues faced when designing pediatric formulations. The optimization of oral drug administration has been one of the most difficult tasks in pediatric pharmacology. The pace or degree of drug absorption, and thus bioavailability, may be affected by crushing tablets. Cutting tablets is another popular method that may be okay for some drugs, but it can be dangerous for others. introduce considerable variability between doses. Extemporaneous oral

suspension or solution can also having issue with stability, handling, addition of flavoring agent or use of a different brand, may alter the stability of the final product or the absorption characteristics of the drug. For babies and children, commercially accessible oral liquid drugs provide a more dependable, ready-to-use preparation, but bioequivalence with solid oral dose forms is still unknown. The shortcomings of currently available formulations underscore the need for innovative solutions that are both simple to use and capable of delivering consistent serum medication concentrations and better taste **[4]**.

Vomiting happens when the emetic (vomiting) centre in the medulla oblongata is stimulated. Vomiting can be caused by a variety of factors. The nucleus tractus solitarius (NTS) and the chemoreceptor trigger zone (CTZ) in the region postrema are the most important relay locations for afferent impulses arising in the gastrointestinal tract, throat, and other viscera. Because the CTZ is not protected by the blood-brain barrier, it is vulnerable to blood-borne medicines, mediators, hormones, poisons, and other substances. The release of 5-HT from enterochromaffin cells by cytotoxic drugs, radiation, and other gastrointestinal irritants activates 5-HT3 receptors on extrinsic primary afferent neurons (PAN) of the enteric nervous system (ENS), which connect with vagal and spinal visceral afferents to send impulses to NTS and CTZ. 5-HT may potentially flow into circulation and reach CTZ if it is released in big quantities. Inflammatory mediators may also release it from platelets. However, 5-HT is not the only messenger implicated in such signals; peptides and other messengers play a role as well. The CTZ and NTS contain a number of receptors, including histamine H1, dopamine D2, serotonin 5-HT3, cholinergic M, and opioid, which convey emetic signals and may be targets for antiemetic medication action. Various unpleasant sensory cues, such as a terrible odour, a ghastly sight, acute pain, fear, remembrance of an irritating incident, and anticipation of an emetic stimulus (repeat dosage of cisplatin), trigger nausea and vomiting through higher centres. Reduced stomach tone and peristalsis accompany nausea. The esophageal sphincter and oesophagus relax during the emetic reaction, whereas the duodenum and pyloric stomach constrict in a retrograde way. Rhythmic diaphragm and abdominal muscle contractions then compress the stomach and force the contents out through the mouth. Vomiting is more likely in conditions that prevent stomach emptying **[5]**.

Chocolate drug delivery system via the oral route, particularly the buccal route, was used as a platform for Histamine receptor antagonists in the current investigation, allowing for local impact drug administration. Ondansetron competitively blocks the action of serotonin onthe 5-HT3 receptor which suppresses the nausea and vomiting centers in medulla oblongata of the brain. In local effect, the intention is to attain a site specific release of the drug on mucosa, whereas the systemic effect involves drug absorption through the mucosal barrier to reach systemic circulation. The buccal mucosa is highly vascularized and presents a reduced enzymatic activity when compared to gastro intestinal, rectal and nasal mucosa **[4]**.

MATERIALS AND METHODS

Materials

Ondansetron was procured from McW Healthcare Pvt. Ltd. Indore. Soya lecithin and sucrose was procured from Purix store and Isochem laboratories respectively Sodium benzoate was procured from Agrawal drug Pvt. ltd. Cocoa power, Cocoa butter and Chocolate flavor, milk powder was purchased from local market.

Formulation & Development of Medicated chocolate: All the ingredients were weight accurately in one beaker, sugar and water was taken and sugar syrup was prepared on heating mantle. Cocoa butter was heated in a separate beaker, then the powder mixture was added to melted cocoa base and thoroughly combined to get a fine consistency. Further soya lecithin as an emulsifier was added and mixed. Finally the Ondansetron was added in above prepared chocolate base. Then flavoring agent was added before going to be set in moulds. Then the prepared chocolate containing drug was poured in moulds and kept in freeze to set over night. The six formulations prepared for ondansetron medicated chocolates is mentioned in **Table 1 [7]**.

