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NOVEL APPROACH TO PEDIATRIC ANTI-NAUSEA: FORMULATING & EVALUATING ONDANSETRON-INFUSED CHOCOLATE

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ABSTRACT*:* Ondansetron is a widely used anti-emetic for managing nausea and vomiting caused by chemotherapy, gastroenteritis, motion sickness, and morning sickness. Traditional formulations include dispersible tablets, syrups, and injections, but these can be challenging for pediatric patients due to the bitter taste of ondansetron. To enhance palatability and patient compliance, we propose the development of a novel dosage form: ondansetron-infused chocolate. This innovative approach leverages chocolate's natural appeal to pediatric patients, effectively masking the drug's bitterness. By utilizing a chocolate base, we aim to improve the acceptability of ondansetron, thereby ensuring better adherence to treatment regimens. This chocolate drug delivery system represents a versatile and child-friendly technology, potentially transforming how pediatric anti-emetic therapy is administered.

Keywords: Ondansetron, Pediatric, conventional formulation

1. INTRODUCTION

Frequent oral administration of various drugs can be challenging, especially for pediatric patients who often struggle with swallowing. To address this, pharmaceutical companies are developing innovative formulations like disintegrating tablets, dry syrups, lozenges, and oral films. Pediatric patients require specially designed oral drug delivery systems due to their ongoing development and varying dosing needs. Conventional formulations are not always suitable, leading to practices like manipulation and compounding. Developing age-appropriate formulations is complex, requiring careful consideration of pharmaceutical and clinical factors to ensure quality, safety, and efficacy, as drug pharmacokinetics and pharmacodynamics can vary significantly with a child's developmental stage. [1] Ondansetron is used to prevent nausea and vomiting that is caused by cancer medicines (chemotherapy) or radiation therapy. It is also used to prevent nausea and vomiting that may occur after surgery. Its Molecular Weight is 293.4g/mol, Class: Serotonin 5- HT3 – receptor antagonist, belong to II class of BCS

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classification, its Half life is 8hours (8mg), Chemically it is Weak base and Soluble in water, methanol, ethanol. Its Color is Yellow colour.

1.1. Therapeutic Benefits Of Chocolate[13,14,15]

1. Diuretic properties
2. Vasodilation
3. Improving cardiac functioning
4. Fighting against tooth decay
5. Muscle relaxation
6. Anti-cancer and anti-inflammatory properties
7. Prevention of heart disease
8. Anti-depressant properties.
9. Improving memory

1.2 Mechanism of Chocolates

Cocoa is rich in natural antioxidants, such as procyanidins, epicatechin, and catechin, which protect cell membranes, DNA, and prevent LDL cholesterol oxidation, thereby reducing atherosclerosis risk. Dark chocolate, with 12 mg of catechins and 41.5 mg of epicatechins per 100 gm, enhances HDL cholesterol levels and offers various health benefits, including improved antioxidant activity, fat oxidation, and resistance to LDL oxidation. Epicatechin, a key bioactive compound, improves endothelial function, lowers blood pressure in hypertension, and protects against endothelial dysfunction, partly through nitric oxide.

