International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

Formulation and Evaluation of Medicated Chewing Gum Delivery of Vitamins

Drx. L.Gopi[1]*M.Pharm., S.Yamunadevi[2], P.Jothika[3], M.Ayesha Siddikha[4], K.Rohini[5], Y.Vishnu Priya[6], R.Yuvasree[7].

[1] Assistant Professor, Department Of Pharmaceutics, [2,3,4,5,6,7] B.Pharm Student.
Aadhibhagawan College Of Pharmacy, Rantham, Thiruvannamalai, Tamil Nadu.

Date of Submission: 01-11-2024 Date of Acceptance: 10-11-2024

ABSTRACT:
This study focuses on the formulation of medicated chewing gum using the melting technique. A comprehensive review of literature was conducted to guide the selection of excipients, which included sucrose, glucose, glycerin, sorbitol, calcium carbonate, and mint. The prepared chewing gums were evaluated for key parameters such as weight variation, hardness, thickness, drug content, and in-vitro dissolution, all of which met standard specifications. Comparative analysis of six formulations revealed that formulation F2 exhibited the highest drug release (98.52%) within 30 minutes. This formulation shows promise as an effective treatment for mouth ulcers, offering potential benefits for patients.

Keywords: Chewing Gum, Riboflavin, Vitamin C, Niacin, Folic Acid, Mouth Ulcer.

I. INTRODUCTION:

Buccal drug delivery offers several advantages over traditional oral administration. Delivering compounds via the oral mucosa bypasses pre-systemic metabolism in the gastrointestinal (GI) tract and hepatic first-pass elimination. Furthermore, the buccal mucosa is a well-vascularized tissue, making it easily accessible for both the application and removal of drug delivery devices. This route also allows the inclusion of permeation enhancers, enzyme inhibitors, or pH modifiers for both local and systemic effects. However, the main drawbacks of buccal drug delivery include the relatively low permeability of the buccal membrane and its limited surface area.

The buccal mucosa lines the inner cheek, and buccal formulations are placed between the upper gums (gingiva) and the cheek to treat both local and systemic conditions. The buccal route is a promising delivery pathway for large, hydrophilic, and unstable compounds such as proteins, oligonucleotides, and polysaccharides, in addition to conventional small drug molecules. The oral cavity serves as an effective site for both local and systemic drug delivery.

The challenges associated with buccal drug delivery can vary depending on whether local or systemic action is desired. For local action, one challenge is the rapid elimination of the drug due to the flushing effect of saliva or the ingestion of food, which may necessitate frequent dosing. Additionally, the non-uniform distribution of the drug in saliva after its release from a solid or semisolid delivery system may result in some areas of the oral cavity not receiving effective drug concentrations. For both local and systemic action, patient acceptability remains a concern, particularly regarding taste, irritancy, and mouth feel. Moreover, once the drug delivery patch is placed at the absorption site, it should not be disturbed, and eating or drinking must be avoided until complete absorption has occurred.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

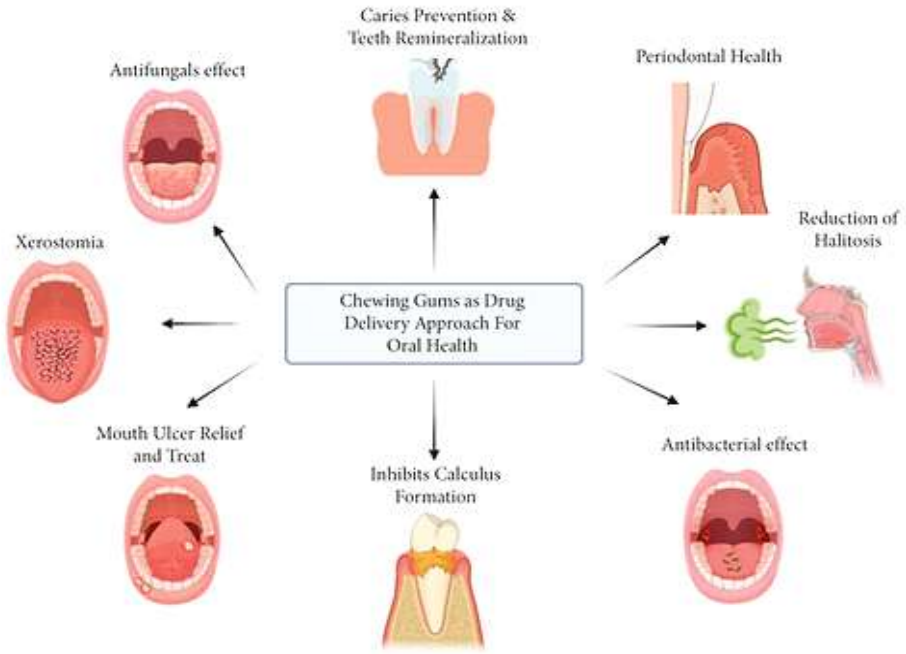


Figure: 1 Chewing Gum Drug Delivery System

II. DISEASE PROFILE:

A mouth ulcer, also known as an oral or mucosal ulcer, is a painful lesion that forms on the mucous membrane of the oral cavity, typically on the inside of the cheeks or lips. These round or oval sores are common and often occur without a serious underlying cause. Mouth ulcers can be triggered by a variety of factors, including nutritional deficiencies (such as iron, vitamin B12, and vitamin C), poor oral hygiene, infections, stress, indigestion, mechanical injury, food allergies, hormonal imbalances, and certain skin diseases. Also referred to as aphthous ulcers, they can cause discomfort while eating, drinking, or brushing teeth. Essentially, a mouth ulcer involves the loss or erosion of part of the delicate tissue lining the inside of the mouth.

Mouth ulcers can have multiple causes, with the most common being injury, such as accidentally biting the inside of the cheek. Other potential causes include aphthous ulceration, certain medications, skin rashes in the mouth, viral, bacterial, and fungal infections, exposure to chemicals, systemic medical conditions, and, in rare cases, malignancy. In most instances, mouth ulcers are harmless and typically heal on their own within 10 days without the need for treatment. Aphthous ulcers, which are recurring and have no known cause, affect approximately 20 to 30 percent of the population. If mouth ulcers persist beyond a few days or occur frequently, it is advisable to consult a dentist for further evaluation.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

Figure: 2 Mouth Ulcer

III. DRUG PROFILE:

3.1 Riboflavin:

The yellow vitamin of the B complex, essential for metabolic energy production, is riboflavin (also known as Vitamin B2). It is found in a variety of foods, including milk, liver, eggs, and green vegetables, and is also synthesized by the intestinal flora.