Table 1: Formulation of medicated chocolate

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Ondansetron	4	4	4	4	4	4
Cocoa powder	700	700	700	700	700	700
Cocoa butter	350	360	390	340	380	370
Lecithin	50	40	10	60	20	30
Sucrose	170	170	170	170	170	170
Milk powder	200	200	200	200	200	200
Sodium benzoate	40	40	40	40	40	40
Chocolate Flavor	0.001	0.001	0.001	0.001	0.001	0.001
Total weight	1514	1514	1514	1514	1514	1514

Figure 1: Formulation and Development of Medicated chocolate
A. Preparations of medicated chocolate base, B-Medicated chocolate base was poured in Molds, C-Medicated chocolate molds kept in fridge, D- Final medicated chocolate was prepared

EVALUATION OF CHOCOLATE BASE

Taste, Texture and Mouth feel Characteristics Assessment: Taste, mouthfeel, and texture properties of chocolate were assessed by a panel of ten human volunteers **[7]**.

Viscosity: The viscosity (in cps) of the prepared chocolate base was measured using a Brookfield Rotational digital viscometer (Model No. 220). The spindle (91A) was moved at 20 revolutions per minute **[8]**.

EVALUATION OF MEDICATED CHOCOLATES

General Appearance: General Appearance of Medicated Chocolate variable such as chocolate color, odour, flavor, and surface texture was performed **[9]**.

Weight Variation Test: The twenty medicated chocolate were selected randomly from every formulation and their average weight was determined. All medicated chocolate were weighed individually and compared with average weight **[10]**.

Dimensions: The dimension of chocolate was measured by vernier calipers **[11]**.

Hardness: The hardness of Medicated chocolate was determined using Monsanto hardness tester **[10]**.

Moisture Content Determination: Moisture content was determined by using Desiccator. Initial weight of Medicated chocolate was recorded and the chocolate was kept in desiccators containing charged silica in desiccator for 24 hrs. The formulations were taken out, weighed and %moisture content was calculated by using formula **[8]**.

Blooming Test [12]:

- **Fat bloom**: When these development of the white thin layer of fat crystals on the surface because which chocolate will lose its appearance. Recrystallization of fats and/or

migration of a filling fat to the chocolate layer produce fat bloom. A fat bloom's look inhibited if stored at a constant temperature.

- **Sugar Bloom**: On top of the medicated chocolate formulation is a rough and uneven covering. Sugar bloom is caused by condensation. Because of the wetness, the sugar in the chocolate dissolved. The sugar re-crystallizes on the surface when the water evaporates, forming rough, uneven crystals. This gives the appearance that the chocolate is unpleasant.

Three treatment cycles were applied to each sample:

(1) 11 hours at 30°C

(2) A temperature change of one hour

(3) At 18°C for 11 hours.

Melting point of Medicated chocolate [**13]**: The temperature of melted chocolate was determined by thermometer and the reading was taken.

Drug Content Determination: Drug content of a medicated chocolate was determined by using UV Spectrometer.

Method of sample preparation: Medicated chocolate was taken and mixed in 10 ml phosphate buffer pH 6.8 in 25mL beaker. Then this mixture was sonicated in bath sonicator. Then sonicated sample was poured in a centrifuge tubes and it was then centrifuged for 15min at 2500 rpm. Supernatant was clear liquid containing drug dissolved in it other solid layer of chocolate base. This supernatant was then filteredto remove any traces of chocolate remaining in it. Then this liquid sample was analyzed by UV spectrophotometer against phosphate buffer pH 6.8 as a blank **[12]**.

***In Vitro* Drug Release:** In vitro drug release study of Medicate Chocolate formulation was performed in USP dissolution apparatus Type 1 (Basket), using pH 6.8 phosphate buffer as a dissolution media. The jars of the dissolution apparatus was filled with 900 mL of phosphate buffer pH 6.8 was placed and allowed to attain a temperature of 37±0.5ºC at 50 rpm. Medicated chocolate put in vessel. Apparatus was turned on at 50 rpm for 80 minute 10ml sample was withdrawn at every 10 minute interval and volume was replaced with equal quantity of fresh medium. The collected samples were filtered using whatman filter paper. Appropriate dilutions was prepared and analyzed by UV Spectrophotometer at 310nm. Concentration of Ondansetron and % cumulative percentage release was determined **[12]**.

STABILITY STUDY

Stability Studies was done according to short term stability study. The formulation was packed in aluminium foil and kept in wide mouth air tight container, kept in a stability chamber at specified temperature (25 ± 5°C) and refrigerated condition (0-8°C) for one month. The chemically stability of the formulation was assessed by the estimation of %CDR in the formulation and physical stability was assessed by monitoring any change in general appearance and drug content **[4]**.

