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Formulation And Evaluation Of Oral Thin Film Of Betahistine Dihydrochloride

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Abstracts: Betahistine Dihydrochloride, a histamine analogue, is widely used in the management of Ménière's syndrome to alleviate symptoms such as vertigo, tinnitus, hearing loss, and nausea by improving inner ear blood flow and reducing pressure. In the present study, fast dissolving oral thin films (OTFs) of Betahistine Dihydrochloride were developed to enhance patient compliance and achieve rapid drug release. OTFs were prepared using polymeric carriers, and Fourier Transform Infrared (FTIR) spectroscopy confirmed the absence of drug–excipient interactions, indicating compatibility for formulation. The prepared films were subjected to various physicochemical and quality evaluation parameters, including thickness, weight variation, folding endurance, surface pH, disintegration time, in-vitro diffusion, drug content uniformity, kinetic modeling, and stability testing. Results demonstrated that all formulations met pharmacopeial limits for thickness, surface pH, and drug content. Among the formulations, F1 exhibited the highest percentage drug diffusion within 20 minutes, confirming its superiority in rapid release. Kinetic modeling of the in-vitro release profile revealed that the optimized formulation followed first-order kinetics and Higuchi's model, suggesting diffusion-controlled release. The Korsmeyer–Peppas model further indicated non-Fickian (anomalous) diffusion, reflecting a combination of diffusion and polymer relaxation mechanisms. Accelerated stability studies confirmed that the optimized F1 formulation remained stable under stress conditions without significant changes in physicochemical parameters or drug release behavior. Overall, Betahistine Dihydrochloride fast dissolving films demonstrated promising potential as a patient-friendly, stable, and effective dosage form for the management of Ménière's syndrome.

Keywords: Betahistine Dihydrochloride, Oral Thin Films, Fast Dissolving Films, In-vitro Diffusion, Kinetic Modeling.

INTRODUCTION

Ménière's syndrome is a chronic disorder of the inner ear characterized by recurrent episodes of vertigo, tinnitus, fluctuating hearing loss, and nausea. These symptoms significantly impair the quality of life, particularly in elderly patients. Betahistine, a structural analogue of histamine, has been widely prescribed for the management of Ménière's syndrome. It acts primarily by enhancing microcirculation in the inner ear, improving vestibular compensation, and reducing endolymphatic pressure. However, conventional dosage forms of Betahistine Hydrochloride such as tablets and capsules have limitations, including delayed onset of action, difficulty in swallowing among geriatric patients, and variable gastrointestinal absorption. These limitations necessitate the development of an alternative delivery system that ensures rapid onset of therapeutic action, improved patient compliance, and consistent bioavailability.[1-3]

Oral thin films (OTFs) have emerged as a novel and patient-friendly drug delivery platform designed for immediate drug release and enhanced systemic availability. OTFs are thin, flexible, polymeric strips that rapidly disintegrate upon contact with saliva, eliminating the need for water and facilitating ease of administration. They are particularly advantageous for populations with swallowing difficulties (dysphagia) such as pediatric, geriatric, and psychiatric patients. The films ensure accurate dosing, faster onset of action, improved stability, and better patient acceptance compared to conventional oral solid dosage forms. Moreover, OTFs bypass first-pass metabolism to some extent, thereby improving drug bioavailability.[4-5]

In recent years, several drugs have been successfully incorporated into OTFs for rapid therapeutic action. Betahistine Hydrochloride, being water-soluble and requiring a rapid onset of action in vertigo management, is an ideal candidate for this dosage form. The present research focuses on the formulation and evaluation of Betahistine Hydrochloride fast dissolving oral thin films. The study includes compatibility assessment through FTIR, physicochemical characterization, in-vitro diffusion studies, kinetic modeling, and stability evaluation to optimize a formulation that can deliver enhanced therapeutic efficacy with improved patient compliance.[6]