- **Molar mass:** 376.36 g/mol
- **Formula:** $C_{17}H_{20}N_4O_6$
- **Melting point:** 280 °C
- **Other names:** lactochrome, lactoflavin, vitamin G
- **Excretion:** Urine
- **IUPAC :** 7,8-Dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypentyl] benzo [g] pteridine-2,4-dione

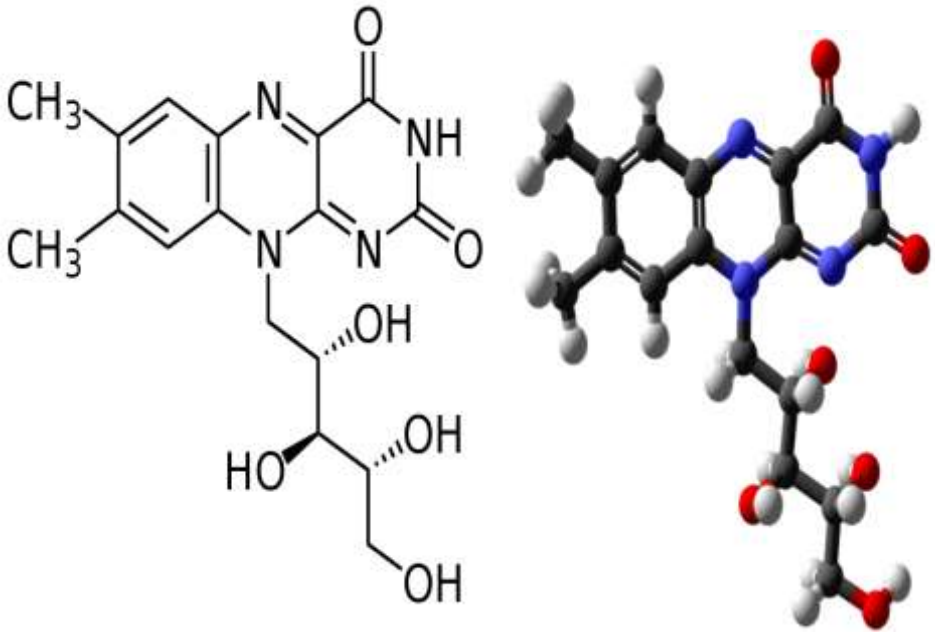


Figure: 3 Structure Of Riboflavin

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

3.2 Niacin:

Niacin, also known as vitamin B3 or nicotinic acid, is a B vitamin that plays a crucial role in converting food into energy. It is essential for maintaining the health of the nervous system, digestive system, and skin. While niacin is often included in daily multivitamins, most people obtain sufficient amounts through their diet. Niacin is an organic compound that can be synthesized by both plants and animals from the amino acid tryptophan, making it an essential nutrient for humans.

IUPAC ID: pyridine-3-carboxylic acid
Formula: $C_6H_5NO_2$
Molar mass: 123.1094 g/mol
Melting point: 237 °C
Soluble in: Water

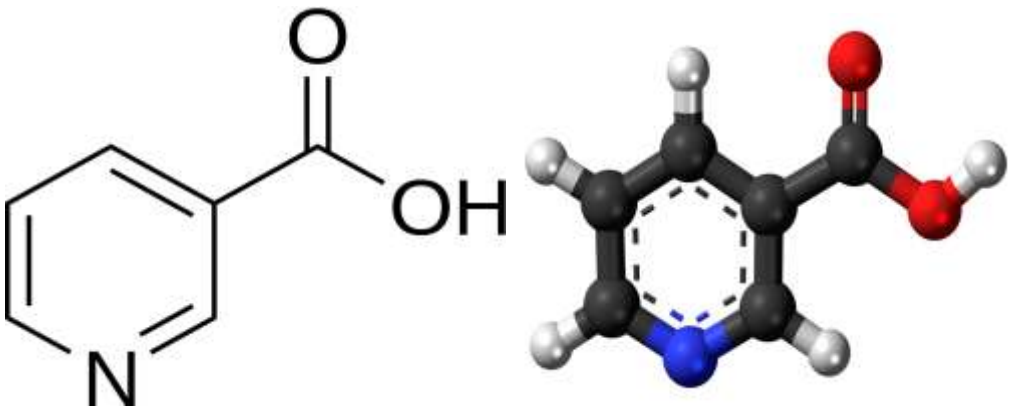
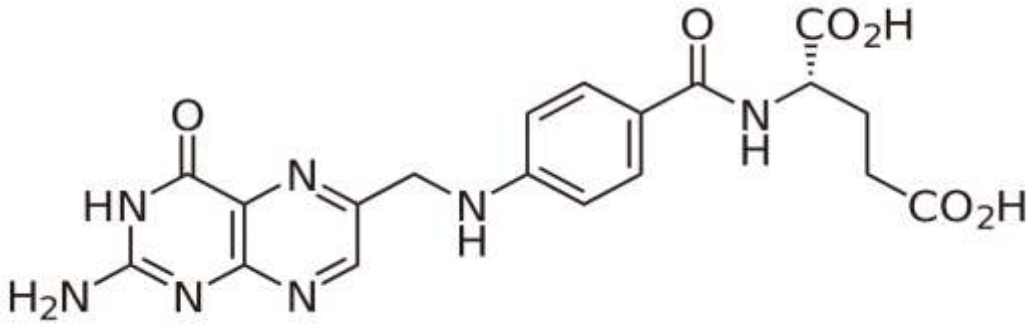


Figure: 4 Structure Of Niacin

3.3 Folic Acid:

Folic acid, a B vitamin, plays a crucial role in helping the body produce healthy new cells. It is an essential nutrient for everyone, but it is particularly important for women who may become pregnant. Adequate folic acid intake before and during pregnancy can help prevent major birth defects of the baby's brain and spine, making it a critical nutrient for maternal and fetal health.

IUPAC: (2S)-2-[(4-{[(2-amino-4-hydroxypteridin-6-yl)methyl]amino} phenyl) formamido]pentanedioic acid
Formula: $C_{19}H_{19}N_7O_6$
Molar mass: 441.4 g/mol
Melting point: 250 °C
Soluble in: Water
Metabolism: Liver



International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

Figure: 5 Structure Of Folic Acid

3.4 Ascorbic Acid:

Ascorbic acid, also known as vitamin C, is used to prevent or treat vitamin C deficiency in individuals who do not obtain enough of the vitamin from their diets. Most people with a balanced diet do not require additional ascorbic acid. A deficiency in vitamin C can lead to scurvy, a condition characterized by fatigue, gum disease, and skin issues. Vitamin C is a water-soluble vitamin found in a variety of foods and is commonly available as a dietary supplement. It is an essential nutrient that plays a vital role in tissue repair, collagen formation, and the enzymatic production of certain neurotransmitters.