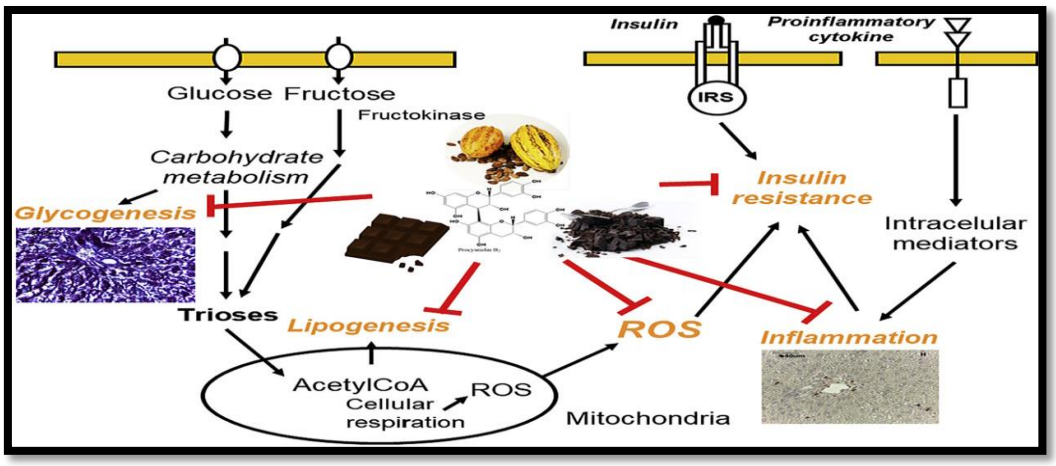

Figure 1: Mechanism Action of Chocolate

ISSN: 2519-9889
Impact Factor: 5.958

1.3 Chocolate Manufacturing Processes [12, 13]

- **Mixing**: Ingredients like cocoa liquor, sugar, cocoa butter, milk fat, and milk powder are mixed in batch or continuous mixers. Batch mixing lasts 12–15 minutes at 40–50°C, while continuous mixing uses automated kneaders to achieve a tough texture and plastic consistency.
- **Refining**: This process smooths the chocolate by reducing particle size to under 30 µm using two- and five-roll refiners. It affects the texture and sensory properties of the final product.
- **Conching**: The final step in chocolate production, conching involves agitating chocolate at over 50°C for several hours to enhance texture, flavor, and reduce moisture and undesirable volatiles.
- **Tempering**: To prevent uncontrolled crystallization and rough surfaces, tempering selects the optimal crystal form of cocoa butter.
- **Molding and Demolding**: Chocolates are poured into molds of desired size and shape, with molds lubricated for easy removal of the finished product.

1.4 Mechanism Action of Anti-Emetics

- Centrally acting antiemetics are generally much more effective than peripheral-acting antiemetics. Centrally acting antiemetics that work on the medullary vomiting center are often more effective than those that act just at the chemoreceptor trigger zone.
- Promazine derivatives (e.g., chlorpromazine, prochlorperazine) are effective centrally acting antiemetics, but they can cause hypotension due to α-adrenergic blocking activity.
- Metoclopramide works at the chemoreceptor trigger zone and is also a gastric prokinetic. Metoclopramide can sometimes cause abnormal behavior and even vomiting (possibly due to excessive gastric prokinetic activity).
- The 5-HT_3 receptor antagonists ondansetron and dolasetron are among the most effective anti-emetics used in human as well as animals, and they have very few side effects.

Table 1: Formulation of medicated chocolate

S.No.	INGREDIENTS	CATEGORY	QUANTITY(mg)		
			F1	F2	F3
1	Ondansetron	Drug	4	4	4
2	Cocoa powder	Principle ingredient	1445	1540	1536
3	Cocoa butter	Solidifying agent	1080	1096	1100
4	Milk powder	Emulsifier	_	830	845
5	Pharmaceutical grade sugar	Sweetening agent	1471	1530	1500
6	Mango essence	Flavouring agent	_	_	15
		Total Weight	4000	5000	5000

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Impact Factor: 5.958

2. EVALUATION PARAMETER

2.1 Preformulation Studies[30]

A) Determination of Solubility of Drugs

The solubility of Ondansetron was determined by using stimulated gastric fluid without enzymes at pH 1.2, pH 6.8 (phosphate buffer) and pH 7.4 (phosphate buffer) respectively. The solubility of the API was determined by the equilibrium solubility method.

B) Determination of Melting Point

Melting point was determined to check the purity of substance .It was performed by capillary tube method. Capillary tube with drug was filled up to 3mm high and sealed at one end. It was placed in the melting point apparatus (Guna) with the closed end pointed down. Temperature was recorded when the sample first starts to melt and ends when sample is completely melted.

