Title:

Full Title: Formulation and Evaluation of Nanosponges Loaded Metformin Hydrochloride Tablets**.**

Short Title: Formulation and Evaluation of Nanosponges Loaded Metformin Hydrochloride Tablets.

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FORMULATION AND EVALUAION OF PIZOTIFEN BASED DRUG DELIVERY SYSTEM FOR TREATMENT OF MIGRAINE

1.Abstract

This study aims to develop and evaluate a fast-dissolving Pizotifen oral thin film (OTF) using the solvent-casting method [1]. Films were assessed for physical (thickness, weight), mechanical (tensile strength, folding endurance), chemical (drug content, FTIR compatibility), and performance attributes (disintegration time, in-vitro release) [2]. The optimized film demonstrated uniform drug loading (~98–104%) [3], rapid disintegration (~30 s) [4], and high drug release (~90% within 20 min) [1], indicating it may offer enhanced bioavailability and faster onset compared to conventional oral tablets [5].

Keywords

Pizotifen, oral thin film, fast-dissolving, solvent casting, migraine, in-vitro release

2.Introduction

Migriane may be a inveterate neurological **clutter** characterized by **throbbing cerebral pains**, **sickness**, photophobia, and phonophobia [3]. Pizotifen **could be a** serotonin (5-HT_2) receptor **adversary utilized** for **Migraine** prophylaxis [5]. **Be that as it may**, it **experiences broad** first-pass **digestion system**, **diminishing** its **verbal** bioavailability to around 78% [6]. **Verbal lean movies** (OTFs) offer an **successful elective** by **upgrading solvency**, **decreasing** onset time, and bypassing hepatic **digestion system** [1]. **Headache could be a inveterate** neurological **clutter** characterized by **repetitive direct** to **serious migraines frequently went with** by **sickness**, **heaving**, photophobia, and phonophobia [3]. It **influences roughly** 15% of the **worldwide populace**, **altogether disabling** quality of life and **efficiency** [9]. The pathophysiology of **headache includes** complex neurovascular **instruments**, **counting** serotonin receptor **balance**, trigeminal nerve **actuation**, and neurogenic **irritation** [10]. Pizotifen **could be a** serotonin (5-HT_2) receptor **adversary broadly utilized** for **headache** prophylaxis due to its **capacity** to **repress** vasoconstriction and neurogenic **irritation** [5]. **In spite of** its clinical **viability**, **verbal organization** of Pizotifen tablets **frequently** leads to **deferred** onset of **activity** and **diminished** bioavailability due to **broad** first-pass hepatic **digestion system** and **destitute** water **dissolvability** [6,11]. **Additionally**, **customary** tablets can cause gastrointestinal **bothering**, which **contrarily influences understanding** compliance [12].

Later propels in **medicate conveyance frameworks** have **centered** on **making strides** the **restorative viability** and **understanding** compliance of **headache medicines**. **Verbal lean movies** (OTFs) are an **developing innovation outlined** to **quickly break down** or **crumble within the verbal depression**, **empowering fast medicate discharge** and **retention** through the mucosa [1]. This **course** bypasses first-pass **digestion system**, **possibly improving** bioavailability and **giving quicker** onset of **restorative impact** [13]. OTFs offer **a few preferences**, **counting** ease of **organization** without water, **moved forward understanding** compliance **particularly** for pediatric and geriatric **populaces**, and **decreased chance** of choking [14]. **A few ponders** have **illustrated fruitful detailing** of OTFs for drugs **utilized** in **headache administration**, such as zolmitriptan and rizatriptan, highlighting their potential to **make strides** clinical **results** [1,4].

Given these benefits, **defining** Pizotifen as an **verbal lean** film **seem** address the **confinements** of **ordinary verbal dose shapes**, **progress** onset time, and **improve persistent** compliance in **headache** prophylaxis. This **think about points** to **create** and **assess** Pizotifen OTFs with optimized physicochemical and mechanical properties to **guarantee adequacy** and **understanding worthiness**.

3.Preformulation Studies

Preformulation studies play a vital role in assessing the physicochemical characteristics of a drug substance and its compatibility with excipients used in formulations. These evaluations help guarantee the stability of the drug and the successful development of dosage forms (15).

1 Solubility Study: The solubility of Pizotifen was evaluated in a variety of solvents. It was discovered to be freely soluble in phosphate buffer with a pH of 6.8, making it appropriate for oral film formulation in this solution (16).

2 UV Spectroscopy: A UV spectroscopic analysis was conducted utilizing phosphate buffer pH 6.8 as the solvent. The peak absorbance (λmax) was recorded at 234 nm, which confirmed the characteristic UV absorption profile of Pizotifen (17).

3 Fourier Transform Infrared Spectroscopy (FTIR): FTIR analysis was performed to identify any potential interactions between the drug and the excipients. The IR spectrum of the physical mixture displayed all characteristic peaks of Pizotifen, indicating that there was no chemical interaction (18).

4 Melting Point Determination: The melting point of the drug was assessed using the capillary method. The average of three measurements aligned with the values reported in the literature, confirming the drug's purity (18).