Formula : $C_6H_8O_6$
Molar mass : 176.124 $g \cdot mol^{-1}$
Density : 1.694 g/cm^3
Melting point : 190 to 192 °C (374 to 378 °F)
Boiling point : 552.7 °C (1,026.9 °F)
Elimination half-life: Varies according to plasma concentration
Bioavailability: Rapid and complete
Excretion: Kidney

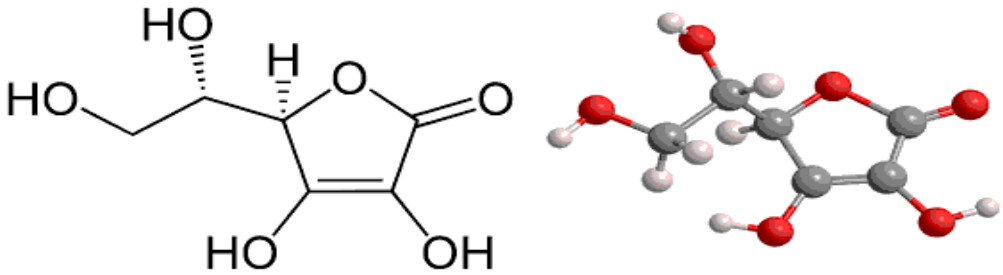


Figure: 6 Structure Of Ascorbic Acid

IV. MATERIALS AND METHODS:

4.1 Formulation Of Medicated Chewing Gum By Melting Methods:

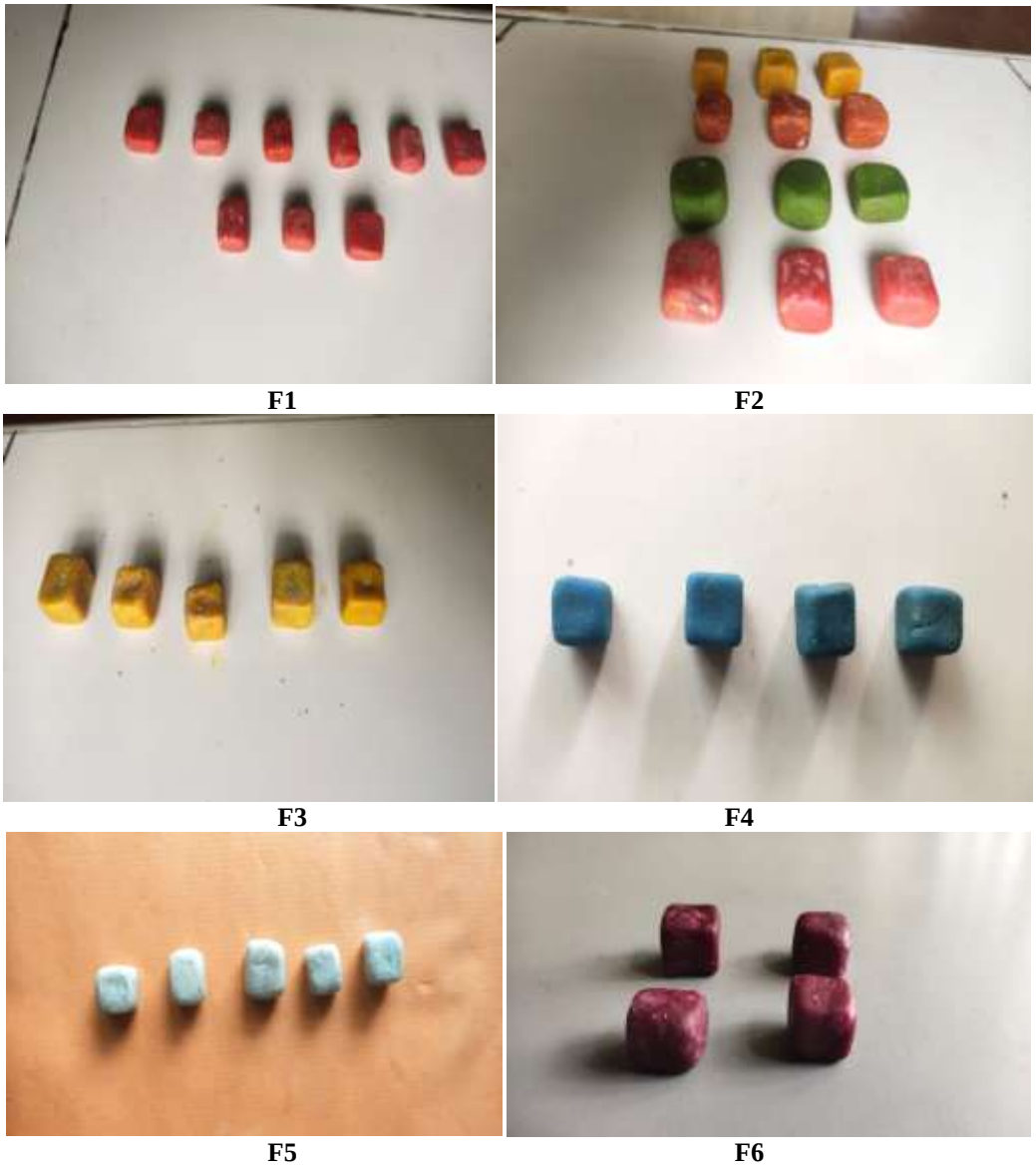
S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
1	Riboflavin	20	20	20	20	20	20
2	Niacin	10	10	10	10	10	10
3	Folic Acid	5	5	5	5	5	5
4	Ascorbic Acid	15	15	15	15	15	15
5	Gum Base	200	200	200	200	200	200
6	Glycerin	10	15	10	15	10	15
7	Sucrose	80	80	80	80	80	80
8	Glucose	20	20	25	25	30	30
9	Sorbitol	80	80	75	75	70	70
10	Calcium Carbonate	35	35	35	35	35	35
11	Flavor	5	5	5	5	5	5
12	Color	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table: 1 Formulation Of Medicated Chewing Gum

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

Procedure:

Preparation Of Medicated Chewing Gum By Melting Method (Conventional Traditional Method): Chewing gum is prepared by melting the gum base at a temperature of 60–70°C until it softens. To this molten mass, liquid glucose and glycerol are added and mixed well. The mass is then removed from the heat, and all other ingredients are added and mixed thoroughly. Finally, the mixture is rolled in calcium carbonate powder, cut into the desired size and shape. Total Weight Of Each Chewing Gum – 400 Mg



F1 **F2**

F3 **F4**

F5 **F6**

Figure: 7 Medicated Chewing Gum

4.2 Evaluation Of Medicated Chewing Gum:

4.2.1 Physical Parameter:

The general appearance of chewing gum, including its size, shape, color, odor, and taste, should be observed. It is important for the gum to have a good appearance for consumer acceptance. Physical changes may occur during storage, which can be determined by measuring the pH and melting point using a pH meter and a melting point apparatus.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

4.2.2 Thickness:
The thickness and diameter of the formulated chewing gum were measured using a Vernier caliper.

4.2.3 Weight Variation:
The formulated chewing gum was tested for weight uniformity. Twenty pieces of chewing gum were weighed both collectively and individually. The average weight was calculated from the collective weight. Each individual chewing gum's weight was then compared with the average weight to determine whether it falls within permissible limits.