C) Determination of Partition Coefficient

oil-water partition coefficient, crucial for drug absorption and delivery, was studied using n-octanol as the oil phase and water (1:1) as the aqueous phase. Equal volumes of the two phases were mixed in a separating funnel, with a weighed amount of drug added. After saturating for 2 hours at room temperature, the partition coefficient was determined. The two phases were separated and drug content was analyzed. The partition coefficient was measured by using the formula

(Log p= Conc of drug in oil phase / Conc of drug in aqueous phase)

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

- **Preparation of Calibration Curve of Ondansetron:**

Calibration curve of Ondansetron in phosphate buffer pH 6.8: The calibration curves of Ondansetron in phosphate bufferpH 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. 1N HCl: The calibration curves of Ondansetron in 0.1N HCl was prepared and shown below and absorbancevalues.

- **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 for ondansetron and for the drug and cocoa powder combination

ISSN: 2519-9889
Impact Factor: 5.958

2.2. Formulation and Optimization Of Chocolate Base

2.2.1. Optimization of cocoa butter Concentration

Chocolates were formulated with a total fat of 25-35% (w/w) from cocoa liquor and cocoa butter with more than 34% total cocoa, Chocolate base was prepared as per composition specified for dark chocolate (European Commission Directive, 2000; Codex Revised Standard, 2003)

2.2.2. Method of preparation of Chocolate base

Sugar and water were heated in an oven at 50ºC for 4-5 minutes to prepare a syrup. Cocoa butter was also heated in the oven for 1 minute. The sugar syrup was then combined with cocoa powder and mixed thoroughly, ensuring the temperature remained controlled. The mixture was cooled to a semisolid consistency before adding flavor.

2.2.3. Formulation of Medicated Chocolate [41]

Oven was set at 50°C. Then chocolate base was melted till it becomes free flowing liquid. After above step; required quantity of drug was added. Then whole mass was stirred well with the help of magnetic stirrer to ensure uniform mixing. Then the above mixture was poured in a polycarbonate set mould and refrigerated for 15 min3 until solidification.

2.3 Post-Formulation Studies [32]

Physical Observation

Ten medicated toffee was weighed and observed physically to study the surface characteristics and shape. Surface characteristics and shape of the medicated toffee was evaluated by physical observation. It is important to check for the absence of pitting, fat blooming, sedimentation and migration of active ingredients**.**

Hardness

The hardness of the medicated chocolate were determined using Monsanto Hardness tester. It is expressed in kg/cm$^{2.}$ Six chocolate were randomly picked from each formulation and the mean and standard deviation value were calculated

Weight Variation:

Medicated toffee can be weighed on an automatic balance, obtaining the weight of 10 medicated toffee. All the medicated toffee was weighed and average weight was calculated. Then all the medicated toffee was weighed individually and the variation from average weight was calculated.

Thickness and diameter

The thickness and diameter of the ten medicated toffee is the only dimensional variable related to the molding process. Thickness and diameter of the dosage form were measured by Vernier caliper. The deviation of each is calculated and the deviation of individual unit from t

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Impact Factor: 5.958

Viscosity

Viscosity, put simply, resistance to flow is a critical material property for many manufactured liquids. Accurate viscosity measurements under relevant test conditions are a necessity for anybody involved in the formulation, transport, storage and handling of suspensions, emulsions, solutions and melts. The mean diameter should not exceed ± 5%.

Determination of Drug Content

Drug content of a medicated chocolate was measured by dissolving it in 10 ml ethanol and it is sonicated. Then this sonicated mixture was centrifuged for 15 min at 2500 rpm. Supernatant solution was filtered to remove any chocolate traces and the drug content was analysed and determined by using UV Spectrometer maximum absorbance at 310 nm with water.