5 Differential Scanning Calorimetry (DSC) :The DSC thermogram for the pure drug revealed a distinct endothermic peak at its melting point. This peak remained unchanged in the mixtures with excipients, indicating no interaction (19).

4.MATERIALS AND METOHD :

Materials

Materials

Pizotifen maleate was obtained from **Yarrow Chem Products, Mumbai (India)**. **Hydroxypropyl methylcellulose (HPMC E5)**, serving as the film-forming polymer, was sourced from **Loba Chemie Pvt. Ltd., Mumbai (India)** [20]. **Crospovidone (CP)** and **Croscarmellose sodium (CCS)** were utilized as superdisintegrants and were kindly provided as **gift samples by a local pharmaceutical company** [21]. **Glycerine**, used as a plasticizer, was procured from **S.D. Fine Chemicals, Mumbai (India)** [22]. All additional reagents and solvents were of **analytical grade** and used as received without further purification.

Methods

1. Preparation of Solid Dispersion of Pizotifen

Solid dispersions of **Pizotifen maleate** with **polyvinylpyrrolidone K30 (PVP K30)** were developed using the **kneading method** to enhance the drug's aqueous solubility and dissolution rate [23]. Varying weight ratios of drug to polymer (1:1, 1:2, 1:3, and 1:4) were studied. The accurately weighed quantities of drug and PVP K30 were blended and moistened with a hydroalcoholic solution (ethanol:water = 1:1 v/v) to obtain a uniform paste. The mixture was subjected to kneading in a mortar for approximately **45 minutes** until a homogeneous mass was achieved. The paste was then **air-dried in a hot air oven at 45°C for 24 hours**. The solidified mass was pulverized using a mortar and pestle and subsequently passed through a **60-mesh sieve** to obtain a fine, free-flowing powder for further use [24].

Evaluation of Solid Dispersion

2.1 Determination of Percentage Yield

The percent yield of solid dispersions was calculated to evaluate the efficiency of the kneading method. After drying and sieving, the weight of the final solid dispersion was compared with the total theoretical weight of the drug and polymer. The yield was calculated using the formula:

% Yield = (Practical Yield / Theoretical Yield) × 100 [25].

2.2 Drug Content Estimation

Accurately weighed samples (equivalent to 10 mg of Pizotifen) from each solid dispersion batch were dissolved in phosphate buffer pH 6.8, followed by filtration through Whatman filter paper. The solution was analyzed using a UV-Visible spectrophotometer at 234 nm, and the drug content was calculated from a previously prepared calibration curve [26].

2.3 Saturation Solubility Studies

Saturation solubility of pure Pizotifen and solid dispersions was determined in phosphate buffer (pH 6.8). Excess quantity of each sample was added to 10 mL of buffer and shaken in a water bath shaker at $37 \pm 0.5°C$ for 24 hours. After equilibrium, samples were filtered, appropriately diluted, and analyzed spectrophotometrically at 234 nm [27]. The results were used to compare the solubility enhancement by the polymer.

2.4 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed to evaluate any possible chemical interaction between Pizotifen and PVP K30 in solid dispersion. The FTIR spectra of pure drug, polymer, and prepared solid dispersions were recorded using an FTIR spectrophotometer in the range of 4000–400 cm^{-1} by the KBr pellet method [28]. Characteristic peaks of Pizotifen were compared across spectra to assess compatibility. The absence of significant peak shifting or disappearance indicated no major drug–excipient interaction [29]

2.Formulation of Oral Film by Solvent Casting Method

Oral films of **Pizotifen maleate (as solid dispersion)** were developed using the **solvent casting method**. The formulation utilized **HPMC E5** as the film-forming polymer, **glycerine** as a plasticizer, and **Croscarmellose Sodium (CCS)** as the superdisintegrant.

Preparation Method

A weighed quantity of **HPMC E5** was slowly dispersed into distilled water with constant magnetic stirring until a uniform polymeric gel was formed. **Glycerine** (20% w/w of the polymer) was then added to improve film flexibility and mechanical strength [30].

Solid dispersion of Pizotifen (prepared using PVP K30 via kneading method) was incorporated into the polymeric solution under continuous stirring. **Croscarmellose Sodium (CCS)** was added at concentrations of **2%–4% w/w** of the total formulation to enhance the disintegration property of the films [31].

The solution was sonicated for 10 minutes to remove air bubbles. It was then cast onto a **clean, leveled glass Petri plate (90 mm diameter)** and dried at **40 ± 2°C for 24 hours** in a hot air oven. After drying, the film was carefully peeled off, cut into uniform **2 cm × 2 cm** squares, and stored in a **desiccator** until further evaluation [32].

3.Calculation of amount of solid dispersion to be added in petri plate

Dose of pizotifen =1.5 mg

Area of petri plate =50.24 cm^2

Step 1: How much solid dispersion is needed to get 1.5 mg of drug?