RESULTS AND DISCUSSION

Formulation of Ondensetron Medicated Chocolate

General Appearance: The color, odour and nature of powder of ondansetron were observed visually **(Table 2)**.

Determination of Wavelength by UV-visible spectrophotometer: The maximum Wavelength of Ondansetron in 0.1 N HCl was determined at 310 nm **(Figure 2)**.

Determination of Wavelength using UV-visible spectroscopy: The maximum Wavelength of Ondansetron in phosphate buffer (pH6.8) was measured at 310nm **(Figure 3)**.

Preparation of Calibration Curve of Ondansetron:

Calibration curve of Ondansetron in phosphate buffer pH 6.8: The calibration curves of Ondansetron in phosphate buffer pH 6.8 was prepared and shown below in **Figure 4** and the absorbance values are mentioned in **Table 3**.

Calibration curve of Ondansetron in 0. 1 N HCl: The calibration curves of Ondansetron in 0.1N HCl was prepared and shown below **Figure 5** and absorbance values are shown in **Table 4**.

Melting Point of Drug Determination:- Melting point of Ondansetron was determined by capillary method. The melting point of Ondansetron was studied and the results are shown below in **Table 5**.

Drug Excipients Compatibility Studies using FTIR:

FTIR spectra of Ondansetron showed that, the drug was in stable form in the chocolate formulation and also there were not any interaction showed by the excipients. Between physical mixture of drug and cocoa powder, FTIR of pure drug showed that the drug was free from impurities hence the drug was in pure from. The FTIR spectral band is shown below in **Figure 6** and **Table 6** for ondansetron and **Figure 7 and Table 7** for the drug and cocoa powder combination.

EVALUATIONS OF DRUG AND EXCIPIENT

Evaluation of Chocolate Base

Taste, texture and mouth feel characteristics assessment: Taste, texture & mouth feel characteristics of chocolate were evaluated by taking panel of 10 human volunteers. The results of taste, texture and mouth feel characteristics are shown in **Table 8**.

Viscosity determination of Chocolate formulations: Viscosity of Chocolate base was determined by Brookfield Rotational Digital Viscometer and results are shown in **Table 9**.

Evaluation of Medicated chocolates:-The following Parameters were evaluated of medicated chocolate and results are shown in below

General Appearance: General appearance of medicated chocolate of Ondansetron were studied and the results are shown in **Table 10**.

Hardness, Melting point and Dimension of medicated formulations: The Hardness, Melting point and Dimension of medicated chocolate of Ondansetron were studied and the results is shown in **Table 11**.

Moisture content, Weight variation and Drug content of medicated formulation: Moisture loss, Weight variation and Drug content of medicated chocolate of Ondansetron were studied and the results are shown in **Table 12**.

Blooming test: There was no blooming observed in any formulation F1-F6

***In Vitro* Drug Release Study:** The result for percentage cumulative drug release from formulations F1 to F6 (n = 3) of Medicated chocolate of Ondansetron is shown **Table 13**.

STABILITY STUDY OF MEDICATED CHOCOLATE OF BEST FORMULATION

Stability study of medicated chocolate was performed and was found to be stable at room temperature (25ºC/75% RH) and refrigeration temperature (2ºC-8ºC). Hence, there was no significant change found in physical appearance. These were shown in the **Table 14**.