4.2.4 Hardness:
The strength of the chewing gum, defined as the force required to break the gum by compression in the diametric direction, was measured in triplicate using a Pfizer tablet hardness tester.

4.2.5 Moisture Content:
The sample was weighed and crushed in a mortar. From this, one gram of the sample was weighed and placed in desiccators for 24 hours. After 24 hours the sample is weighed. The moisture content is determined by the abstracting the final weight from initial weight of chewing gum.

4.2.6 Sensory Evaluation:
Sensory evaluation of chewing gum was done, following parameters were considered like color, taste, flavor, consistency and overall acceptability. On the basis of this evaluation following results came out.

4.2.7 In-Vitro Drug Release:
In vitro release studies were conducted using USP Apparatus II (Paddle type). The dissolution test was performed with 900 mL of phosphate buffer (pH 6.8) at 37 ± 0.5°C and 50 rpm. Samples (5 mL) were collected at predetermined time intervals and replaced with an equal volume of fresh medium. The collected samples were then analyzed using a UV-Visible spectrophotometer.

4.2.8 In-vitro Release Kinetics:
To study kinetics, data obtained from in vitro release were plotted in various kinetic models.

(A) Zero order equation:
If the release rate follows Zero order then, the slope can be obtained by plotting % drug released Vs time in hours. It is an ideal release profile to achieve pharmacological prolonged action. The release rate was independent of concentration.

$$C=K_0t$$

Where,
K_0 – Zero order constant in con/time
t – Time in hours

(B) First order equation:
The graph was plotted as log % cumulative drug remaining Vs Time in hours.

$$\text{Log } C = \log C_0 - Kt /2.303$$

Where,
C_0 - Initial concentration of drug.
K- First order constant and t- Time.

(C) Higuchi kinetics:
The graph was plotted as % Cumulative drug released Vs square root of time

$$Q = Kt^{1/2}$$

Where,
K – Constant reflecting design variable system.
t -Time in hours

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one, then the particular dosage form is considered to follow Higuchi kinetics of drug release.

(D) Korsmeyer – Peppas equation:
To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs time

$$M_t / M_\infty = Kt^n$$

Where,
M_t / M_∞ -fraction of drug released at time t
t – Release time
K – Kinetic constant
n - Diffusional exponent indicative of the mechanism drug release.

The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log time.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

4.2.9 HPLC Analysis:

(A) Sample Preparation:

- **Weighing the Chewing Gum**: Accurately weigh a known amount of chewing gum (typically 1–2 grams depending on the gum's ingredients and the test requirements).
- **Extraction**: Chewing gum contains insoluble gum base materials, so it needs to be extracted before HPLC analysis. The extraction process will vary based on the compound of interest (e.g., flavor compounds, sweeteners, or active pharmaceutical ingredients). A common extraction method is:
- **For water-soluble compounds**: Use water or an aqueous buffer (e.g., phosphate buffer) to dissolve the soluble components.
- **Sonication**: The sample may be sonicated for 10–15 minutes to facilitate extraction.
- **Filtration or Centrifugation**: Filter the extract (using a 0.45 µm filter or centrifuge if necessary) to remove particulate matter.
- **Dilution**: Dilute the extract with an appropriate solvent if necessary to bring the concentration of analytes within the linear range of the HPLC method.

(B) Preparation of Calibration Standards

- Prepare a series of known concentrations of the analytes you want to measure (e.g., sweeteners, flavor compounds, or active ingredients) in the same solvent or buffer used for the sample preparation.
- Run a calibration curve by analyzing these standards with HPLC to establish the relationship between peak area or height and concentration.

V. RESULTS AND DISCUSSION:

5.1 Physical Evaluation:

S.NO	PARAMETER	F1	F2	F3	F4	F5	F6
1	Colour	Red	Green	Yellow	Blue	White	Brown
2	Odour	Aromatic	Aromatic	Aromatic	Aromatic	Aromatic	Aromatic
3	Taste	Aromatic	Aromatic	Aromatic	Aromatic	Aromatic	Aromatic
4	$_{P}H$	7.3	7.4	7.3	7.2	7.1	7.2
5	Melting Point	200°c	190°c	190°c	195°c	195°c	190°c
6	Thickness (Mm)	2.0 ± 0.06	2.0 ± 0.10	1.9 ± 0.01	1.9 ± 0.03	1.8 ± 0.03	1.9 ± 0.02
7	Weight Variation (gm)	397.1 ± 1.30	396.9 ± 1.33	397.5 ± 0.08	396.8 ± 0.49	396.6 ± 0.21	397.1 ± 0.10
8	Hardness (Kg/Cm^2)	1.2 ± 0.20	1.3 ± 0.11	1.3 ± 0.15	1.3 ± 0.20	1.2 ± 0.06	1.0 ± 0.10
9	Moisture Content	0.6	0.3	0.3	0.5	0.6	0.3
10	Texture Feel Or Appearances	Good	Good	Good	Soft	Hard	Soft
11	Stickiness	Nil	Nil	Nil	Nil	Nil	Nil

Table: 2 Physical Evaluation

5.2 Sensory Evaluation:

S.NO	PARAMETER	F1	F2	F3	F4	F5	F6
1	Color	8.5	8.5	8.5	8.5	9	10
2	Taste	7.5	8.5	8	7.5	9	9
3	Flavour	8.5	8.5	8.5	7.5	9	9
4	Shape	8.5	8.5	7.5	8.5	10	10
5	Consistency	8	8.5	8	8	9	9

1: extremely dislike, 2: strongly dislike, 3: moderate dislike, 4: slight dislike, 5:neutral, 6: slight like, 7: moderate like, 8: strongly like, 9: extremely like, 10: excellent

Table: 3 Sensory Evaluation

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

5.3 In-Vitro Drug Release:

S.NO	TIME (min)	F1	F2	F3	F4	F5	F6
1	5	19.56	18.43	21.07	17.02	22.07	31.78
2	10	33.78	37.65	40.16	28.71	35.16	44.66
3	15	54.89	59.05	61.97	40.91	49.05	59.13
4	20	68.72	75.14	79.58	62.56	70.44	68.56
5	25	84.32	89.87	88.63	78.89	86.56	79.05
6	30	95.73	98.52	91.77	93.58	88.12	89.31