Since **solid dispersion contains 20% Pizotifen**, we use the formula:

Amount of solid dispersion required=Desired drug amount/Drug fraction in dispersion=1.5/0.20= 7.5 mg

Step 2: Solid dispersion needed for entire Petri plate

If you are casting **one film across the full 50.24 cm^2**, and each **unit area (e.g., 2 cm × 2 cm = 4 cm^2)** is supposed to deliver **1.5 mg drug**, let's first calculate how many **dose units** fit into the full plate:

Number of films=50.24/4 =12.56 mg= 12 films

So total drug required:

Total drug=12×1.5=18 mg of Pizotifen

so, calculate total solid dispersion required:

Total solid dispersion=180/0.20=90 mg

Figure 1 .Optimised Formulated Oral Film

Formulation Details of oral film:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pizotifen S.D.	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg
HPMC	300mg	100mg	500mg	500mg	100mg	500mg	300mg	100mg	300mg
CCS	24mg	5mg	25mg	100mg	2mg	40mg	15mg	8mg	6mg
Glycerine	0.067 ml	0.067 ml	0.067 ml	0.067 ml	0.067 ml	0.067 ml	0.067 ml	0.067 ml	0.067ml
Citric acid	60mg	60mg	60mg	60mg	60mg	60mg	60mg	60mg	60mg
SLS	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg
Sucrose	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg
Ethanol	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml

4.Evaluation of Oral Films

To ensure the reliability and quality of the prepared oral films of Pizotifen, various evaluation tests were conducted. These assessments covered physical, mechanical, and functional properties of the films.

4.1 Physical Appearance

Each film was examined visually under normal light to assess attributes such as transparency, uniformity, smoothness, flexibility, and the presence of any imperfections like cracks, air bubbles, or discoloration. Only those films exhibiting a uniform and smooth surface without any physical defects were considered acceptable for further testing [33]

4.2 Thickness Uniformity

Film thickness was measured using a **digital screw gauge** at five different locations (four corners and the center) of each film. The average thickness and standard deviation were calculated. This parameter ensures consistent drug content across different film areas [34].

4.3 Film Weight Variation

Individual film pieces (2 cm × 2 cm) were weighed on an **analytical balance** to assess weight variation. The average weight and standard deviation were determined from three film samples per batch. Low variability indicates uniformity in casting and drying during film preparation [35].

4.4 Folding Endurance

To evaluate flexibility and mechanical strength, each film was repeatedly folded at the same place until it broke. The number of folds a film could withstand before breaking was recorded as the folding endurance. A high number of folds indicates good mechanical properties and resistance to handling stress [36].

4.5 Surface pH

The surface pH of the films was measured to ensure mucosal compatibility. A small amount of distilled water was added to the surface of each film to moisten it, and the pH was recorded using a **digital pH meter**. The pH values close to neutral indicate the absence of irritation potential to buccal tissues [37].

4.6 Drug Content Uniformity

An individual film (2 cm × 2 cm) was dissolved in phosphate buffer (pH 6.8), filtered, and analyzed for drug content using a **UV-Visible spectrophotometer** at 234 nm. The drug concentration was determined from a pre-established calibration curve, and the results were expressed as the percentage of label claim [38].

4.7 Disintegration Time

Disintegration time was assessed by placing one film in a Petri dish containing 10 mL of phosphate buffer (pH 6.8) maintained at 37°C. The time required for the film to completely break apart and dissolve without agitation was recorded in seconds. Short disintegration time is essential for rapid onset of action [39].

4.8 In Vitro Drug Release Study

The drug release profile from the films was evaluated using the **USP Type I (basket) apparatus**. The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C and stirred at 50 rpm. At predetermined time intervals, 5 mL aliquots were withdrawn, filtered, and analyzed at 234 nm. An equal volume of fresh medium was added after each sampling to maintain sink conditions [40].

4.9 FTIR Analysis of Final Film

FTIR spectroscopy was performed on the optimized film to identify any interaction between the drug and excipients after formulation. The spectrum was obtained using the **KBr pellet method** over a range of 4000–400 cm^{-1}. The retention of major functional group peaks of Pizotifen confirmed the absence of significant chemical interactions [41].

4.10 Stability Study

Stability testing of the optimized formulation was conducted as per **ICH guidelines**. Films were packed in aluminum foil and stored at **40°C ± 2°C and 75% RH ± 5% RH** for 30 days. Samples were evaluated at 0, 15, and 30 days for physical appearance, drug content, and disintegration time. No significant deviations were observed, indicating the formulation's stability under accelerated conditions [42].

Result and Discussion

The organoleptic evaluation of Pizotifen revealed the following characteristics:

Property	**Observation**
Appearance	White to off-white powder
Odour	Odourless
Taste	Bitter
Solubility	Slightly soluble in water, soluble in ethanol and methanol

These results indicate that the drug is poorly water-soluble, which necessitates enhancement techniques such as solid dispersion for oral film formulation.

Melting Point Determination

The melting point of Pizotifen was found to be **142–146°C**, which complies with the standard reported range. This confirms the purity of the drug

Compatibility Studies (FTIR)

FTIR spectroscopy was used to evaluate possible interactions between **Pizotifen** and the selected excipients

Solubility Studies

The solubility of Pizotifen in various solvents was studied to understand its dissolution profile and guide excipient selection:

Solvent	Solubility
Distilled Water	Poor
Ethanol	Freely Soluble
Methanol	Soluble
Phosphate Buffer (pH 6.8)	Slightly Soluble

These findings justify the need to enhance solubility using techniques such as **solid dispersion**, which was subsequently employed in formulation.