Table 2: General appearance of drug

S. No.	Parameters	Observation
1	Colour	White
2	Odour	Odourless
3	Nature of powder	Amorphous powder

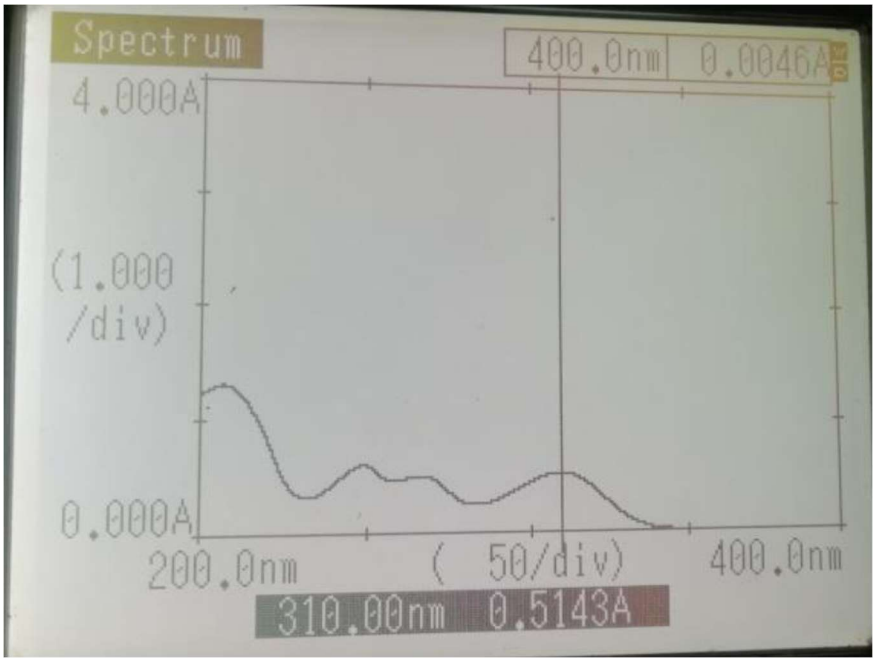

Figure 2: Absorption maximum of Ondansetron in 0.1 N HCl

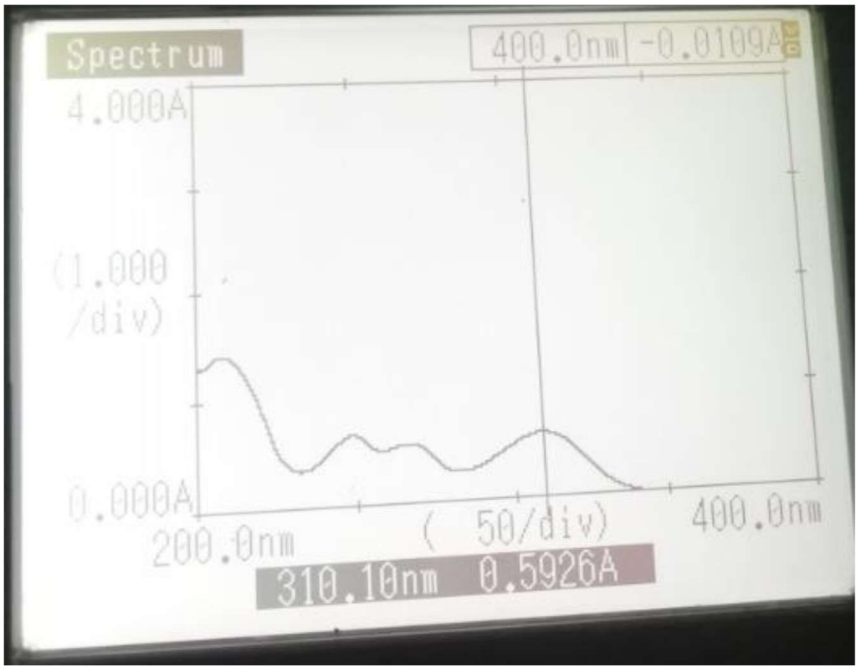

Figure 3: Absorption maximum of Ondansetron in phosphate buffer (pH6.8)

Table 3: Absorbance of ondansetron in phosphate buffer pH 6.8

S. No.	Concentration (µg/ml)	Absorbance
1	2	0.204 ± 0.0015
2	4	0.451 ± 0.0015
3	6	0.685 ± 0.0025
4	8	0.898 ± 0.001
5	10	1.04 ± 0.02