Table: 4 In-Vitro Drug Release

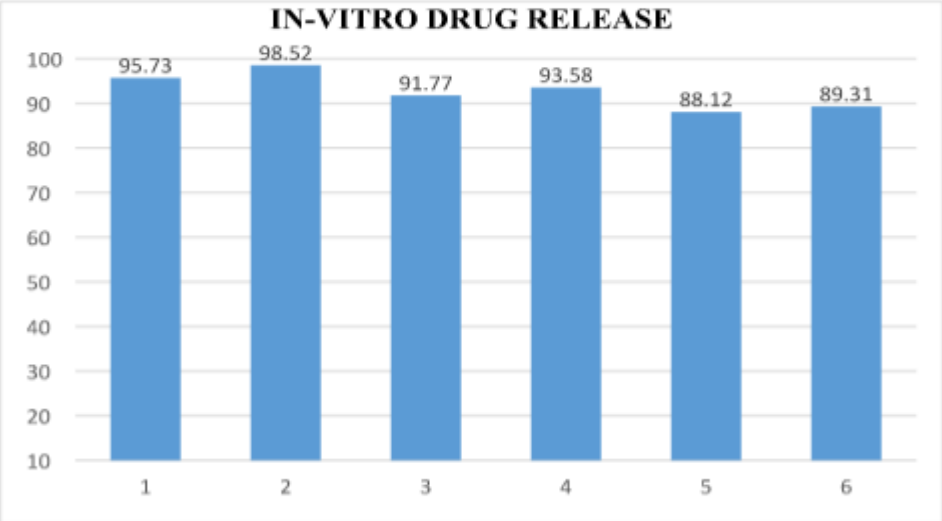


Figure: 8 In-Vitro Drug Release (F1-F6)

