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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF ORODISPERSIBLE FILM OF FEXOFENADINE HCl ANTIHISTAMINIC DRUG IN TREATMENT OF ALLERGY

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ABSTRACT:

Background:
Antihistamines play a crucial role in managing allergic conditions, and the newer, less sedating antihistamines are preferred due to their good safety profile and long-term efficacy. Fexofenadine HCl is a second-generation antihistamine primarily used to treat allergic rhinitis and chronic urticaria. Despite its efficacy, conventional dosage forms, such as tablets and syrups, pose challenges, particularly for paediatric and geriatric patients who may experience difficulty swallowing solid dosage forms. To address these limitations, orodispersible films (ODFs) have emerged as promising alternative dosage forms because of their ability to disintegrate rapidly upon contact with saliva, thus offering ease of administration without the need for water.

Materials and Methods: During pre-formulation studies, the drug excipient compatibility, flow properties, and disintegration time were thoroughly analyzed. Out of the polymers used, HPMC and HPC proved to be the most effective in creating the film.

Results and Discussion: The drug maintained its initial crystallinity and physical and chemical properties in the formulated ODF. By adding a surfactant and plasticizer, the tensile strength of the oral strip increased.

Conclusion: The solvent casting method was employed to fabricate the ODF using different polymers. HPMC and HPC were found to be optimal for film formation. The fexofenadine HCl drug retained its initial properties in the formulated ODF. Surfactant and plasticizer additives enhanced the film's tensile strength, ensuring stability and ease of distribution. The ODF exhibited excellent thickness, contributing to taste masking.

Keywords:
Allergic Rhinitis, Antihistamine, Fexofenadine Hydrochloride, Solvent Casting, In-Vitro Diffusion

INTRODUCTION

The history of antihistamine development was significant. First-generation antihistamines were introduced to the market earlier than others. Second-generation antihistamines were first available in 1980 and later.[1]

Antihistamines are commonly used to treat allergic conditions. There are two main types of antihistamine-sedating- sedating (first-generation) and less sedating (second-generation). Fewer sedating antihistamines are equally effective and can be taken long-term with a good safety profile. They are the mainstay treatment for mild to moderate allergic reactions, causing allergen-specific mast cell degranulation. Notably, antihistamines have no role in the acute management of anaphylaxis.[2]

The newer H1 antihistamines are recommended for allergic conditions, and they can be taken long-term without loss of efficacy. Antihistamines include loratadine, cetirizine, desloratadine, and fexofenadine. Therefore, it is important to consider dose reduction in patients with severe liver or kidney dysfunction. For ocular allergies, topical antihistamines with or without mast cell stabilizers, are recommended. Some topical products, such as ketotifen, azelastine, and olopatadine, have both antihistamine and mast cell-stabilizing effects.[3,4]

It is advised to avoid sedating antihistamines, especially in patients with known food allergies, as their sedative effects may mask the deterioration in consciousness caused by the underlying allergic reaction, indicating the onset of anaphylaxis and the requirement for adrenaline (epinephrine). However, fewer sedating antihistamines have fewer adverse effects. Although rare, idiosyncratic hypersensitivity reactions have been described for each antihistamine. Other reported adverse effects include headaches, fatigue, drowsiness, insomnia, and rash.[5]

Pharmacology of Fexofenadine

Fexofenadine HCl is a second-generation antihistamine primarily used to treat allergic rhinitis and chronic urticaria. Its pharmacology involves antagonizing the effects of histamine, which is a key mediator in allergic reactions. Here's a discussion on the antihistamine activity of fexofenadine HCl along with references:

Mechanism of Action:

- Fexofenadine HCl competitively antagonizes histamine at H1 receptors, preventing histamine from binding and exerting its effects.[6]
- By blocking the histamine receptor, fexofenadine inhibits the histamine-induced vasodilation, increased vascular permeability, and bronchoconstriction characteristic of allergic reactions.[7]

Pharmacokinetics:

- Fexofenadine is rapidly absorbed from the gastrointestinal tract after oral administration.
- It undergoes minimal metabolism in the liver, primarily via the enzyme P-glycoprotein, and is excreted largely unchanged in the urine.
- The drug reaches peak plasma concentrations within 1-3 hours after oral administration.[8]

Clinical Efficacy:

- Clinical studies have demonstrated the efficacy of fexofenadine HCl in relieving symptoms associated with allergic rhinitis and chronic idiopathic urticaria.
- It effectively reduces sneezing, nasal itching, rhinorrhea, and ocular symptoms in allergic rhinitis.
- In chronic urticaria, fexofenadine alleviates pruritus and reduces the number and size of hives.[9]

Despite its efficacy, conventional dosage forms of Fexofenadine HCl, such as tablets and syrups, pose challenges, particularly for pediatric and geriatric patients who may experience difficulty swallowing solid dosage forms. To address these limitations, oro-dispersible films (ODFs) have emerged as promising alternative dosage forms because of their ability to disintegrate rapidly upon contact with saliva, thus offering ease of administration without the need for water. ODFs adhere to the oral mucosa, facilitating rapid drug absorption and the onset of action, making them particularly suitable for drugs intended for immediate release. Additionally, ODFs offer advantages, such as precise dosing, improved patient compliance, and enhanced bioavailability.[10]

The formulation of ODFs involves the selection of appropriate film-forming polymers, plasticizers, and other excipients to achieve the desired mechanical properties, disintegration characteristics, and drug-release profiles. Various polymers, such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and sodium alginate have been investigated for their suitability in ODF formulations. Plasticizers such as glycerine and propylene glycol are commonly used to impart flexibility and improve film formation.[11]

The delivery of drugs through the oral mucosa provides several benefits when compared to the traditional oral route. By bypassing contact with the tongue, pharynx, esophagus, and stomach, the drug avoids potential degradation and metabolism. The absence of physical and enzymatic digestive activity in the mouth also slows down the effects of food on the drug, resulting in reduced systemic availability and efficacy compared to fasting conditions. Orodispersible films are a preferred dosage form due to the various advantages they offer. They eliminate the risk of choking, which is especially crucial for pediatric and geriatric patients. Additionally, orodispersible dosage forms should be easy to handle, allowing patients to easily consume liquids while taking the medication. In the case of slow-release drugs, it is particularly important to use drug-coated orodispersible films as they rapidly disintegrate, ensuring that the oral mucosa is in contact with the drug, leading to wider distribution in the mouth.[12,13]

MATERIALS AND METHODS

Fexofenadine HCl was received as a gift sample from Dr. Reddy's Laboratories Pvt Ltd, Hyderabad, India. Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), and Maltodextrin, and Croscarmellose Sodium were procured from S.D. Fine Chem, Mumbai, and all other chemicals and solvents were of analytical grade. Sweeteners and natural flavoring agents were used to add sweetness to the taste.

METHODS

Preformulation study

Physical characterization: Fexofenadine HCl. Color, odor, and appearance were analysed manually.

Melting point determination: The melting point of Fexofenadine HCl was estimated with a digital melting point apparatus having a temperature range of up to 350^{o}C with a heating rate of 1–20^{o}C per minute. The sample under examination was filled in glass melting point capillaries and placed into the holder and the melting point apparatus was operated. The melting point obtained in the experiment was compared with the standard melting point of Fexofenadine HCl reported in the literature or official compendia.

Solubility analysis: The qualitative solubility analysis of Fexofenadine HCl was performed in ethanol, ethanol:0.1 M HCl (50:50), and water. A small amount of Fexofenadine HCl (10–20 mg) was added to a test tube containing solvent and manually shaken for a few minutes. The solubility was determined by physical observation.

Calibration curve for Fexofenadine HCl

The solution of Fexofenadine HCl was prepared in solvent ethanol. This solution was scanned in a UV-spectrophotometer region (200-400nm) and maximum absorbance was determined for this solution.