Caliberation Data of Pizotifen in Phosphate Buffer pH 6.8 at 234 nm

Sl. No	Concentration (ppm)	Absorbance			Mean Absorbance
		1	2	3	
1.	10	0.632	0.638	0.629	0.633
2.	20	0.753	0.742	0.758	0.751
3.	30	0.842	0.837	0.838	0.839
4.	40	0.998	0.995	0.997	0.996
5.	50	1.028	1.041	1.056	1.041
6.	60	1.212	1.198	1.216	1.208
7.	70	1.501	1.478	1.509	1.496
8.	80	1.742	1.752	1.748	1.747
9.	90	2.013	2.021	2.009	2.014
10.	100	2.092	2.092	2.091	2.092

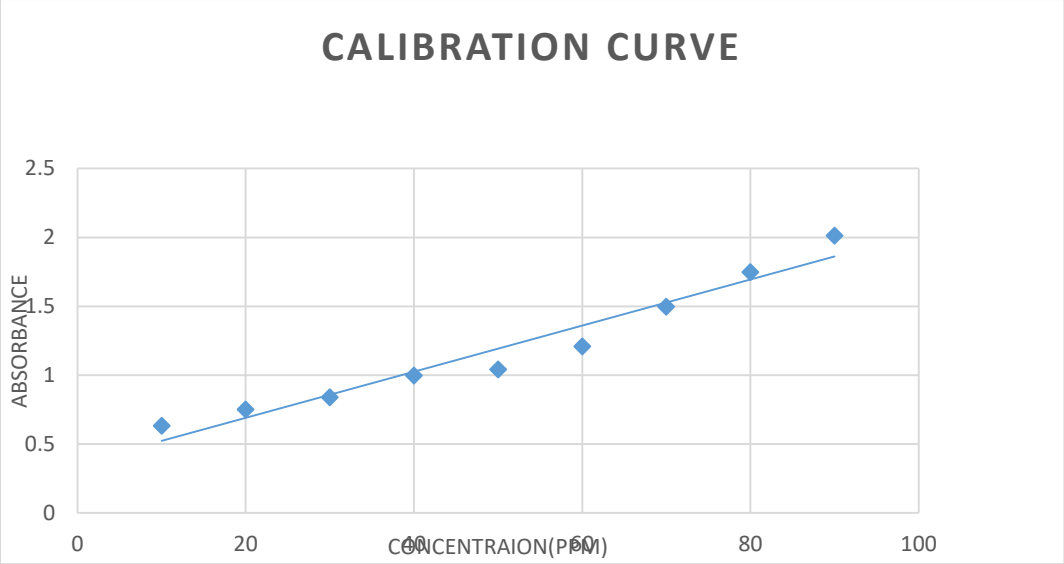


Figure- 2: Caliberation of of Pizotifen in Phosphate Buffer pH at 254 nm

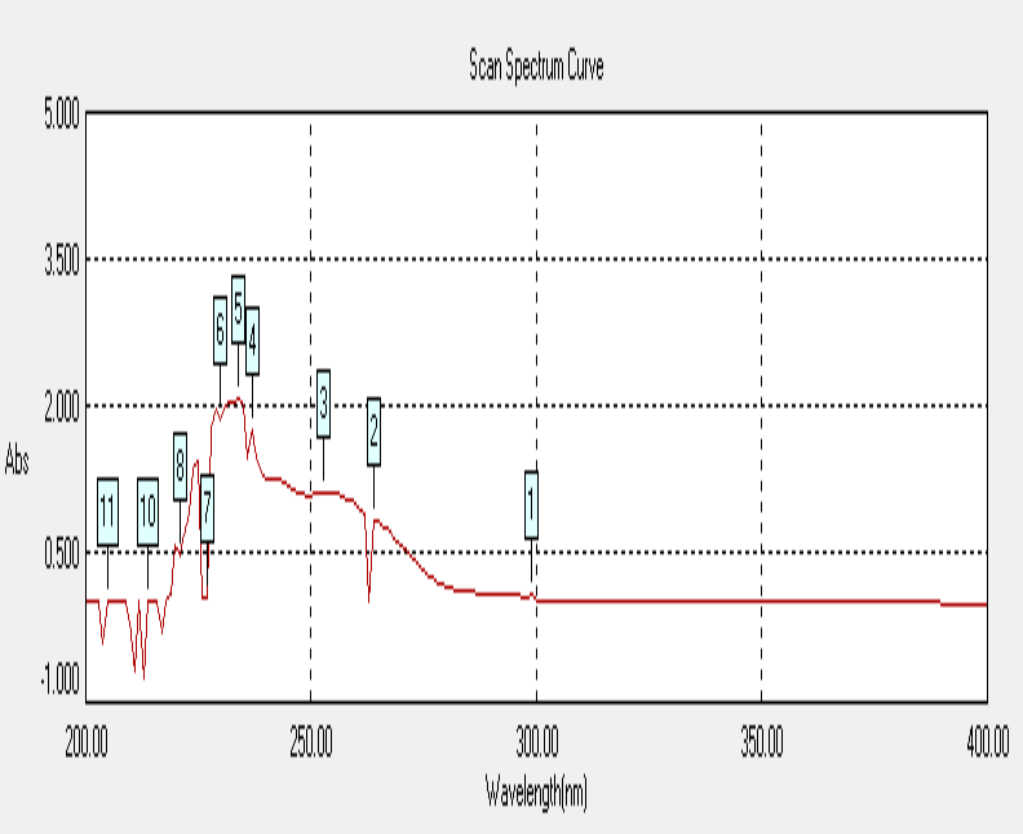


Figure- 3: wavelength of Pizotifen in Phosphate Buffer pH at 254 nm

Characterisation of Solid Dispersion

Solid Dispersion	Solubility (mg/ml)	Percentage Yeild	Percentage Drug Content
S.D. 1	0.940	85%	82%
S.D. 2	1.330	86.66%	83%
S.D. 3	1.312	87.5%	84%
S.D. 4	1.502	89.33%	86%

"Solid dispersions of pizotifen were prepared in drug-to-carrier ratios from 1:1 to 1:4. Among these, the 1:4 ratio demonstrated the highest improvement in solubility and dissolution rate, indicating its superiority."

Physicochemical Evaluation of Pizotifen MDF

Formulation Code	Weight (mg)	Thickness (mm)	Folding Endurance	Surface pH	Disintegration Time (Second)
F1	43.36 ±2.13	0.10 ±0.01	412.66±5.132	6.66 ±0.01	62 ±2.21
F2	24.0 ± 3.6	0.096 ±0.005	358.66 ±6.65	6.70 ±0.01	65 ±3.50
F3	75.0 ±2.65	0.113 ±0.005	530 ±5.21	6.70 ±0.01	70 ±2.64
F4	73.0 ±1.0	0.113 ±0.005	554 ±2.00	6.75 ±0.01	78 ±3.51
F5	26.0±2.13	0.098 ±0.002	352.33 ±6.50	6.78 ±0.01	70 ±2.64
F6	72.33 ±3.60	0.110 ±0.015	549.33 ±5.0	6.76 ±0.01	61±3.21
F7	45.56 ±3.18	0.126 ±0.005	423.66 ±7.50	6.77 ±0.01	70 ±3.05
F8	25.0±3.6	0.096 ±0.005	356.66 ±7.095	6.79 ±0.01	59 ±2.01
