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Formulation and Evaluation of Orodispersible Film using Folic Acid

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Abstract: *The present study aimed to formulate and evaluate folic acid-loaded orodispersible films (ODFs) to enhance patient compliance and improve the drug's solubility. Folic acid was characterized through organoleptic evaluation, melting point determination, UV spectroscopy, and FTIR analysis, confirming its purity and stability. Various formulations (F1–F6) were developed using different concentrations of HPMC E15 and PVA polymers. The films were assessed for physical parameters, including thickness, weight variation, surface pH, moisture content, and drug content. In vitro drug release studies were performed using Franz diffusion cells, showing that formulation F3 exhibited the highest cumulative release of 98.02% over 180 minutes. Spectroscopic analysis confirmed the compatibility between drug and excipients. The study successfully demonstrated that orodispersible films are an effective and patient-friendly method for delivering folic acid with enhanced release profiles.*

Keywords: Folic acid, Orodispersible film, In vitro drug release, HPMC E1, Franz diffusion cell.

I. INTRODUCTION

In recent years, the pharmaceutical industry has experienced a paradigm shift toward patient-centric drug delivery systems, focusing on improving patient compliance, convenience, and therapeutic efficacy. Among the innovative dosage forms developed to meet these goals, orodispersible films (ODFs) have emerged as a promising alternative to conventional oral dosage forms, particularly for pediatric, geriatric, and dysphagic patients. These films are thin, flexible sheets that rapidly disintegrate or dissolve in the oral cavity without the need for water, thereby offering an attractive solution for patients with swallowing difficulties. The incorporation of folic acid, a vital B-complex vitamin, into ODFs has garnered considerable interest due to its broad spectrum of health benefits and the challenges associated with its conventional oral administration.

Folic acid, also known as vitamin B9, plays a critical role in various physiological functions including DNA synthesis, repair, methylation, and amino acid metabolism. It is essential for rapid cell division and growth, making it particularly important during periods of rapid growth such as pregnancy and infancy. Folic acid deficiency can lead to several health issues including megaloblastic anemia, neural tube defects in fetuses, cardiovascular diseases, and cognitive impairments. Despite its importance, folic acid is prone to degradation due to environmental factors such as heat, light, and pH variations, which poses significant challenges in developing stable and effective dosage forms.

Traditional folic acid supplementation is typically administered through tablets or capsules. However, these conventional dosage forms are often associated with poor patient compliance, especially in populations with swallowing difficulties. Moreover, gastrointestinal degradation and first-pass metabolism can significantly reduce the bioavailability of folic acid, thereby limiting its therapeutic effectiveness. To overcome these challenges, researchers have explored alternative delivery systems, among which orodispersible films have shown promising potential. ODFs can enhance the stability, bioavailability, and patient acceptability of folic acid, making them a suitable option for vitamin supplementation.

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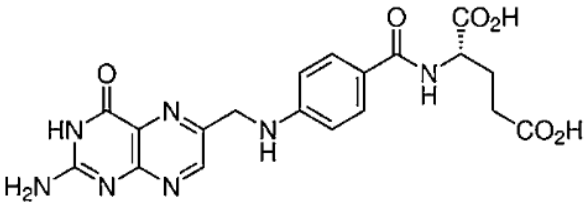
TABLE NO 1 : FOLIC ACID

Chemical Structure	
Chemical Name	(2S)-2-[[4-[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methylamino]benzoyl]amino]pentanedioic acid
Molecular Formula	C19H19N706
Molecular Weight	441.40g/mol
Description	Yellow or orange-yellow crystalline powder; odorless; water-soluble vitamin (Vitamin B9).
Melting Point	Decomposes at around 250 °C
Category	Vitamin (B-complex family), Nutritional supplement, Antianemic agent
Storage	Store below 25°C; protect from light and moisture; keep in tightly closed container.
Solubility	Slightly soluble in water; practically insoluble in alcohol, acetone, and chloroform.
Pharmacodynamics	Essential for DNA synthesis, repair, and methylation; crucial for cell division and erythropoiesis.
Pharmacokinetics	Absorbed in small intestine; converted to tetrahydrofolate; widely distributed; mainly excreted in urine.
Uses	Prevents folate deficiency and neural tube defects; treats megaloblastic anemia; lowers homocysteine levels; supplement during pregnancy and certain therapies.