MATERIALS AND METHODS

Materials

Betahistine dihydrochloride was procured from Intas Pharma, India. Hypromellose (Balaji Drugs), Carbomer 974 (Corel Pharma), Polyethylene glycol (Arrow Fine Chemicals), Glycerin (Manali Petrochemicals), Polyvinyl alcohol (Nippon Gohsei), and Kollicoat IR (BASF) were used as film-forming agents and plasticizers. Other excipients included benzoic acid and sodium benzoate (preservatives), citric acid (pH adjusting agent), sucralose (sweetener), strawberry flavor (IFF), Kyron T114 (ion exchange resin, Corel Pharma), β-cyclodextrin (complexing agent, Roquette Pharma), croscarmellose sodium and polyplasdone (superdisintegrants, Ashland). Purified water was used as vehicle. All chemicals and reagents used were of analytical grade.

Equipment and Instruments

The instruments used in this study included: electronic balance (OHAUS), mechanical sifter and sieves (#20, #30, #40, #60; Electrolab, India), stainless steel SS 316 vessels, IR moisture analyzer (OHAUS MB-45), hot plate and mechanical stirrer (Effem; Remi Motor Pvt. Ltd.), digital pH meter (Lab India), magnetic stirrer (Equitron), viscometer (Brookfield), Vernier caliper and thickness gauge (Sunshine Instruments), HPLC system (Waters), UV–Visible spectrophotometer (Shimadzu, Japan), DSC-60 (Shimadzu, Japan), FTIR-1800 (Shimadzu, Japan), and texture analyzer (Insent-TS-5000Z, Higuchi).

Analytical Methods[7]

1. **Organoleptic Properties** The color, odor, and physical nature of Betahistine dihydrochloride were evaluated by visual and sensory inspection.
2. **Identification Tests**

- **FTIR spectroscopy:** Drug samples were mixed with dried KBr powder and scanned to record IR spectra for characteristic peaks.
- **UV spectroscopy:** A 10 ppm solution in 0.1 N HCl was scanned in the range of 200–400 nm to determine absorption maxima.

3. **Melting Point** The melting point was determined by capillary method using a Thiele's tube containing liquid paraffin.
4. **Solubility** Solubility studies were performed in water, alcohol, acetonitrile, and buffer solutions of pH 1.2 and 6.8. Saturated solutions were equilibrated for 24 h at room temperature, filtered, diluted appropriately,

and analyzed at 261 nm using UV spectrophotometer.

5. **Drug Content by HPLC**
   HPLC analysis was performed using ammonium acetate buffer (pH 4.7) and acetonitrile (65:35 v/v) containing sodium lauryl sulfate as mobile phase. The column was maintained at 40 °C, flow rate 0.5 mL/min, and detection at 254 nm. Drug content was calculated by comparing assay sample peak areas with those of standard preparation.

Formulation of Oral Thin Films[8]

Oral thin films were prepared by solvent casting method. Water-soluble polymers were dissolved in distilled water under continuous stirring at 1000 rpm and heated to 60 °C. Plasticizers, sweetener, flavor, and other excipients were dissolved separately and mixed with the polymeric solution. The drug was dissolved in a suitable solvent and incorporated into the polymeric blend. The solution was degassed under vacuum to remove entrapped air and cast onto a glass plate. Films were dried at ambient temperature, peeled, and cut into 2 × 2 cm^2 pieces (containing equivalent to 16 mg drug). Twelve formulations (F1–F12) were prepared by varying the concentration of polymers and excipients.

Evaluation of Oral Thin Films[9-11]

1.Physical Appearance:

The color, homogeneity, transparency, smell, and texture of the OTFs are examined visually and sensually. They should be evaluated especially in terms of taste and flavor characteristics.

2. pH:

Determining the pH of OTFs is important in terms of their solubility/dispersion in the oral cavity, taste properties, and rapid release of the drugs. For this purpose, 1.5%-2% (w/v) agar is added to the isotonic solution and dissolved. Then this solution is poured into a petri dish and incubated until it forms a gel at room temperature. Thin-film samples are placed on it. Subsequently, pH papers with a pH range of 1-11 are touched to OTFs, and their pH is determined according to the change in the color of the paper.