F9	46.55 ±2.18	0.136 ±0.005	425.66 ±7.37	6.73 ±0.02	75 ±2.64

Physicochemical Evaluation of Pizotifen MDF

Formulation	% Drug Content	% Moisture Absorption	% Moisture Loss	Tensile Strength (N/mm^2)
F1	95.42 ± 1.21	6.82 ± 0.34	5.91 ± 0.28	21.4 ± 1.2
F2	96.18 ± 1.10	6.25 ± 0.29	5.42 ± 0.31	22.8 ± 1.0
F3	94.86 ± 1.34	7.15 ± 0.41	6.38 ± 0.35	20.1 ± 1.3
F4	93.92 ± 1.42	7.92 ± 0.48	6.85 ± 0.39	19.3 ± 1.5
F5	97.05 ± 1.08	5.98 ± 0.26	5.18 ± 0.24	23.6 ± 1.1
F6	95.63 ± 1.26	6.75 ± 0.33	5.88 ± 0.30	21.9 ± 1.2
F7	96.54 ± 1.15	6.10 ± 0.27	5.36 ± 0.29	22.9 ± 1.0
F8	99.12 ± 0.84	4.92 ± 0.22	4.35 ± 0.21	26.8 ± 0.9
F9	97.48 ± 1.03	5.74 ± 0.25	5.02 ± 0.23	24.1 ± 1.0

In- Vitro Drug Release Study of Pizotifen MDF

Time (min) Code	5 Min	10 Min	15 Min	20 Min	25 Min	30 Min
F1	44.418±1.56	55.073±2.045	68.49±2.360	81.918±2.70	86.101±2.692	95.46±2.56
F2	52.80±1.85	58.08±2.53	72.30±2.56	82.39±1.72	91.52±6.38	96.12±1.34
F3	38.32±2.14	42.46±1.21	55.50±3.56	72.32±3.21	81.52±352	90.80±2.14
F4	39.40±3.12	45.31±2.53	56.52±3.21	75.218±3.12	82.23±3.125	92.34±3.42
F5	54.52±1.23	58.55±2.12	72.54±2.31	83.35±2.16	91.82±3.56	97.40±2.01
F6	40.42±2.56	46.32±1.21	56.58±3.21	76.80±3.52	83.34±356	93.32±2.01
F7	45.81±1.21	58.80±2.12	69.50±2.12	81.92±2.16	88.32±3.61	96.52±2.01
F8	55.46±2.561	60.193±1.180	73.616±1.562	85.93±1.76	93.985±3.68	98.00±3.57
F9	46.32±2.12	59.60±2.32	70.81±3.21	82.00±3.16	89.32±3.61	96.66±3.25

A 3^2 factorial design was employed for the optimization of the oral film formulations. Among the nine formulations (F1–F9), formulation F8 was identified as the optimized batch. It exhibited the highest drug release of 98% and the fastest disintegration time of 59 seconds, indicating its superiority in terms of both efficacy and patient compliance.