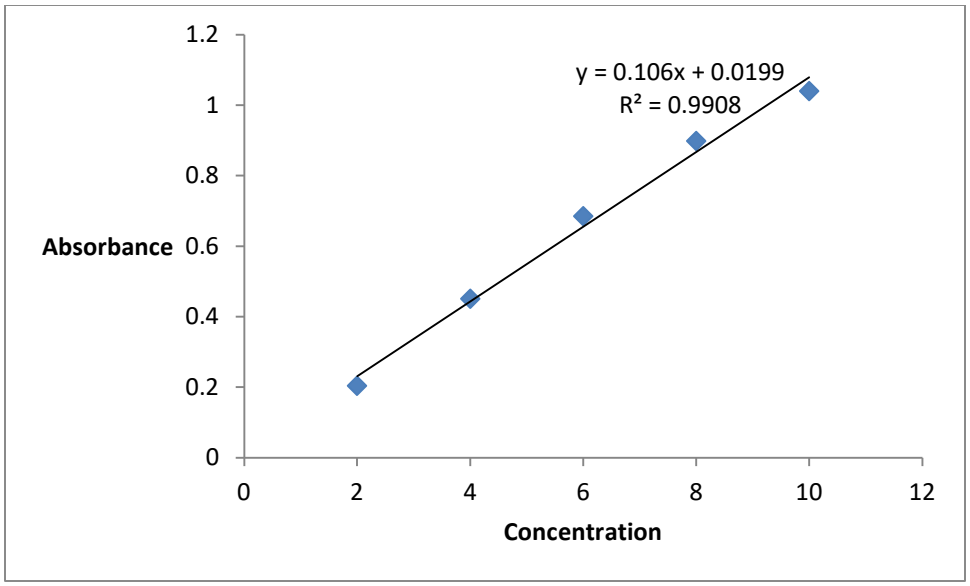

Figure 4: Calibration Graph of phosphate buffer pH 6.8

Table 4: Calibration of ondensatron in 0.1N HCl

S. No.	Concentration (µg/ml)	Absorbance
1	2	0.139 ± 0.0015
2	4	0.338 ± 0.0015
3	6	0.542 ± 0.047
4	8	0.701 ± 0.0508
5	10	0.773 ± 0.0025