3. FTIR Compatibility:

Using FT-IR (ATR) spectrophotometer is measured and examined infrared spectra that all components entering the formulations to detect unwanted interactions between formulation components and the pure API.

4. Thickness:

The thickness measurement is required as it is directly related to the quantity of drug in the OTF. At the same time, a suitable thickness is necessary for the comfortable application of the films. For example, the ideal thickness of oral thin films should be between 50 and 1000 μm. For this purpose, at least five films from each formulation are measured from five different points, and the results are given as mean and standard deviation

5.Weight variation:

1x1-cm2 films are cut from each formulation, and weight variability is calculated by weighing them individually on a sensitive scale.

6.Folding Endurance:

The flexibility of thin films is determined by folding a film repeatedly at the same place at an angle of 180° until it breaks. The number of folds made before breaking is noted. The film that exhibits 300 times or more folding endurance is considered to have excellent flexibility.

7.Swelling Property:

The swelling of the polymeric film is important in terms of measuring the water absorption capacities of OTFs and obtaining information about their resistance to water. Randomly selected OTFs are weighed individually and kept in simulated physiological fluid in a petri dish within the specified period. Then, each film is weighed and measured at different time intervals until the increase in weight reaches a constant level. The degree of swelling is calculated using the equation below:

% Swelling Degree = (Final Weight – Initial Weight)(Initial Weight) x 100

8.Transparency:

The transparency of OTFs could be measured utilizing a ultraviolet (UV) spectrophotometer. OTF formulation specimens are cut rectangularly and placed inside the UV spectrophotometer cuvette. The permeability of the film is made at a wavelength of 600 nm. The following equation is used for the results obtained:

$$\textbf{Transparency} = \log T_{600}/b$$

[T_{600}= Transmittance at 600 nm, b = film thickness (mm)]

9.Drug Content:

For content uniformity, each film is filtered after being dissolved in a suitable solvent and the drug content in each film is measured by the HPLC method. It is expected that the relative standard deviation % is not more than 6%.

10.In-vitro Disintegration Studies:

The disintegration time is described as the time (seconds) that a film disperses when it comes into contact with saliva or water. Disintegration time is when the thin film begins to disintegrate or disperse. The weight and thickness of the film play a significant role in determining the physical properties of water-soluble films.

The disintegration test apparatus specified in pharmacopoeias can also be used to determine the disintegration times of OTFs. Normally, the disintegration time of the film composition is usually 5-30 s, and this is a phenomenon that varies according to the formulation content. There is no official guide to detecting the disintegration times of films that break down fast.

11.In-vitro Dissolution Studies:

Dispersion of OTF for each batch was performed using a USP type II machine using a paddle. The dispersion area contained 900 ml of phosphate buffer (pH 6.8) 24 hours, stored C. One OTF was fitted to each melting vessel and the rotation speed of at 37 + 0.5 the oar was set at 75rpm. 5ml of sample was dispensed at determined frequency; the same dose of the new substance was changed regularly. Samples were analyzed for drug content at a wavelength of 254 nm using a HPLC. The content of the drug is calculated using the area of the standard.

12.Kinetics Studies

The dissolution results of all film formulations containing API in the pH 6.8 artificial saliva or pure water are applied to the computer program in order to determine the appropriate kinetic model. It is determined by mathematical programs and formulas that the formulations are compatible with 0. degree, 1. degree, Korsmeyer-Peppas or Higuchi models or not.

RESULTS AND DISCUSSION

Analytical Evaluation of Betahistine Dihydrochloride

1. Organoleptic Properties

The organoleptic evaluation of Betahistine Dihydrochloride revealed that the drug appeared as a white, odorless, very hygroscopic powder. The observed results were consistent with the reported literature values, confirming the authenticity and purity of the procured API. These findings indicated that the drug was pharmaceutically acceptable for formulation purposes.