PREPARATION OF FOLIC ACID LOADED ORODISPERSIBLE FILM

FORMULATION TABLE (BATCH SIZE : 100 ml)

INGREDIENTS	FUNCTIONS	QUANTITY
Folic Acid	Active Drug (API)	50 mg
HPMC E15	Film Forming Polymer	4g (4000mg)
Polyvinyl Alcohol (PVA)	Film Forming Polymer	2g (2000 mg)
Propylene Glycol	Plasticizer	1.5 g (1.5ml approx.)
Sucralose	Sweetner	200mg
Citric Acid	Saliva Stimulating Agent	100 mg
Flavouring Agent	Taste enhancer	100mg
Purified Water	Solvent	q.s. 100mL

Procedure

Polymer Solution Preparation**:** Dissolve HPMC E15 and PVA in purified water with continuous stirring until a clear solution is obtained.

Plasticizer Addition: Add propylene glycol to the polymer solution and mix thoroughly.

API Solution:In a separate container, dissolve folic acid in a small volume of purified water.

Combining Solutions:Slowly add the folic acid solution to the polymer-plasticizer mixture with continuous stirring.

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Additives Incorporation:Add sucralose, citric acid, and flavoring agent to the mixture and stir until homogeneous.
Degassing:Allow the solution to stand to eliminate air bubbles.
Casting:Pour the solution onto a flat surface (e.g., glass plate) and spread uniformly using a film applicator**.**
Drying:Dry the film at room temperature or in a drying oven at a controlled temperature until the solvent evaporates completely.
Cutting: Once dried, cut the film into desired sizes containing the appropriate dose of folic acid.
Packaging: Store the films in airtight containers to protect from moisture and light

II. RESULTS AND DISCUSSION

1. Drug characterization

a. Physical appearance:

Physical appearance of drug examined by various organoleptic properties
Color: Yellow to orange-yellow crystalline powder
Odor: Odorless
Taste: Slightly bitter
Solubility: Slightly soluble in water (low solubility), more soluble in alkaline solutions

b. Melting point:

Melting point of the Folic acid was determined by capillary fusion method; one sided closed capillary filled with drug and put into the melting point apparatus. Temperature was noted at which solid drug changes into liquid. It was found to be 151^0c.

2. Spectroscopic analysis

a. Determination of λ max:

The standard solution of Folic acid of concentration 10 µg/ml showed maximum absorbance at the wavelength of 254 nm (Fig No.1).

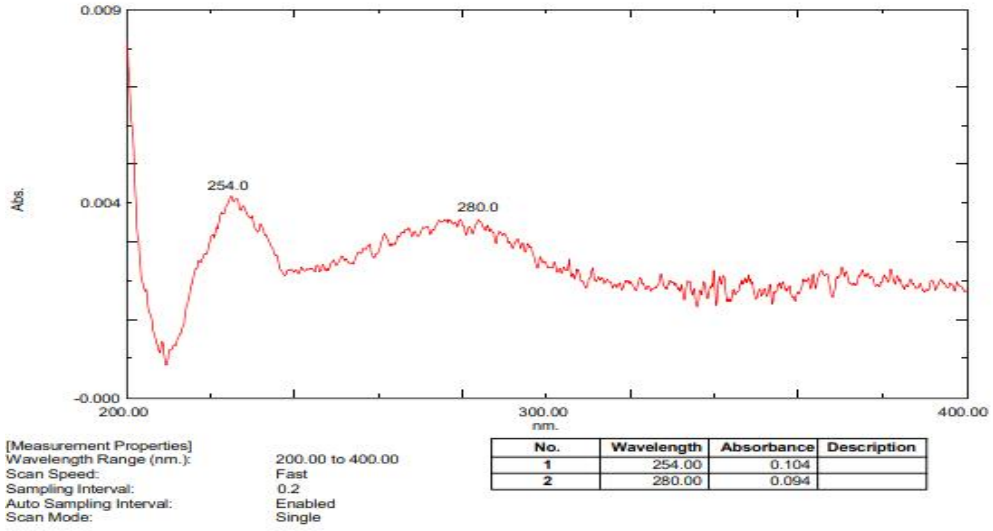

Figure No.:.1. UV spectrum of Folic acid

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b. Calibration curve Folic acid:

Standard calibration curve of Folic acid was obtained by plotting absorbance vs concentration using UV spectroscopy. The λ max of Folic acid in phosphate buffer, (pH 6.8) was determined to be 254 nm respectively, as shown in Figure.2. The absorbance values are tabulated in Table No.2

Table No.:2: Data for calibration curve of Folic acid in phosphate buffer (pH6.8).