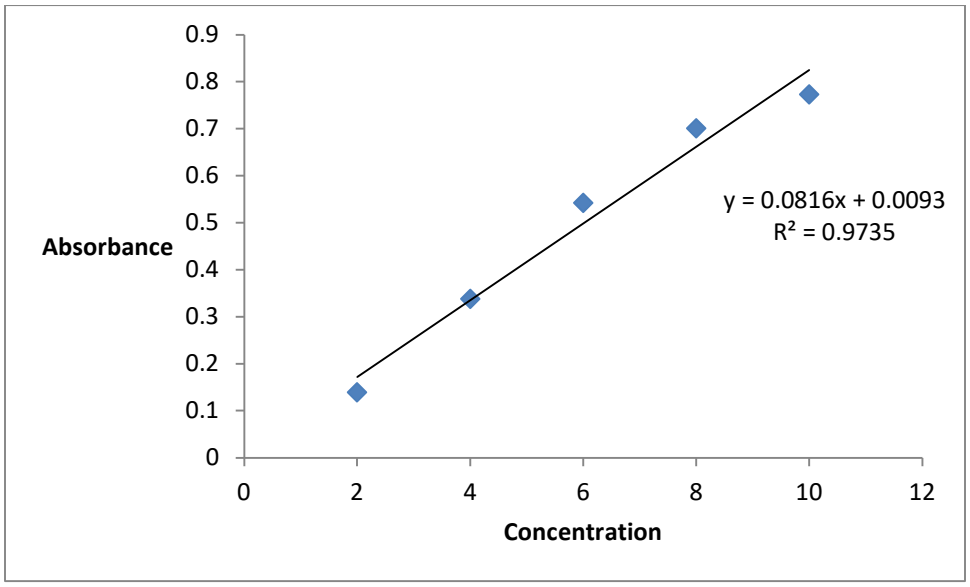

Figure 5: Calibration Graph of ondensetron in 0. 1 N HCl

Table 05: Melting point of ondensatron

S. No.	Melting Point	Reference
1	230-240°C	231-232°C

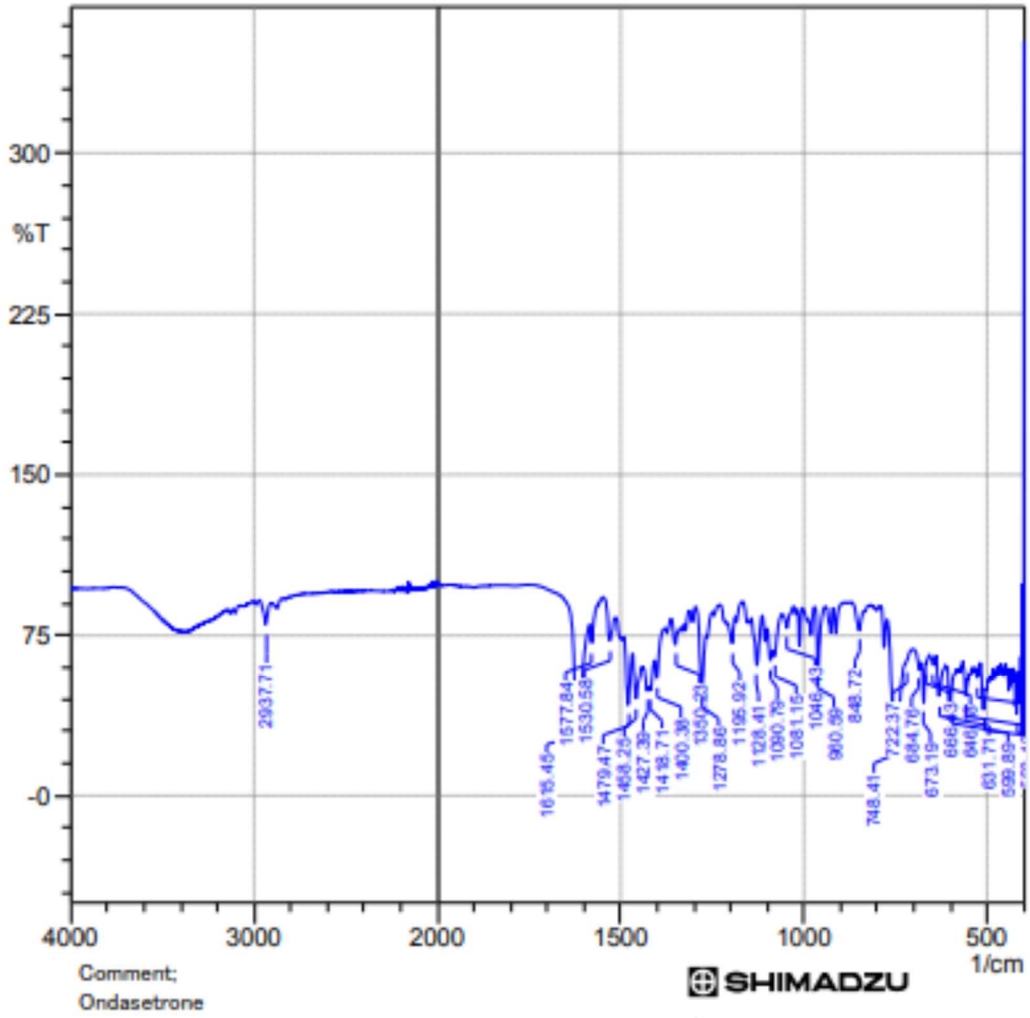

Figure 6: FTIR Spectra of Ondansetron

Table 6: Peaks observed in FT-IR of ondensatron

S. No.	Standard Frequency	Functional Group	Observed Frequency
1	3000 – 3700	N-H	3300-3500
2	1600 – 1500	C-C Aromatic	1577.84
3	1600 – 1900	C=O	1615.45
4	1450 – 1400	αCH2 for ketone Stretching	1458.47
5	1225 – 950	C-H Bending	960.59
6	680 – 610	C-H Bending	684.76