2. Identification Tests

- **FTIR Spectroscopy**: The IR spectrum of Betahistine Dihydrochloride (Figure 1) displayed characteristic absorption bands at 3417 cm^{-1} (N–H stretching), 2923 cm^{-1} (C–H stretching), 1620 cm^{-1} (C=C stretching), and 1485 cm^{-1} (C–N stretching), which were in agreement with standard functional group frequencies. This confirmed the structural integrity of the drug.

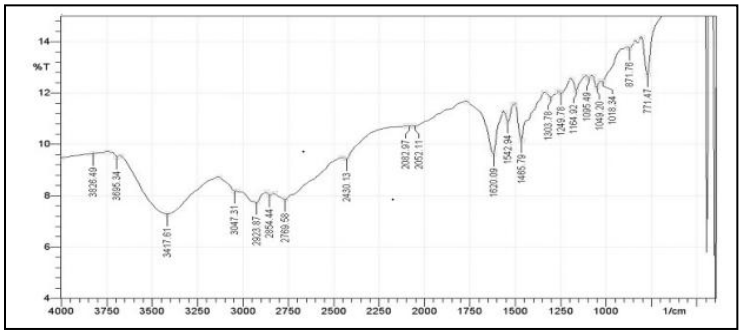

Figure No. 1 IR Spectra of Betahistine Dihydrochloride

- **UV Spectroscopy**: The drug exhibited a λmax at 261 nm in 0.1 N HCl solution (Figure 2). The UV absorption maxima corresponded with reference values, confirming the identity of Betahistine Dihydrochloride.

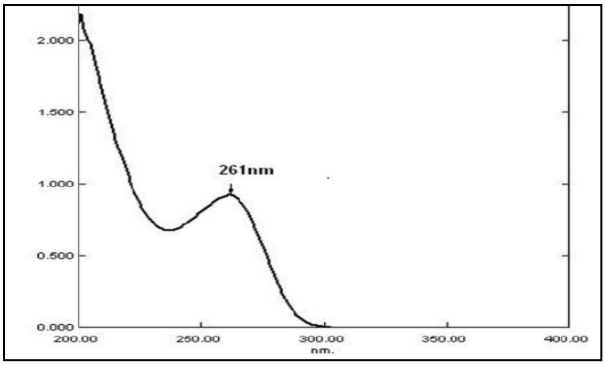

Figure No. 2 UV Spectra of Betahistine Dihydrochloride

3. Melting Point

The melting point of the drug was determined by capillary method and found to be 152 °C, which matched the reported value. This confirmed the purity of the drug substance, as no deviation was observed.

4. Solubility

Solubility studies revealed that Betahistine Dihydrochloride was freely soluble in water, soluble in methanol, pH 1.2 buffer, and pH 6.8 buffer. This high aqueous solubility supports its suitability for oral thin film formulations, as rapid hydration and dissolution are critical for fast drug release.

5. Drug Content by HPLC

The drug content of Betahistine Hydrochloride was quantified using a validated HPLC method. The chromatogram of the assay preparation showed a sharp peak with retention time (RT) of 2.358 min, confirming drug specificity. The obtained peak parameters including area, tailing factor, and asymmetry were within acceptable limits, demonstrating the suitability of the analytical method. The blank chromatogram confirmed no interference at the drug's retention time, ensuring specificity of the method.