Concentration of Folic acid (µg/ml)	Absorbance at 254nm
0	0
2	0.271
4	0.472
6	0.689
8	0.956
10	1.212

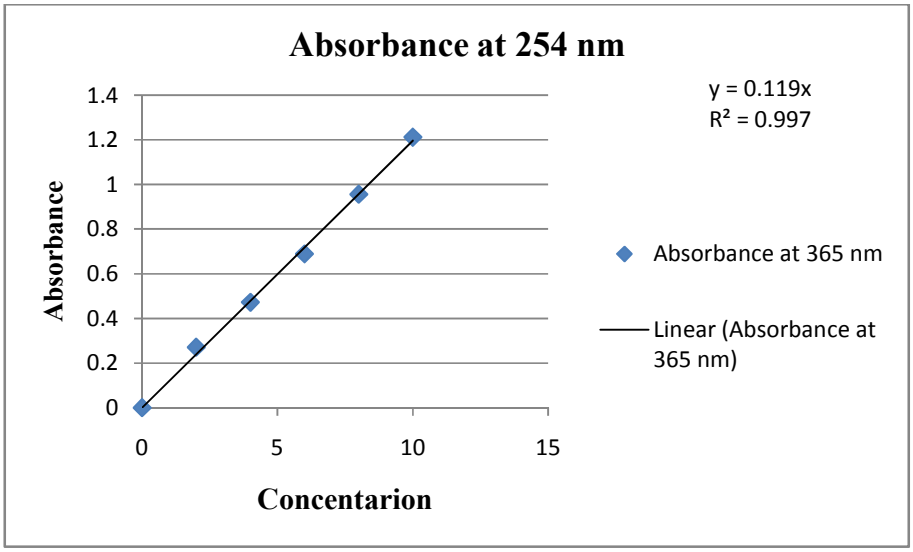

Figure No.: 2: Calibration curve of Folic acid

3. FTIR of Folic acid:

In FTIR spectra of Folic acid (Fig No..3.), all the important peaks were found to be present, which confirmed the purity of sample. Table No..3 shows peaks observed at different wave numbers and the functional group associated with these peaks for drug.

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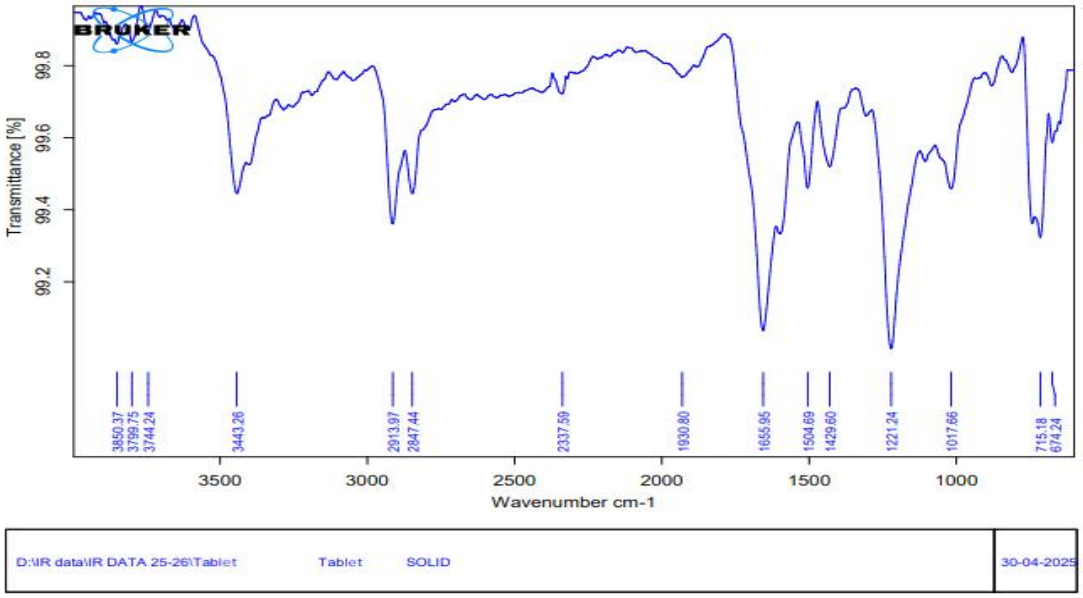

Fig No.3:Formulation trials of folic acid loaded orodispersible film

Table No.3: Formulation Trails of Folic Acid Loaded orodispersible film (Batch Size: 100 mL)

Formulation (mg/film)	F1	F2	F3	F4	F5	F6
Folic Acid (mg)	50	50	50	50	50	50
HPMC E15 (gm)	3	2	4	5	4	3
Polyvinyl Alcohol (PVA)	2	2	2	2	2.5	2.5
Propylene Glycol (gm,1.5 mL approx.)	1.5	1.5	1.5	1.5	1.5	1.5
Sucralose (mg)	200	200	200	200	200	200
Citric Acid (mg)	100	100	100	100	100	100
Flavoring Agent (mg)	100	100	100	100	100	100
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

5. Physical evaluation

5.1 Film thickness

The thickness of the folic acid loaded orodispersible film formulations ranged from 0.16±0.02 mm to 0.21±0.02 mm, as shown in Table 4.