In-Vitro Drug Release [32-33]

In vitro drug release study of medicated toffee was performed in USP dissolution apparatus Type II (Rotating Paddle), using pH 6.8phosphate buffer as a dissolution media. The bowls of the dissolution tester was filled with 900mL of pH 6.8 phosphate buffer was placed and allowed to attain a temperature of 37±0.5ºC and 50rpm. A chocolate formulation was placed in the basket. At predetermined time interval i.e. 1, 2, 3, up to 60 minutes, 10mL sample was withdrawn and volume was replaced with equal quantity of fresh medium.

3. RESULT AND DISCUSSION

3.1 Preformulation Study

3.1.1 Determination of solubility of drug

Ondansetron is a weak base (pKa = 7.4), and under the acidic condition is water soluble. The natural pH of ondansetron hydrochloride solutions is about 4.5 to 4.6. The solubility is markedly reduced in solutions for which the pH greater than or equal to 6.

3.1.2. Determination of melting point

The melting point was determined by capillary method and the results are 230^0 c.The obtained results are similar to value reported in literatures, indicating the purity of the drug substances.

3.1.3. Determination of partition coefficient

Partition coefficient of Ondansetron was determined out in distilled water and n-octanol and the results are 0.12.

3.2. CHARACTERIZATION OF CHOCOLATE BASE

3.2.1. Determination of viscosity of chocolate base

Viscosity was measured by Brookfield rotational digital viscometer and the spindle was rotated at 60 rpm.

ISSN: 2519-9889
Impact Factor: 5.958

3.3. CHARACTERIZATION OF MEDICATED TOFFEE

3.3.1. Physical observation

Table 2: Physical observation

S.No	CHARACTERISTICS	RESULT
1	Colour	Dark brown
2	Odour	Pleasant
3	Taste	Sweet
4	Texture	Smooth
5	Appearance	Glossy
6	Shape	Square

- **Determination of Wavelength using UV-visible spectroscopy**

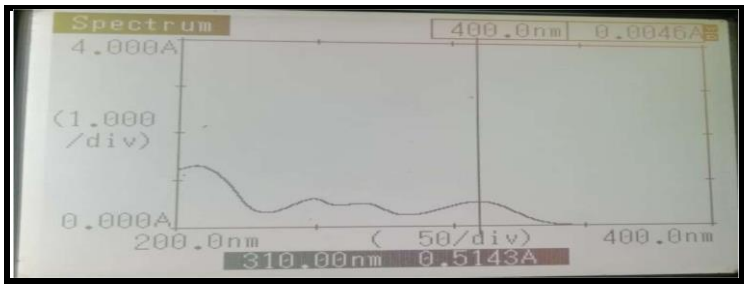

Figure 2: Absorption maximum of Ondansetron in 0.1 N HCl

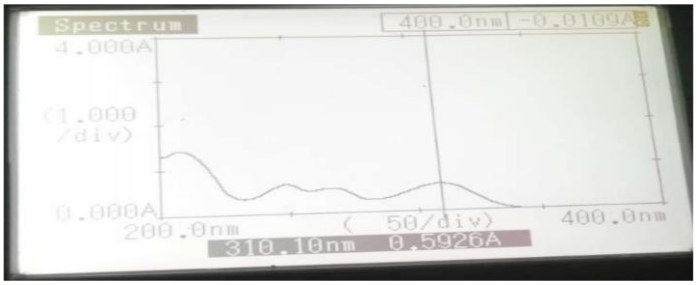

Figure 3: Absorption maximum of Ondansetron in phosphate buffer (pH6.8)

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

S. No.	Concentration (µg/ml)	Absorbance
1	2	0.205 ± 0.0015
2	4	0.450 ± 0.0015
3	6	0.684 ± 0.0025
4	8	0.897 ± 0.001
5	10	1.04 ± 0.02

ISSN: 2519-9889
Impact Factor: 5.958

Table 4: Absorption maximum of Ondansetron in in 0.1 N HCl

S. No.	Concentration (µg/ml)	Absorbance
1	2	0.205 ± 0.0015
2	4	0.452 ± 0.0015
3	6	0.684 ± 0.0025
4	8	0.898 ± 0.001
5	10	1.04 ± 0.02