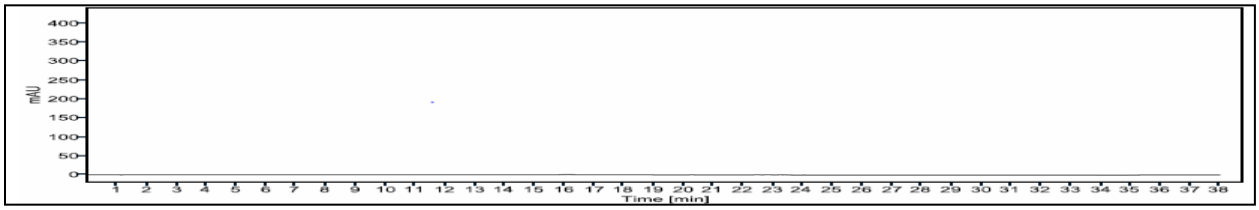

Figure No. 3 Chromatogram of Blank

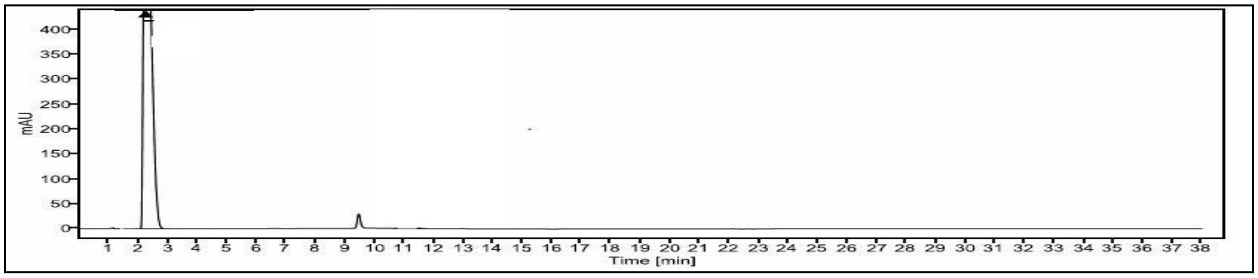

Figure No. 4 Chromatogram of Betahistine Hydrochloride

Table No. 1 Datasheet of Betahistine Hydrochloride

Sr. No.	Name	RT [min]	Area	T. Factor	Asymmetry
1	BHT	2.358	1301.164	2.05679	2.00325

Evaluation of Oral Thin Films of Betahistine Dihydrochloride

Table No. 2 Evaluation of Oral Thin Films of Betahistine Dihydrochloride

Formulation Batch	pH	Thickness (mm)	Weight Variation (mg)	Folding Endurance	Swelling Property (%)	Transparency (%)	Drug Content (%)	In-vitro Disintegration Time (s)
F1	6.9	0.7±0.065	90.64±0.345	135±2.497	59.64	48	97.46	21±1.496

F2	6.7	0.9±0.017	92.17±0.654	165±2.465	60.78	76	98.62	26±1.159
F3	7.2	1.2±0.046	89.54±0.348	174±1.764	61.68	43	96.11	20±1.648
F4	7.1	0.9±0.074	95.34±0.135	144±3.864	58.91	--	95.28	25±1.453
F5	6.5	1.1±0.025	92.46±0.453	196±1.156	60.37	56	96.30	19±1.184
F6	6.8	1.0±0.014	90.58±0.421	147±0.448	64.84	62	95.29	16±1.431
F7	7.3	0.8±0.074	92.75±0.376	185±2.154	62.52	--	96.67	29±1.520
F8	7.4	1.3±0.085	88.96±0.846	194±3.945	63.06	--	98.58	31±1.349
F9	7.6	1.5±0.069	94.45±0.231	161±3.652	69.98	83	97.48	27±1.765
F10	6.9	1.2±0.026	93.53±0.469	137±3.102	67.77	34	94.36	23±1.486
F11	6.7	0.9±0.031	97.12±0.785	149±0.478	61.59	55	96.30	24±1.120
F12	6.5	1.5±0.043	99.24±0.679	173±1.223	62.42	--	94.54	23±1.486

In-vitro Dissolution Studies:

Dispersion of OTF for each batch was performed using a USP type II machine using a paddle. The dispersion area contained 900 ml of phosphate buffer (pH 6.8) 24 hours, stored C. One OTF was fitted to each melting vessel and the rotation speed of at 37 + 0.5 the oar was set at 75rpm. 5ml of sample was dispensed at determined frequency; the same dose of the new substance was changed regularly. Samples were analyzed for drug content at a wavelength of 254 nm using a HPLC.