5.4 Pharmacokinetic Order Of Release:

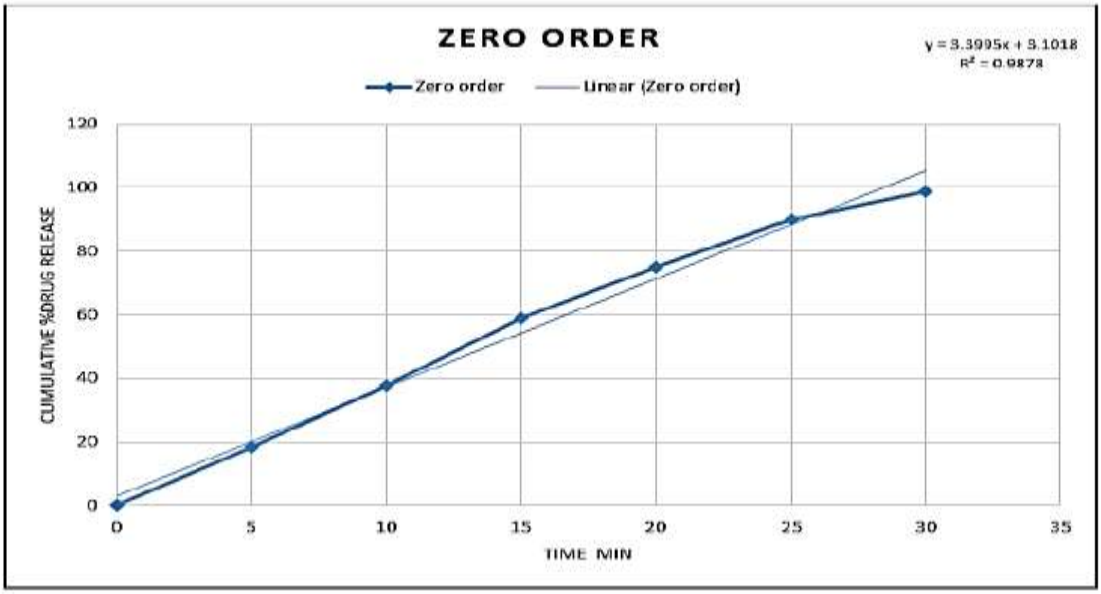


Figure: 9 Zero Order For F2

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

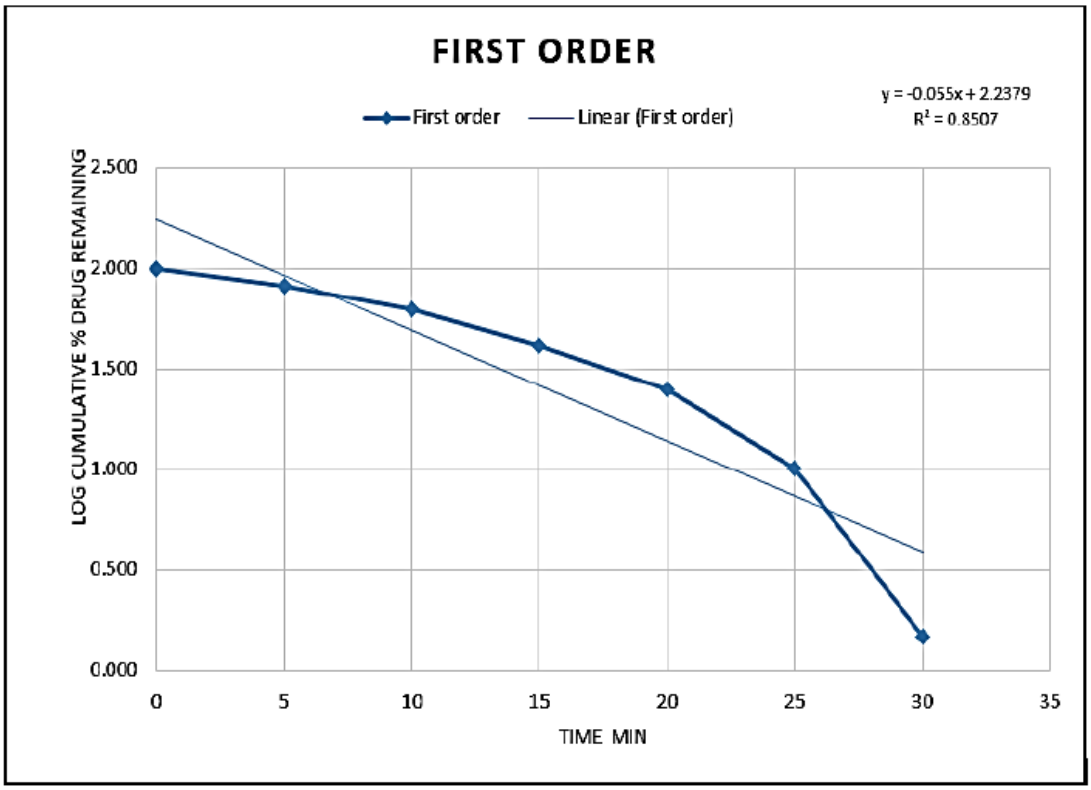


Figure: 10 First Order For F2

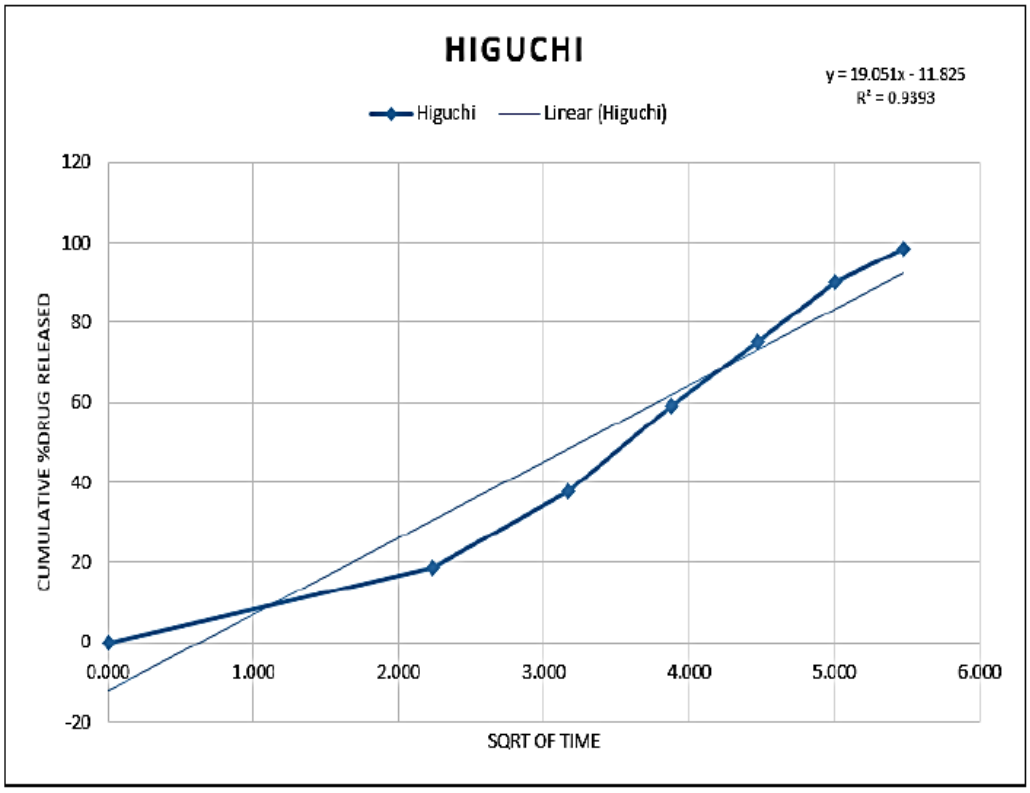


Figure: 11 Higuchi's Plot For F2

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

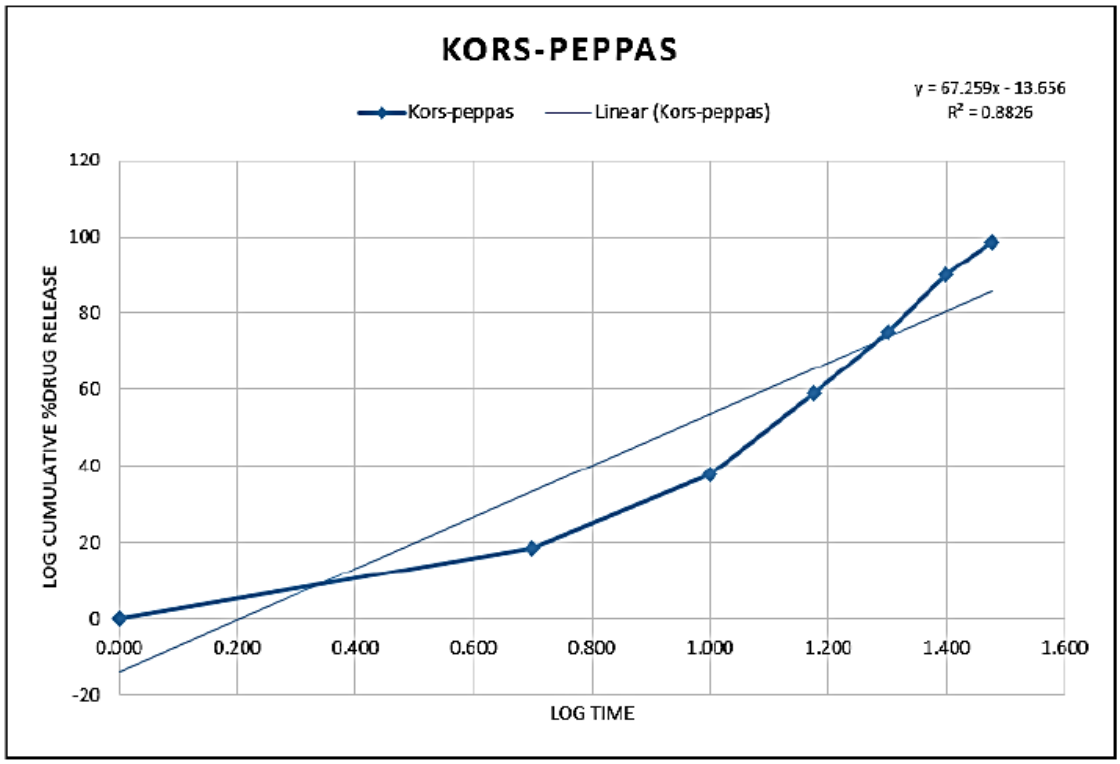


Figure: 12 Peppas's Plot For F2

5.5 HPLC Analysis:

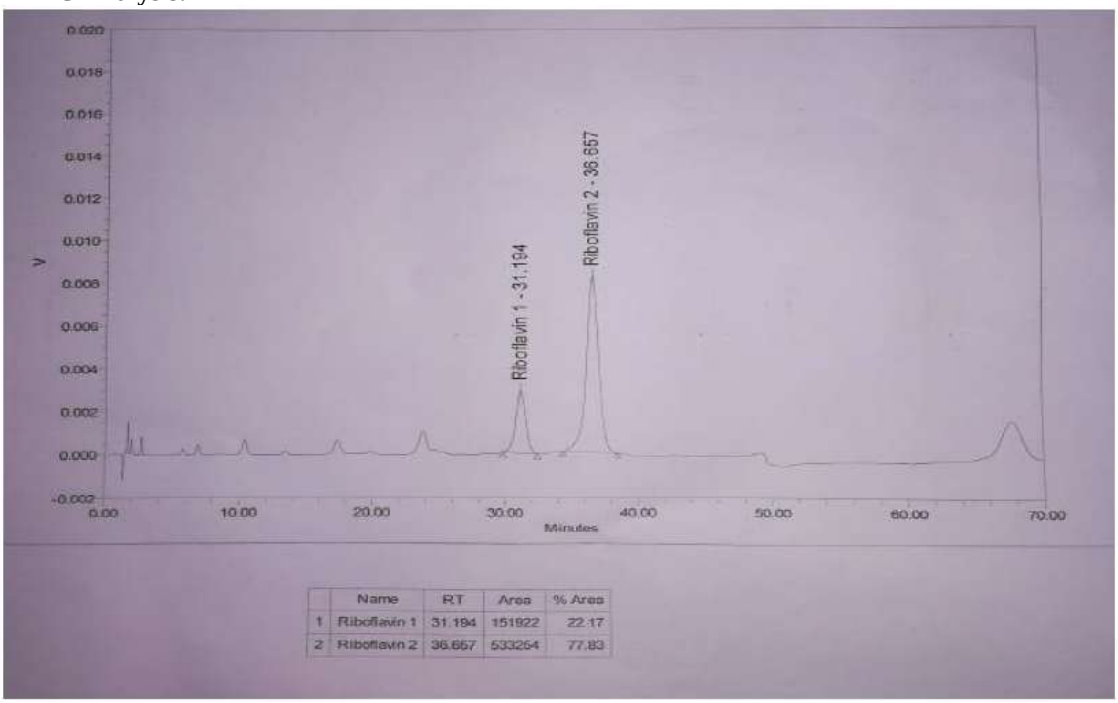


Figure: 13 HPLC Analysis Of Riboflavin (F2)