Fig.4:In -Vitro Drug Release Profile of Different Formulations of pizotifen

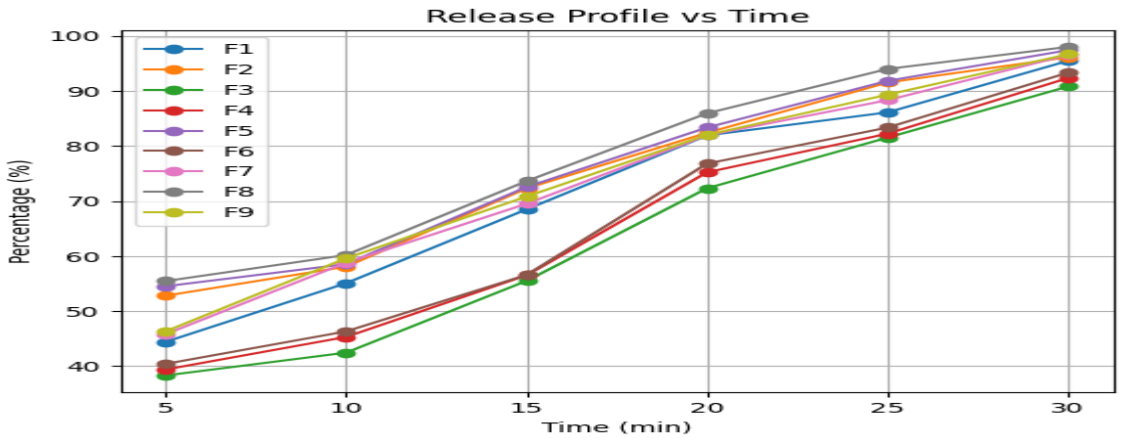


Fig .5 IR Spectra of Pizotifen (Pure Drug)