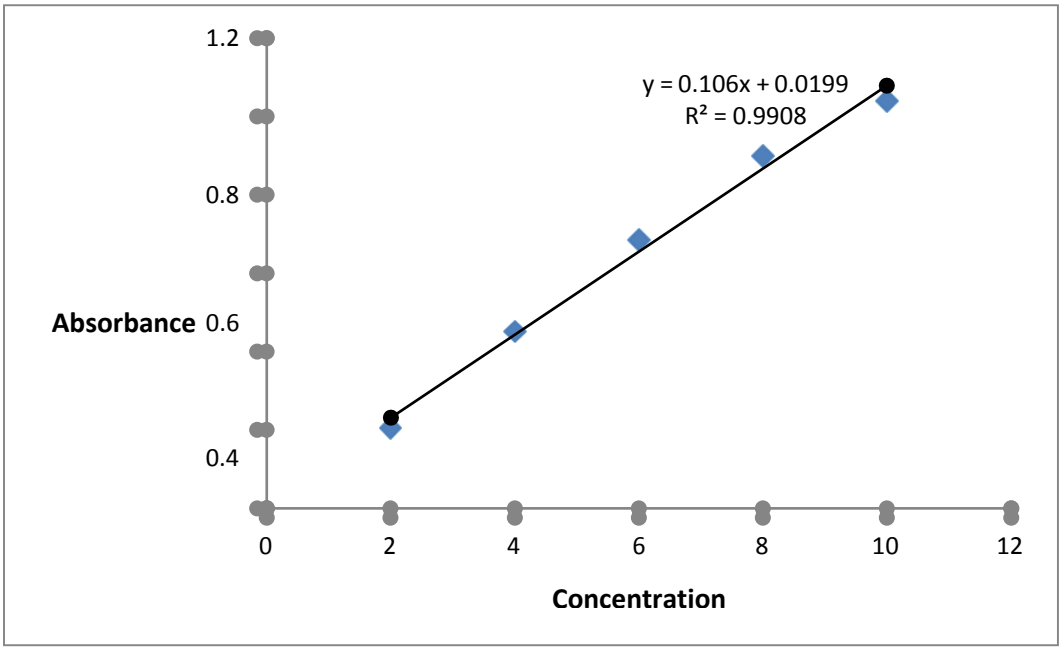

Figure 4: Calibration Graph of phosphate buffer pH 6.8

Table 5: 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

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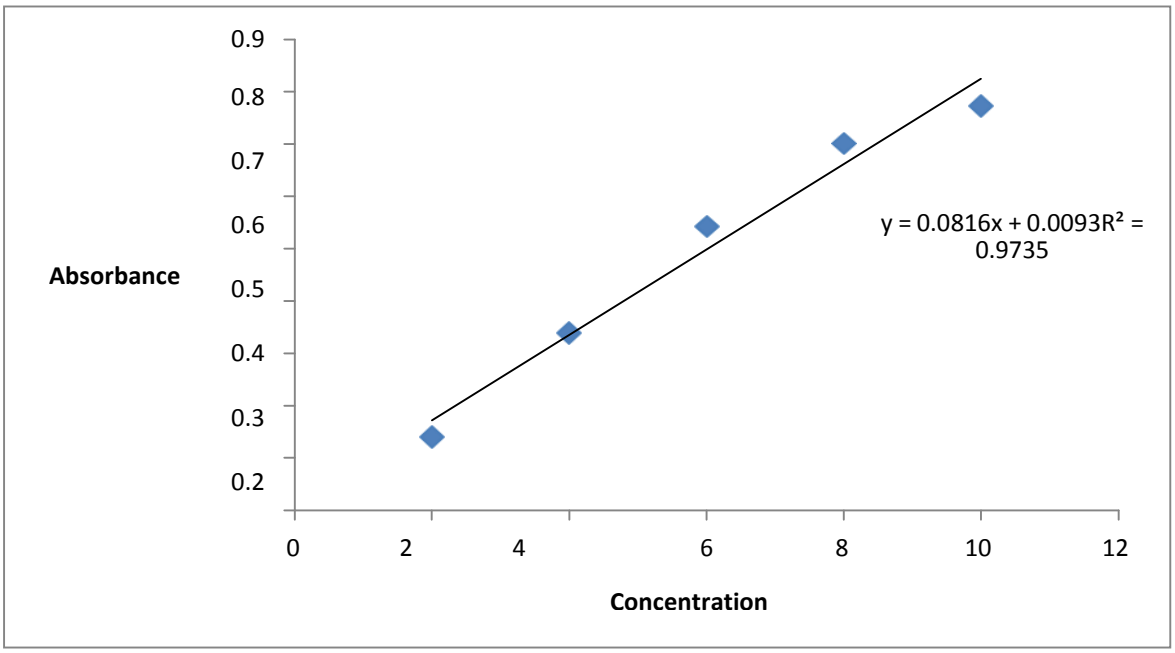
Impact Factor: 5.958