5.2 Weight variations

The peeled film's four corners and the centre were split into three film units, and the average weight was calculated. Table 4. compiles the results of variations from the average weight.

5.3 Surface pH

As demonstrated in Table 4., the folic acid loaded orodispersible films have a surface pH that varies from 5.41 to 6.64. The formulation's measured surface pH was similar to salivary pH, therefore any discomfort to the oral cavity is not anticipated.

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5.4 Moisture Content

The results of the moisture content varied from 1.5±0.7 to 1.9±0.4 %.

Table.4 Evaluation of Physicochemical and mechanical properties of Folic Acid Loaded orodispersible film

Sr. No.	Average Weight variation(mg)	Thickness (mm)	pH	Folding endurance	Drug content	Moisture Content
F1	39.44±0.27	0.19±0.025	5.41±0.15	124.3±1.5	97.73±0.50	2.3±0.2
F2	39.06±0.33	0.17±0.026	5.81±0.04	258.3±0.5	97.93±3.23	1.5±0.7
F3	39.27±0.26	0.18±0.015	6.64±0.10	287.3±1.5	98.61±0.64	2.4±0.1
F4	39.38±0.30	0.20±0.021	6.18±0.04	164.0±1.0	97.41±1.6	1.9±0.5
F5	39.49±0.19	0.21±0.025	6.20±0.08	152.3±2.5	98.54±0.74	2.7±0.4
F6	39.21±0.25	0.16±0.026	5.57±0.06	202.0±3.6	96.13±1.3	1.7±0.2

Figure No.4: Folic Acid Loaded orodispersible film batch F 3.

6: Drug release study in-vitro

The solution of folic acidwas scanned from 200 to 400 nm to obtain the absorption maxima from the U.V. spectrum.

Standard curve plot of folic acid in Phosphate buffer pH 6.8.

In phosphate buffer (pH 6.8), the graph of the folic acid standard was produced. A carefully weighed quantity of the drug was dissolved in 100ml of buffer (pH 6.8). A ultraviolet (UV) visible spectrophotometer was used to measure the absorbance of test solutions at varied concentrations (2 µg/ml to 8 µg/ml) in comparison to a blank phosphate buffer solution with a pH of 6.8.

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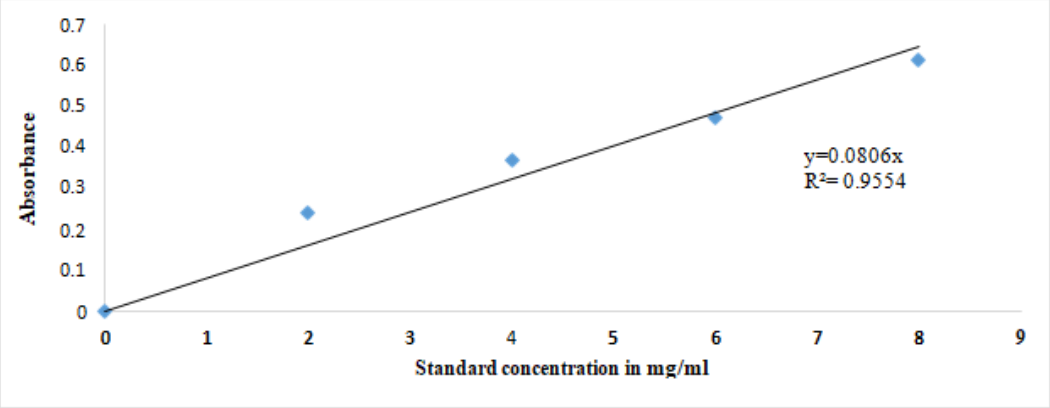

Figure No.:5: Standard Curve of folic acid in pH 6.8 phosphate buffer

Table.5 Standard curve plot of folic acid phosphate buffer p^H6.8 at λ max 254nm

Sr. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.241
3	4	0.368
4	6	0.471
5	8	0.612

7. *In vitro* drug release through cellophane membrane.