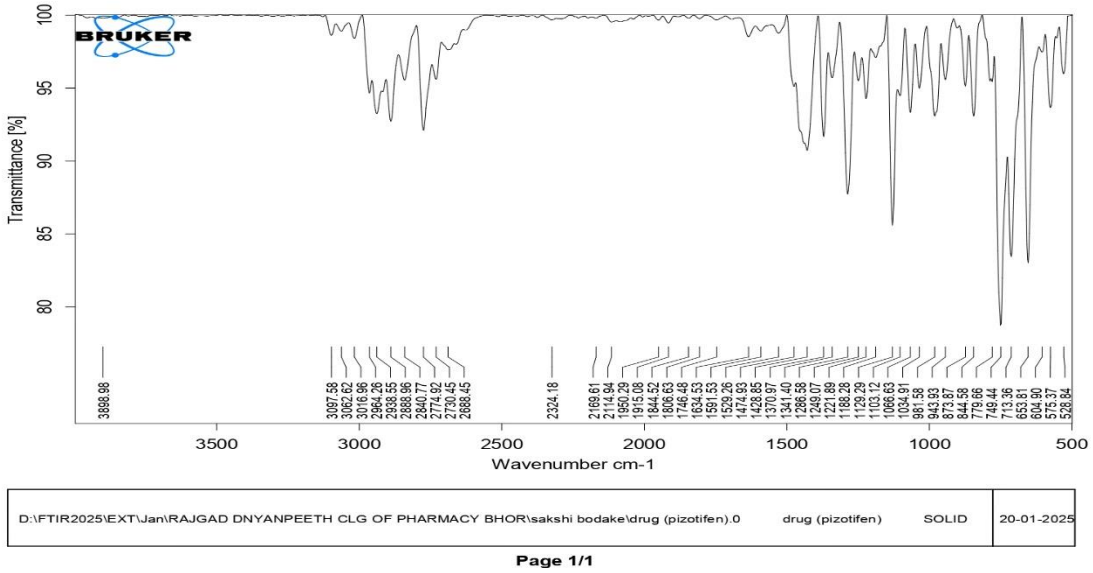


Figure 6. IR Spectrum of HPMC

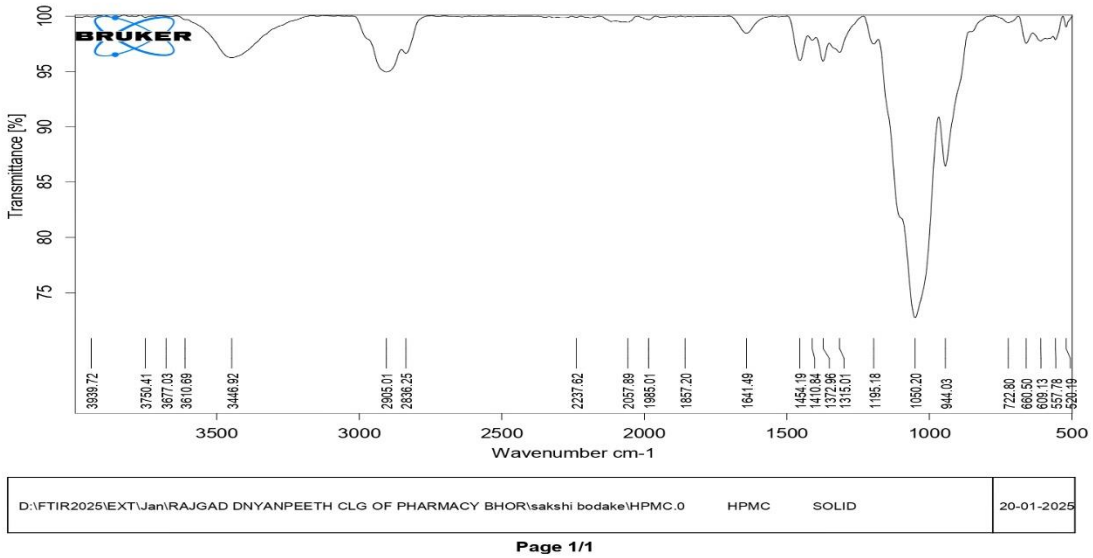


Fig.7. IR Spectrum of CCS

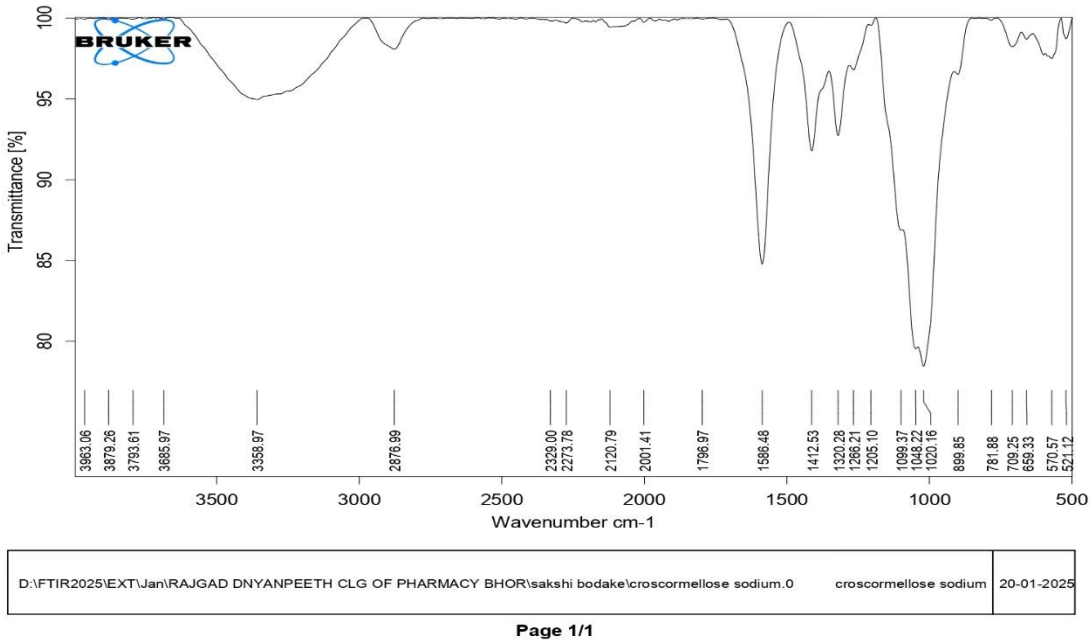


Fig.8. IR Spectrum of Formulation FDFP

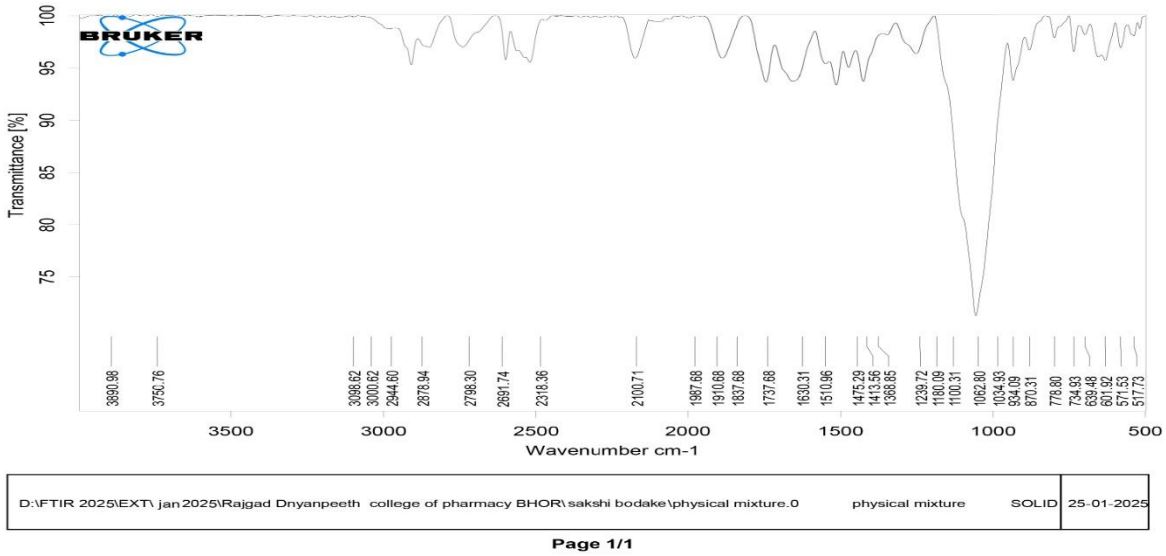
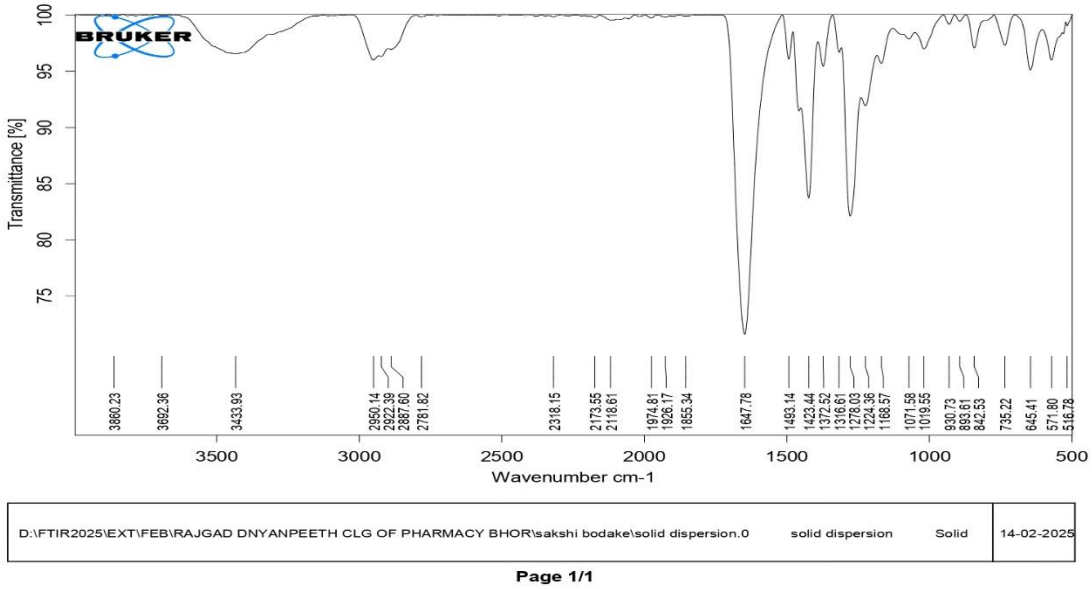
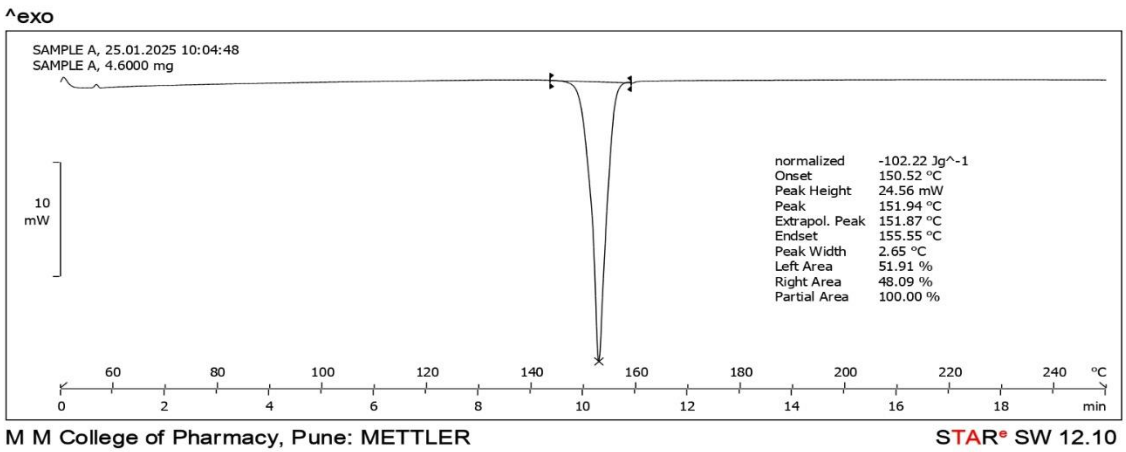


Fig.9. IR Spectrum of Solid Dispersion



The FTIR spectra of the pure drug, excipients, solid dispersion, and the optimized oral film formulation indicated that there were no significant shifts or disappearance of characteristic peaks. This confirms the absence of any chemical interaction between the drug and excipients, as well as between the solid dispersion and the components of the oral film

Fig.10 DSC Thermogram of Pizotifen



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