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

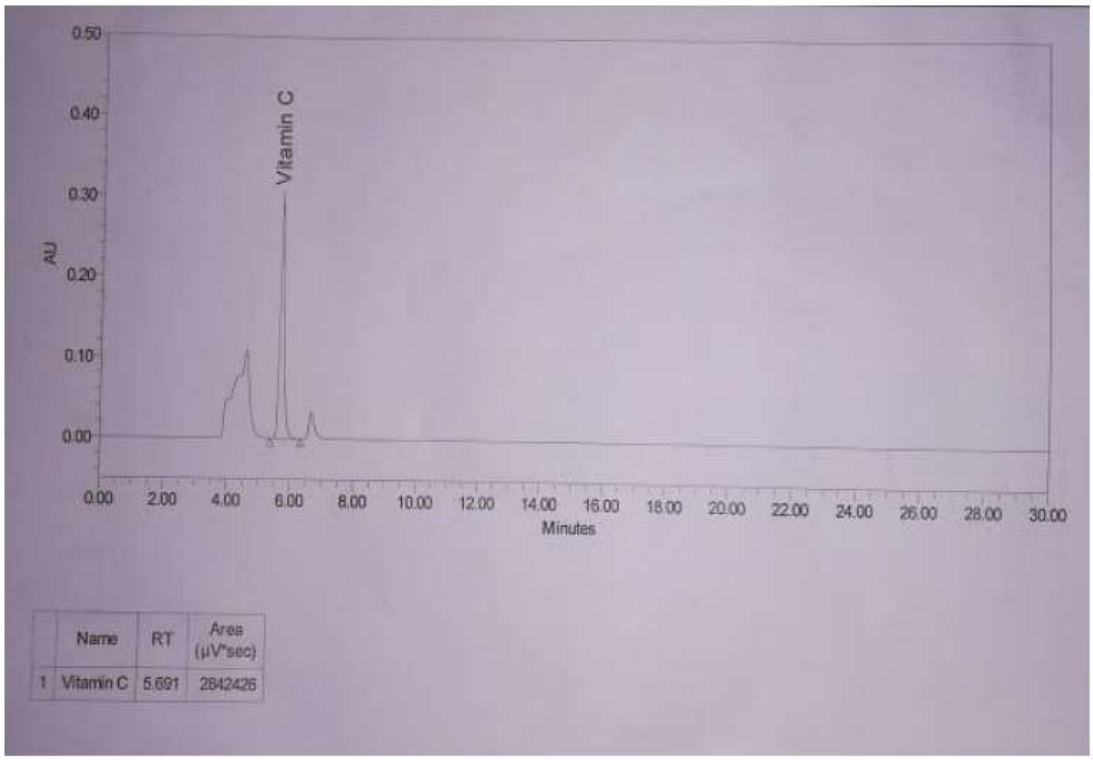


Figure: 14 HPLC Analysis Of Ascorbic Acid (Vitamin C) (F2)

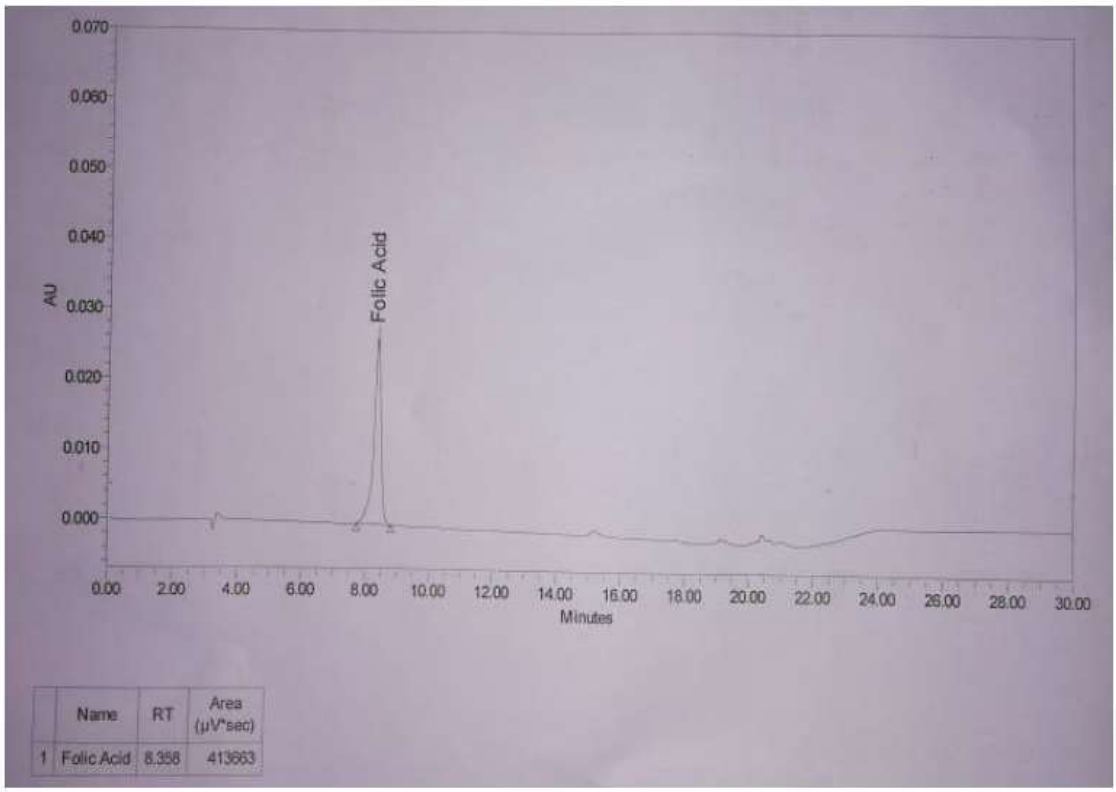


Figure: 15 HPLC Analysis Of Folic Acid (F2)

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 177-190 www.ijprajournal.com ISSN: 2456-4494