Table No. 3 In-*vitro* Dissolution Time of Oral Thin Films

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	00	00	00	00	00	00	00	00	00	00	00	00
2	29	27	31	25	19	17	21	18	14	26	28	32
5	42	39	43	41	34	31	36	39	29	42	43	48
10	63	66	67	64	51	53	49	50	48	61	58	66
15	81	86	82	79	69	67	73	74	69	84	76	78
20	96	94	91	92	86	85	90	89	83	91	92	95
25	--	--	--	--	92	90	--	93	95	--	--	--

Kinetics Studies

The dissolution results of all film formulations containing API in the pH 6.8 artificial saliva or pure water are applied to the computer program in order to determine the appropriate kinetic model. It is determined by mathematical programs and formulas that the formulations are compatible with 0. degree, 1. degree, Korsmeyer-Peppas or Higuchi models or not.

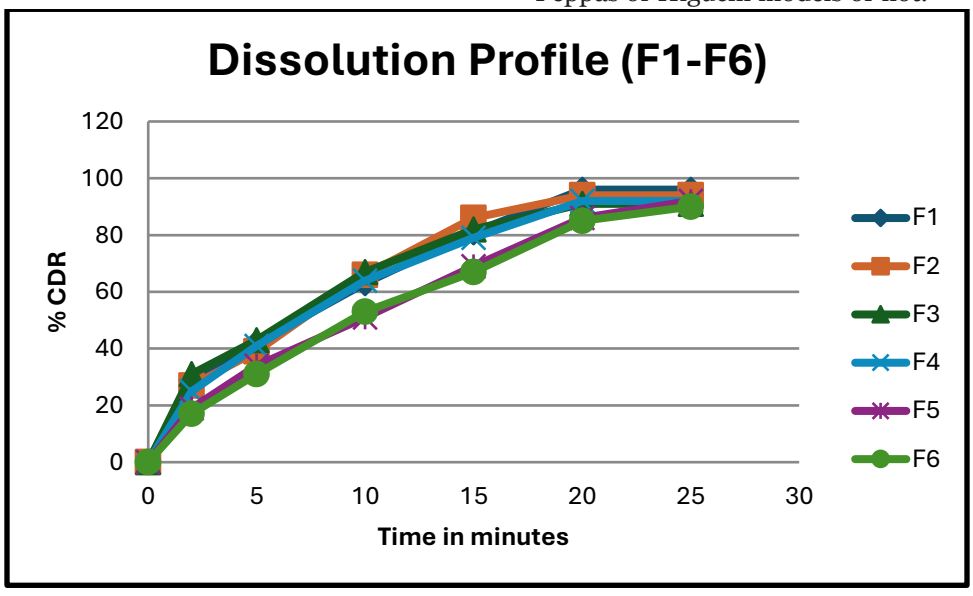

Figure No. 5 Dissolution Profile (F1-F6)