To determine the wavelength of maximum absorption (λmax) of the drug, different solutions of the drug (10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml, and 60µg/ml) in ethanol was scanned using UV-spectrophotometer within the wavelength region of 200-400nm against ethanol as blank. The absorption curve shows characteristics of absorption at 220 nm for Fexofenadine HCl.

Drug Excipient Compatibility Study

During pre-formulation studies, the drug excipient compatibility, flow properties, and disintegration time were thoroughly analyzed. All the results were found to be satisfactory for the further process of product development.

Formulation of Fexofenadine HCl (ODF)

The technique known as the solvent casting method was employed to create an orodispersible film of Fexofenadine HCl. The polymer solution was then thoroughly mixed with a stirring device, after which the appropriate dosage of the drug was introduced. Subsequently, both the plasticizer and sweetening agent were added and thoroughly incorporated into the solution. The resulting solution was carefully poured into a spotlessly clean flat stainless steel pan, which had been lined with a clean glass marble on all sides. The solution was poured to achieve a thickness ranging from 3-5 mm and then subjected to a temperature of 50°C ± 20°C to dry out the solvent. Once the film had dried, it was delicately peeled off the marble and transferred to a desiccator. To ensure proper preservation, the films were wrapped in amber-coloredaluminum foil and stored at room temperature until they were ready for further utilization.[14]

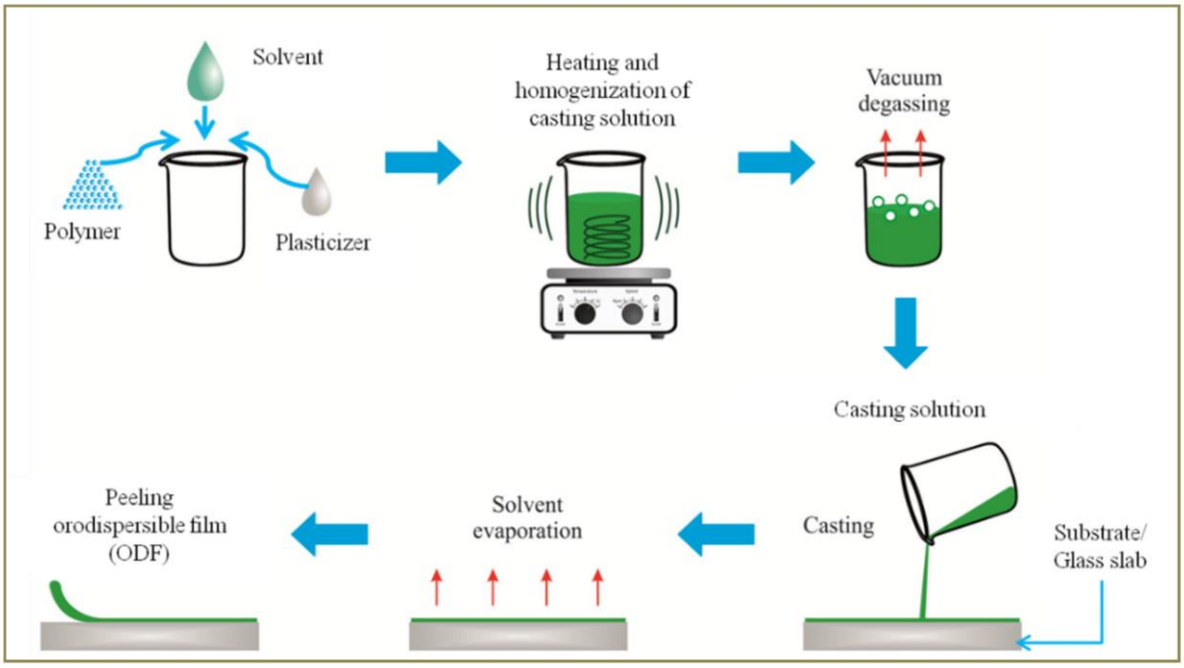


Figure 1: Procedure of Solvent Casting Method for ODF

Table 1:3^2 full factorial Design

3^2 FULL FACTORIAL DESIGN	
INDEPENDENT VARIABLES	X_1= Hydroxypropyl Methylcellulose (HPMC)
	X_2= Hydroxypropyl Cellulose (HPC)
DEPENDENT VARIABLES	Y_1=Tensile strength(N/m^2)
	Y_2=*In-vitro* disintegration time
	Y_3=In-vitro drug release in T80%