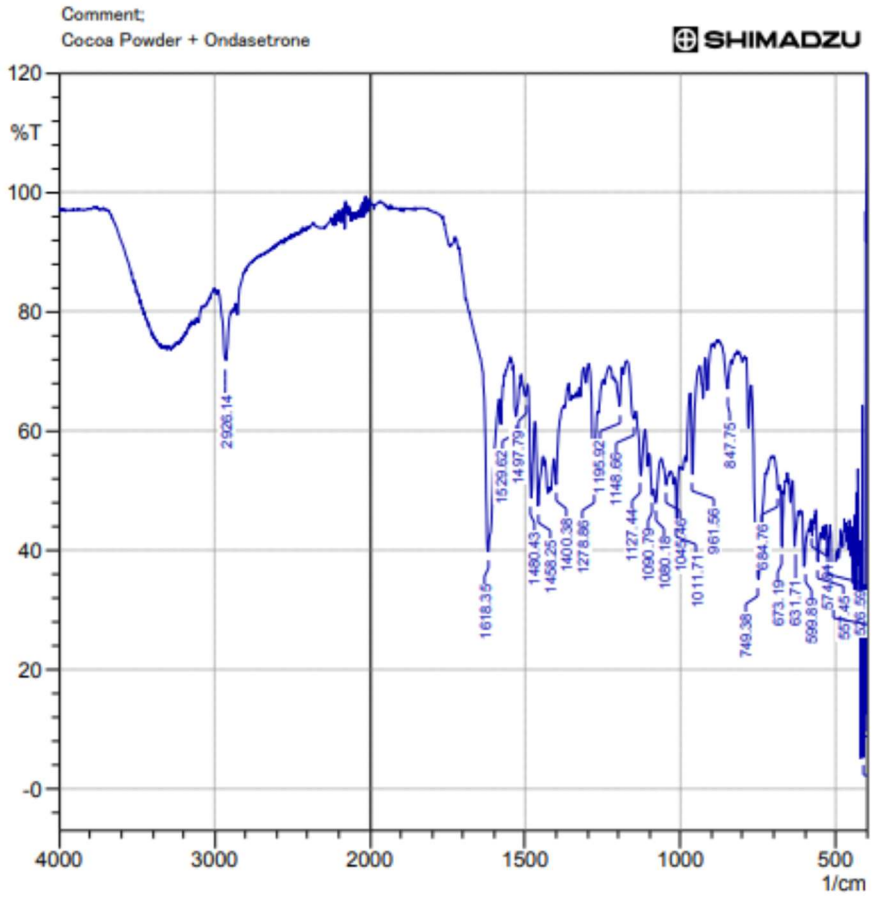

Figure 7: FTIR Spectra of Physical mixture (Ondansetron + Cocoa powder)

Table 7: Peaks observed in FT-IR of ondensatron and cocoa powder mixture

S. No.	Standard Frequency	Functional Group	Observed Frequency
1	3300-3500	N-H	3300-3500
2	1615.45	C=O	1615.45
3	1458.25	sαCH2 for ketone Stretching	1458.25
4	960.59	C-H Banding stretching	960.59
5	684.76	C-H Banding	684.76

Table 8: Taste, texture and mouth feel characteristics sense

S. No.	Characters	Criteria	Results
1	Appearance	Glossy in appearance	1-5 with 5 being the best
2	Smell	Chocolaty smell with flavor, no chemical smell	1-5 with 5 being the best
3	Cracking	Break clean without crumbling or layering.	1-5 with 5 being the best
4	Taste	Chocolaty, good in taste	1-5 with 5 being the best
5	Texture	Creamy and silky, melts in mouth	1-5 with 5 being the best

Table 9: Viscosity of different formulations

S. No.	Formulation	Viscosity of Formulation (cps)
1	F1	1200
2	F2	1400
3	F3	1100
4	F4	1300
5	F5	1200
6	F6	1100

Table 10: General appearance of Formulation F1- F6

S. No.	Formulation	Colour	Odour	Taste	Texture
1	F1	Dark Brown	Pleasant	Semi Sweet	Smooth
2	F2	Dark Brown	Pleasant	Semi Sweet	Smooth
3	F3	Dark Brown	Pleasant	Sweet	Smooth
4	F4	Dark Brown	Pleasant	Semi Sweet	Smooth
5	F5	Dark Brown	Pleasant	Sweet	Smooth
6	F6	Dark Brown	Pleasant	Semi Sweet	Smooth

Table 11: Hardness, Melting point and Dimension of formulations F1 –F6

S. No.	Formulation Code	Hardness (Kg/cm2) Mean ± SD	Melting point (°C)	Dimensions (cm) Mean ± SD
1	F1	2.5±0.1	34°C	1.163±0.03786
2	F2	2.76±0.05774	36°C	1.07±0.0007
3	F3	2.566±0.05774	36°C	1.196±0.03055
4	F4	2.5±0.1	35°C	1.27±0.03464
5	F5	2.533±0.11547	33°C	1.23±0.05568
6	F6	2.4±0.2	34°C	1.18±0.02082

Table 12: Moisture content, Weight variation and Drug content of formulation F1-F6

S. No.	Formulation Code	%Moisture content Mean ± SD	Weight variation (gm) Mean ± SD	Drug content (%) Mean ± SD
1	F1	0.7794±0.0699	1.4833±0.0035	87.06 ± 0.0029
2	F2	0.7474±0.0357	1.4857±0.0439	90.18 ± 0.045
3	F3	0.961±0.0635	1.512±0.002	94.59 ± 0.067
4	F4	0.76033±0.0441	1.4987±0.0031	92.01± 0.087
5	F5	0.623±0.10059	1.508±0.0026	93.20 ± 0.078
6	F6	0.70603±0.00331	1.514±0.002	96.62 ± 0.012

Table 13: Percentage cumulative drug release of Ondansetron (n = 3)