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



Drug Excipients Compatibility Studies using FTIR:

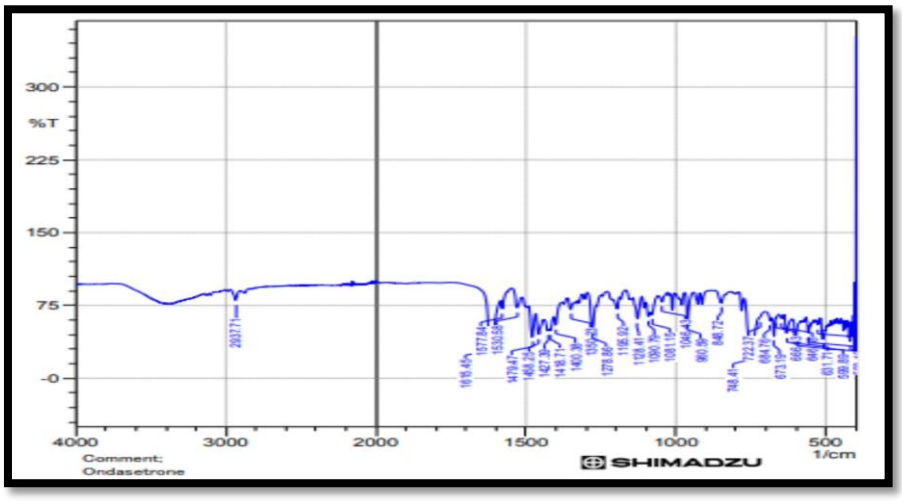


Figure 6: FTIR Spectra of Ondansetron

ISSN: 2519-9889
Impact Factor: 5.958

Table 6: Peaks observed in FT-IR of ondansetron

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

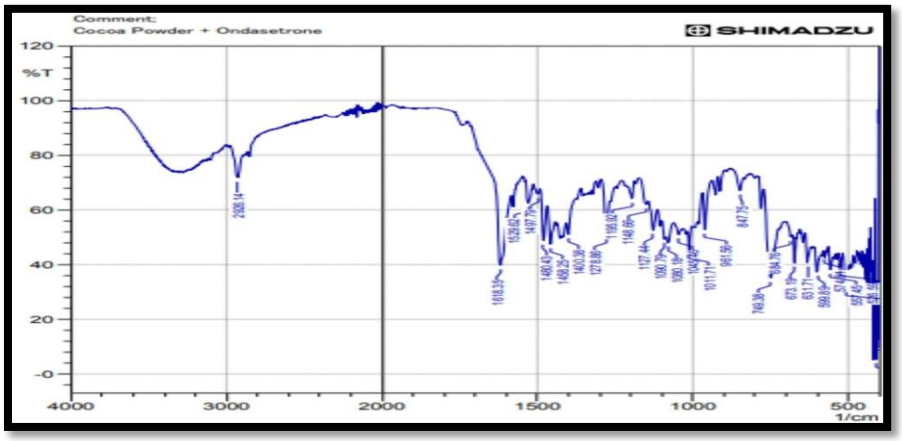


Figure 7: FTIR Spectra of Physical mixture (Ondansetron + Cocoa powder)