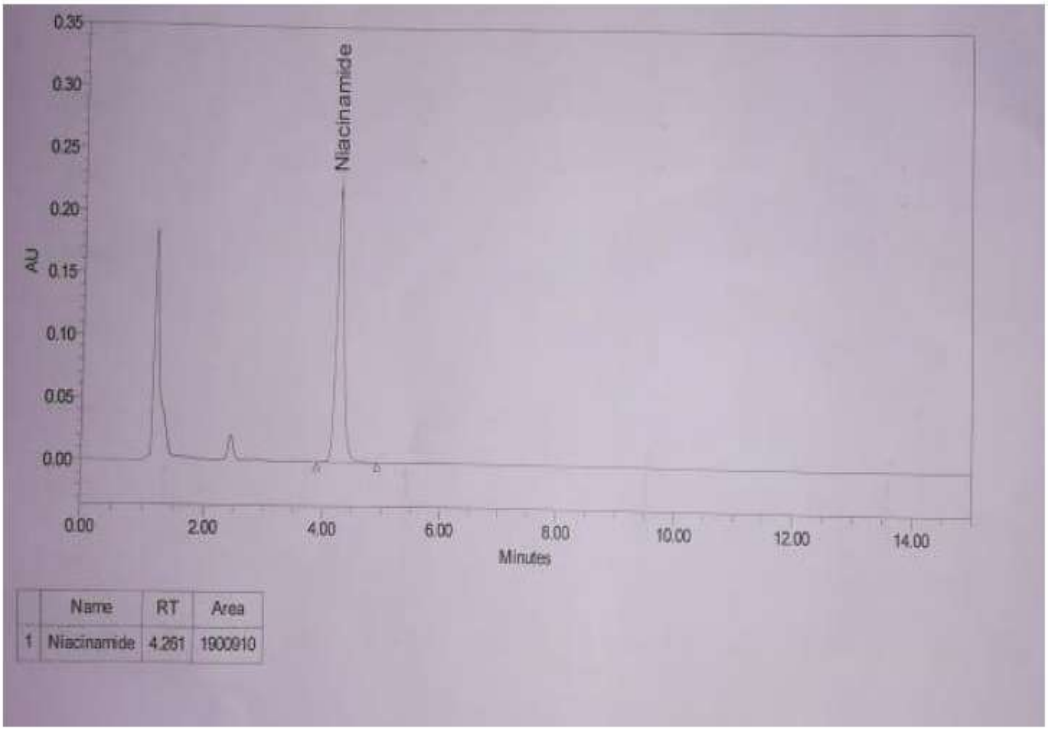


Figure: 16 HPLC Analysis Of Niacinamide (F2)

VI. CONCLUSION:

A comprehensive review of literature regarding the preparation of medicated chewing gum dosage forms, excipient selection, and manufacturing methods has been conducted. In this study, excipient selection was based on the findings from the literature review. The excipients used include sucrose, glucose, glycerin, sorbitol, calcium carbonate, and mint. The prepared medicated chewing gums were evaluated for weight variation, hardness, thickness, drug content, and in-vitro dissolution studies. All these parameters were found to be within the standard limits. Comparative studies were conducted to evaluate the hardness, thickness, and in-vitro dissolution of six different formulations. Among all the batches, formulation F2 exhibited 98.52% drug release at 30 minutes. Based on these results, formulation F2 appears to be a promising candidate for treating mouth ulcers, offering potential benefits for patients.

REFERENCES:

[1]. Navya M, Rao NM. Chewing gum as a drug delivery system. Int J Pharm Bio Sci. 5, 2014, 148-61.
[2]. Jadhav AV, Mohite SV. A comprehensive Review on: medicated chewing gum. J Curr Pharm Res. 4, 2014, 1215-1224.
[3]. Bhaskar DI, Amit SD, Unmesh MJ, Kailash RB. Chewing gum a mobile drug delivery system. Int J Pharm Sci Review.Res. 4, 2012, 106-114.
[4]. Jayaprakash R, Aruna Sharma, Aravindha babu N. Therapeutic chewing gum review. Bio Med Pharmacol J, 8, 2015, 91-97.
[5]. Seppa L, Almenkivi S. Salivary fluoride conc in adults after different fluoride procedures. Acta Odontol Scand, 1997; 55:84-7.
[6]. Asija R, Patel S, Asija S. Oral dosages forms: Medicine containing chewing gum: A review. J Drug Delivery Ther, 2012,90–95.
[7]. Cherukuri S.R., Bikkina K. Tableted Chewing gum composition and method of preparation. 1988, U.S. Patent no.4753805.
[8]. Munksgaard EC, Nolte J, Kristensen K. Adherence of chewing gum to dental restorative materials. Am J Dent,8, 1995, 137-139.
[9]. Weil AT. Coca leaf as a therapeutic agent. Am J Drug Alcohol Abuse, 5, 1978, 75-86.
[10]. Lee WW. Chewing gum as a delivery vehicle for pharmaceutical and

nutraceutical substances. Pharm Tech Online, 2, 2001, 1-11.
[11]. Edgar W, Geddes D. Chewing gum and dental health - A review. Br Dent J, 168, 1999,173-177.
[12]. Conway B. Chewing gum as a drug delivery system. The Drug Delivery Companies Report Autumn/Winter, 2003, 33-35.
[13]. Patel PV, Desai TR, Dedakiya AS, Bandhiya HM. Medicated chewing gum . A review. Int J Univers Pharm Life Sci, 1, 2011, 111-128. [
[14]. Nagasamy VD, Toprani PS, Mukherejee S, Tulasi K. Medicated chewing gums - A review. Int J Pharm Sc, 4, 2014, 581–586.
[15]. Sameja K, Raval V, Asodiya H, Patadiya D. Chewing gum. A modern approach to oral mucosal drug delivery. Int J Pharm Res Dev, 1, 2011, 1–16.
[16]. Weil AT. Coca leaf as a therapeutic agent. Am J Drug Alcohol Abuse 1978; 5(1): 75-86.
[17]. Martin R. Chewing gum. BMJ 1985; 290:1232-1236.
[18]. Edgar WM, Dawes C, O'Mullane D. Saliva and oral health: An essential overview for the health professional. 3rd ed., British Dental Association Publication, London; 2004.
[19]. Sharma NS, Arjariya PA, Jat RC, Fiza F, Sharma G, Rathore SA, Tiwari R. An overview on medicated chewing gum and its applications. IJPFR 2013; 4(3); 3158-73.
[20]. Zyck DJ, Greenberg MJ, Barkla DG, Marske SW, Schnell PG, Mazzone P.. Method of making coated chewing gum products containing various antacids. US Patent 2003; 6: 635-45.
[21]. Kahtani D. Chewing gum: trick or treat. SDJ 1999; 11(1): 27-34.
[22]. Athanikar NK, Gubler SA. Process for manufacturing a pharmaceutical chewing gum. US Patent 2001; 6: 322- 828.
[23]. Subraman CR, Kirshnayya B. Tableted chewing gum composition and method of preparation. US Patent 1988; 4: 753- 805.