S. No.	Time (Min.)	% cumulative drug release					
		F1	F2	F3	F4	F5	F6
1	10	20.12±0.2	31.83±0.004	38.1±0.899	33.74±0.047	27.29±0.67	52.54±0.01
2	20	25.89±0.038	40.27±0.06	51.91±0.008	39.03±0.050	30.73±0.089	62.68±0.04
3	30	45.78±0.003	43.23±0.8	60.66±0.34	49.98±0.002	45.55±0.087	71.27±0.089
4	40	60.56±0.056	57.74±0.1	63.48±0.2	58.29±0.001	47.88±0.078	76.98±0.0021
5	50	70.13±0.034	63.96±0.009	73.43±0.001	64.10±0.001	64.99±0.347	82.83±0.038
6	60	76.00±0.087	69.64±0.6	83.12±0.087	70.98±0.014	70.75±0.678	88.55±0.005
7	70	78.9±0.008	77.70±0.005	85.64±0.08	74.65±0.003	76.51±0.021	91.54±0.067
8	80	79.67±0.006	82.75±0.65	86.96±0.03	86.22±0.09	82.11±0.436	94.52±0.034

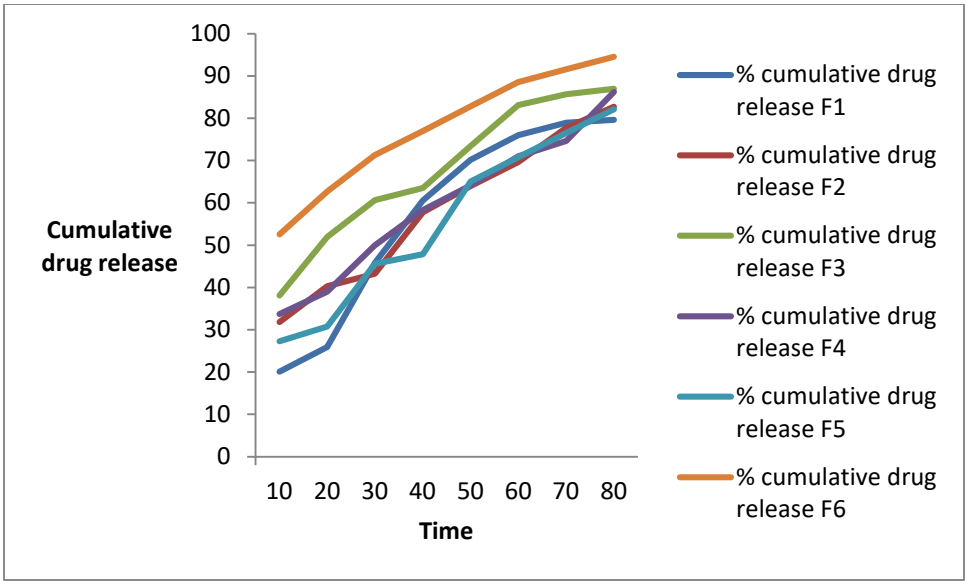

Fig no 8: Percentage cumulative drug release of Ondansetron

Table 14: Stability Study of Medicated Chocolate

S.NO.	Condition	Testing (Day)	Hardness	Melting point (°C)	%CDR
1	Room temperature (25°C/75% RH)	Initial	2.4	34	94.52
2		15 days	2.3	34	94.52
3		30 days	2.0	36	93.56
4	Refrigeration temperature (2°C-8°C)	Initial	2.4	34	94.52
5		15 days	2.5	36	94.52
6		30 days	2.6	38	93.78

SUMMARY AND CONCLUSION

Ondansetron is a carbazole derivative and anti-emetic drug with bitter in taste used vomiting. Ondansetron competitively block the action of serotonin at 5HT3 receptor that suppresses nausea and vomiting center in Medulla Oblongata in brain. In order to make it compatible for pediatric patient's medicated chocolate of Ondansetron was prepared to eliminate its bitter taste.

In this research the preformulation study was performed where drug identification, solubility and drug excipient interaction were done. Then we prepared six batches F1-F6 of medicated chocolate in different concentrations of cocoa butter and lecithin. Medicated chocolate of Ondansetron was formulated using cocoa powder, cocoa butter, sucrose, milk powder, sodium benzoate and chocolate flavor.

Firstly the evaluation of chocolate base was performed on the basis of its taste, texture, mouth feel and viscosity. Then the evaluation of medicated chocolate containing Ondansetron was done by general appearance, weight variations, dimension, hardness, moisture content, blooming test, drug content, melting point of medicated

chocolate, *in-vitro* drug release and stability studies was performed. The evaluation of chocolate base and medicated chocolate provided acceptable result of drug content 96.62% and *in-vitro* drug release 94.52%. From above mention evaluation parameters from all 6 formulations. The F6 formulation was found to be the best from other formulations then F6 formulation were kept for further stability studies.

The objective of the present study was to develop a palatable medicated chocolate formulation for pediatric administration and to increase patient's desire to consume the medication. Further, clinical studies to be done before exploit it into the market.

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