The release profile of drug from folic acid loaded orodispersible films was performed by using Franz diffusion cell. The formulation was placed on cellophane membrane mounted between the donor and receptor compartment of the diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 6.8. solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (0.1 ml) were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer at 361 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The amount of drug released across the cellophane membrane was determined as a function of time. Maximum *in vitro* release was found to be 98.02±0.21% over a period of 180 min in batch F3. These results were further supported by swelling studies results, where highest swelling was shown by batch F3 and hence resulting in faster drug release

Table No.:6.:*In vitro* drug release through cellophane membrane F1-F6 batches

Time (min)	F1	F2	F3	F4	F5	F6
15	11.21±0.25	10.84±0.21	15.84±0.5	12.12±0.23	12..92±0.15	13.10±0.20
30	29.32±0.33	28.54±0.1	34.32±0.1	30.5±0.51	28.63±0.2	26.95±0.4
60	47.58±0.5	48.46±0.2	50.23±0.1	46.44±0.3	45.20±0.2	42.58±0.3
90	66.55±0.1	61.17±0.2	69.41±0.3	68.08±0.2	61.30±0.1	67.22±0.2
120	80.25±0.17	78.47±0.0	81.59±0.3	79.78±0.1	78.86±0.3	81.12±0.5
180	95.13±0.19	93.12±0.2	98.02±0.2	96.35±0.9	91.58±0.4	93.34±0.4

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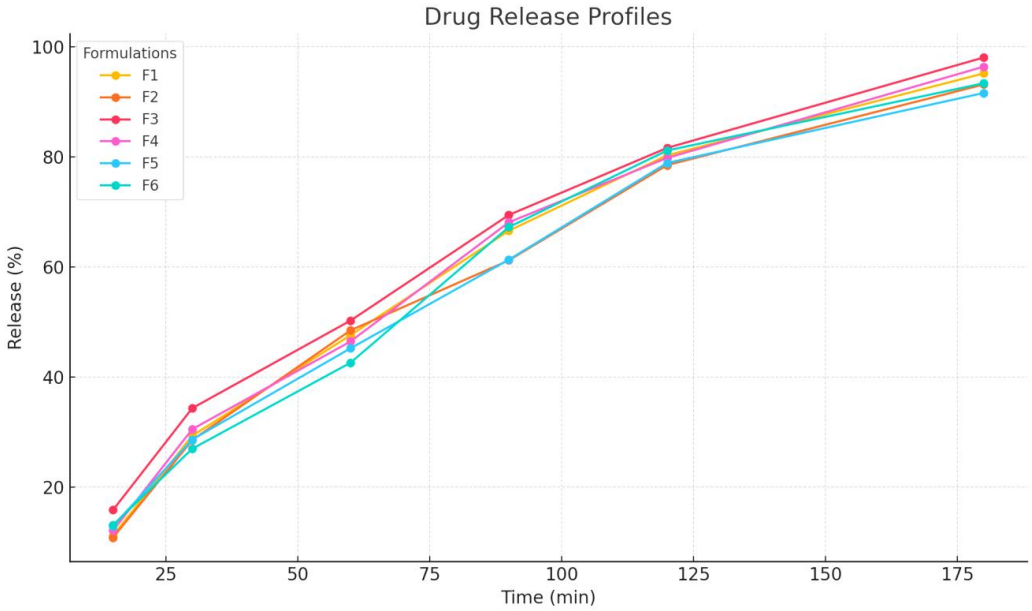

Figure6: *In vitro* drug release of batch F1-F9

III. CONCLUSION

The research successfully formulated and evaluated folic acid-loaded orodispersible films intended for rapid disintegration and enhanced bioavailability. Physical characterization confirmed that folic acid maintained its stability throughout the formulation process. Different formulations varying in polymer ratios were prepared, among which formulation F3 showed optimal physicochemical properties such as appropriate thickness, uniform weight, surface pH close to that of saliva, satisfactory moisture content, and high drug content uniformity.

FTIR studies confirmed the compatibility between folic acid and the selected excipients, while UV spectroscopic analysis supported accurate quantification of drug content and release. The in vitro drug release studies demonstrated that the release rate was strongly influenced by the polymer composition. Specifically, formulation F3 exhibited the highest drug release (98.02% over 180 minutes), suggesting that the optimized polymer concentration enhanced the film's swelling behavior and facilitated faster drug release.

The results indicated that orodispersible films offer a promising alternative to conventional drug delivery systems, particularly for improving patient compliance and providing rapid onset of action. Furthermore, the methodology adopted in this study can be utilized for other poorly water-soluble drugs requiring improved solubility and bioavailability. In conclusion, the developed folic acid orodispersible film could serve as a convenient, effective, and patient-friendly dosage form, potentially broadening the application of ODFs in modern pharmaceutics.

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