Table 7: Peaks observed in FT-IR of ondansetron 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

3.3.2. Weight variation test

The average weight was calculated by weighing 20 medicated Toffee and results were listed in to the below table.

Table 8: Weight variation test

S. No.	Weight of Medicated Chocolate (gm)		
	F1	F2	F3
1	4.04	5.03	5.11
2	4.02	5.10	5.13

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Impact Factor: 5.958

3	4.06	5.05	5.15
4	4.02	5.06	5.16
5	4.04	5.08	5.10
6	4.05	5.12	5.14
7	4.06	5.04	5.06
8	4.02	5.12	5.16
9	4.04	5.09	5.19
10	4.08	5.16	5.18
11	4.10	5.04	5.14
12	4.12	5.03	5.13
13	4.06	5.05	5.15
14	4.18	5.07	5.13
15	4.08	5.08	5.12
16	4.10	5.11	5.18
17	4.06	5.13	5.14
18	4.02	5.06	5.10
19	4.04	5.09	5.15
20	4.05	5.10	5.14
Average weight	**4.06**	**5.08**	**5.13**

Results indicate that none of the individual toffee weight deviates from the average weight by more than the 5% and it complies with IP standard for tablet [If the tablet weight is 250 mg or more, limit for weight variation is ±5%] e, limit for weight variation is ±5%]

3.3.3. Thickness and diameter

Table 9: Thickness of medicated chocolate

S.No.	**Thickness of medicated chocolate [mm]**		
	F1	**F2**	**F3**
1	16.20	16.89	17.03
2	16.23	16.80	17.04
3	16.24	16.85	17.02
4	16.27	16.83	17.06
5	16.25	16.88	17.04
6	16.28	16.86	17.06
Average Thickness	16.24	16.85	**17.04**

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3.4. SELECTION OF OPTIMIZED FORMULATION

Medicated toffee should possess suitable physicochemical property to mask the bitter taste. From the results obtained from the above studies, it was indicated that formulation F3 was found to be ideal and it was chosen for in vitro release and stability studies.

Figure No.8: Optimization Of Medicated Chocolate

3.5. IN VITRO DRUG RELEASE STUDIES

Evaluation of in vitro release from medicated toffee was performed using USP type II dissolution apparatus. The in vitro release behavior of the Ondansetron was summarized and cumulative percentage release shown in the below table.

Table 10: In-vitro drug release

Time[min]	Cumulative percentage release %
	Ondansetron
5	6.3
10	9.5
15	13.4
20	19.7
25	23.7
30	35.5
35	51.8
40	65.7
45	72.4
50	81.5
55	87.2
60	90.6

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Impact Factor: 5.958

4. CONCLUSION

This study focuses on developing an effective and appealing dosage form for pediatric patients by incorporating ondansetron into a medicated toffee. Ondansetron, known for its bitter taste, often leads to poor acceptance among children, who may reject or expel the medication. To address this issue, the medicated toffee formulation was designed to mask the bitterness, making it more palatable and easier for children to consume. This innovative approach not only enhances the acceptability of ondansetron but also improves patient compliance compared to traditional dosage forms such as disperse tablets, syrups, and injections. The use of a chocolate-based toffee leverages the natural appeal of chocolate to create a versatile and attractive drug delivery system, ultimately promoting better adherence to treatment and improving therapeutic outcomes in the pediatric population and batch 3 formulation give best result.

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