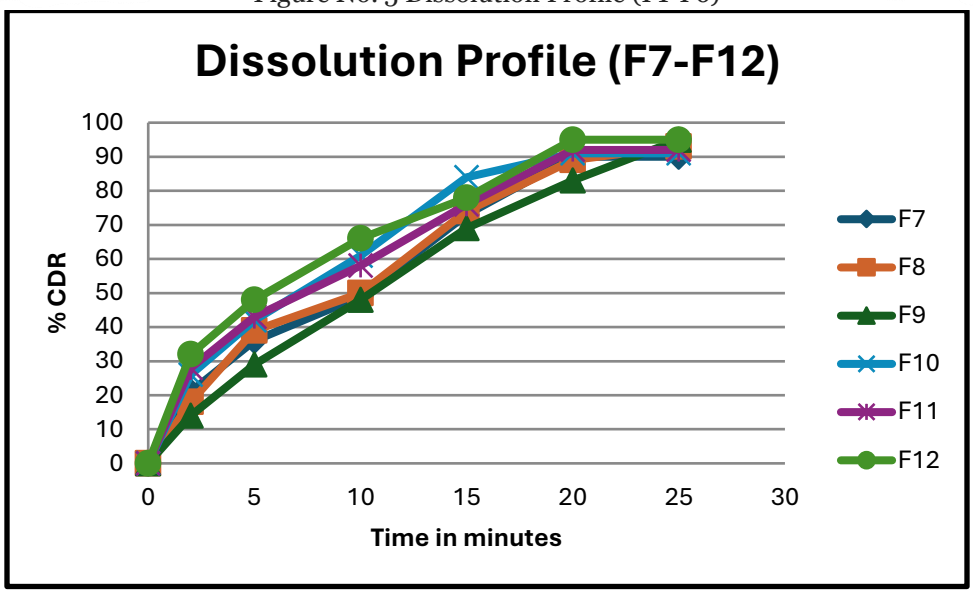

Figure No. 6 Dissolution Profile (F7-F12)

All formulated oral thin films (OTFs) were uniform, smooth, odorless, and exhibited either transparent or opaque appearances, with most batches (F1, F2, F3, F5, F6, F9, F10, F11, F12) being transparent and only F4, F7, and F8 opaque, suggesting that transparency was influenced by polymer–drug miscibility, while opacity could be due to higher polymer content or crystallization. The pH values of the films ranged from 6.5 to 7.6, remaining close to neutrality and thus unlikely to cause mucosal irritation, with F8 (7.4) and F9 (7.6) slightly alkaline but still physiologically acceptable. Thickness varied between 0.7 ± 0.065 mm (F1) and 1.5 ± 0.043 mm (F12), all within the pharmaceutically acceptable range, with thicker films corresponding to higher polymer ratios. Weight variation across formulations was minimal (88.96–99.24 mg) with low standard deviations, confirming reproducibility of the casting method and uniform drug–polymer distribution. Folding endurance ranged between 135 (F1) and 196 (F5), with none reaching the ≥300 standard for excellent flexibility but still showing good mechanical strength; F5 and F8 demonstrated the highest flexibility, while F1 and F10 had lower endurance likely due to reduced polymer content. Swelling indices ranged from 58.91 (F4) to 69.98 (F9), with higher swelling (F6, F9, F10) correlating with enhanced water uptake and faster disintegration, whereas lower values (F4) indicated reduced hydrophilicity. Transparency varied significantly (34–83%), with F2 and F9 being most transparent due to better polymer dispersion, while F3 and F10 exhibited lower values, possibly from drug crystallinity; opaque films (F4, F7, F8) were excluded from measurement. Drug content ranged between 94.36% (F10) and 98.62% (F2), with %RSD values below 1.5, confirming uniformity and compliance with pharmacopeial standards. In-vitro disintegration times were between 16 ± 1.431 s (F6) and 31 ± 1.349 s (F8), with most films disintegrating within the desired 5–30 s range; the fastest disintegration (F6) was associated with higher swelling and optimal polymer–plasticizer ratio, while longer times (F7, F8, F9, F12) correlated with increased thickness and polymer concentration.

CONCLUSION

The evaluation of Betahistine Dihydrochloride OTFs demonstrated that all formulations possessed satisfactory physicochemical and mechanical properties. Films were uniform, with acceptable pH, thickness, and weight variation. Drug content analysis confirmed uniformity and reproducibility. Disintegration and dissolution studies revealed that most films released the drug rapidly within 20 minutes, supporting their application as fast-dissolving oral systems.

Among all formulations, **F1** emerged as the optimized batch, exhibiting balanced mechanical strength, shortest disintegration time (21 s), high transparency, excellent drug content uniformity (97.46%). Stability studies further validated its robustness under storage conditions.

Thus, Betahistine Dihydrochloride OTFs, particularly formulation F1, offer a promising alternative for patients requiring rapid onset of action and improved compliance, particularly in cases where conventional dosage forms pose challenges.

Conflict of Interest:

We declare that we do not have conflict of interest.

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