Table 2:3^2 Full Factorial Design Layouts

Variables	**Levels**		
	Low	**Medium**	**High**
	-1	0	1
Hydroxypropyl Methylcellulose (HPMC)	3	4	5
Hydroxypropyl Cellulose (HPC)	3	4	5

Table 3: Formulation of 3^2 full factorial batches

Ingredients	Batch Code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Fexofenadine HCl	90	90	90	90	90	90	90	90	90
Hydroxypropyl Methylcellulose (HPMC) 15 cps	3	4	4	4	5	3	3	5	5
Hydroxypropyl Cellulose (HPC)	4	3	4	5	4	5	3	5	3
Maltodextrin 15 cps	4	4	4	4	4	4	4	4	4
Croscarmellose Sodium (AcDiSol)	10	10	10	10	10	10	10	10	10
Propylene Glycol	20	20	20	20	20	20	20	20	20
Triethyl Citrate (TEC)	20	20	20	20	20	20	20	20	20
Aspartame	4	4	4	4	4	4	4	4	4
Water	10	10	10	10	10	10	10	10	10

EVALUATION OF THE PREPARED FILMS:

The prepared bioadhesive films were evaluated for various in-vitro and in-vivo properties like appearance, thickness, weight uniformity, folding endurance, drug content uniformity, surface pH, and palatability test. It was observed that the obtained films were uniform in thickness, weight uniform, uniform in drug content, and the drug component was uniformly dispersed in the polymer matrix of the film without any granules of the drug being left out. The folding endurance was determined for the prepared bioadhesive films. It was found to be very high. The weight uniformity of the original method showed a deviation in weight of 0.04 mg, causing a deviation in weight. Henceforth, this method was optimized to be soluble in water. Henceforth, less weight variation can be attained when the weighed dose of the drug in each method is done using a caliper and balance, compared to easily removed and any other film.[15]

Physicochemical Characterization

Dose uniformity of film:

The fexofenadine HCl leave was prepared as a film that was cut into small equal sizes of 1x1 cm. Ten film strips were weighed individually and the weights of each film were recorded. If the weight deviation of the ten film strips did not exceed 10%, it was considered as passing in the uniformity of dosage.[16]

Thickness of film:

The film's thickness was measured using a screw gauge at three randomly selected locations. A precise micrometer screw gauge was used to accurately measure the thickness in millimeters at these points. The surface pH was assessed to determine if there could be any potential irritation in the mouth and degradation of the oral film. The thickness was also measured using a scale at three randomly chosen points on three separate films.[17]

Tensile strength:

In the mechanical test of the orodispersible film, the tensile strength was observed between the film and the clamp of the universal testing machine. The films were stretched, and the change in length was observed. Elongation shows how far the film can be stretched before reaching the breakpoint, and the tensile strength shows how strong it is when stretched. The Young's modulus was also calculated using the standard formula from the slope of the graph obtained during the tensile strength test. Is the maximum stress applied to a point at which the film specimen breaks. The tensile strength (TS) can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it is expressed in force per unit area (kg/cm^2).[18,19]

Folding endurance:

The folding endurance is a measure of the stiffness of the film and is determined by repeatedly folding it at the same place until it breaks. All the film formulations showed values of more than 300. A low value is indicative of a weak film, and it may be due to the loss of volatile plasticizer the stiffening of the films, or the use of a high molecular weight grade of film-forming agents.[20]

In-vitro disintegration time

The in vitro disintegration time was measured for a film of each batch in 10 ml of simulated saliva (pH 6.8). A film sample (2 cm x 2 cm) was placed in 10 ml of simulated saliva on a Petri plate. The medium was swirled every 5 seconds. The time for complete dissolution of the film was recorded as disintegration time. The average of three measurements was taken into consideration.

Content Uniformity

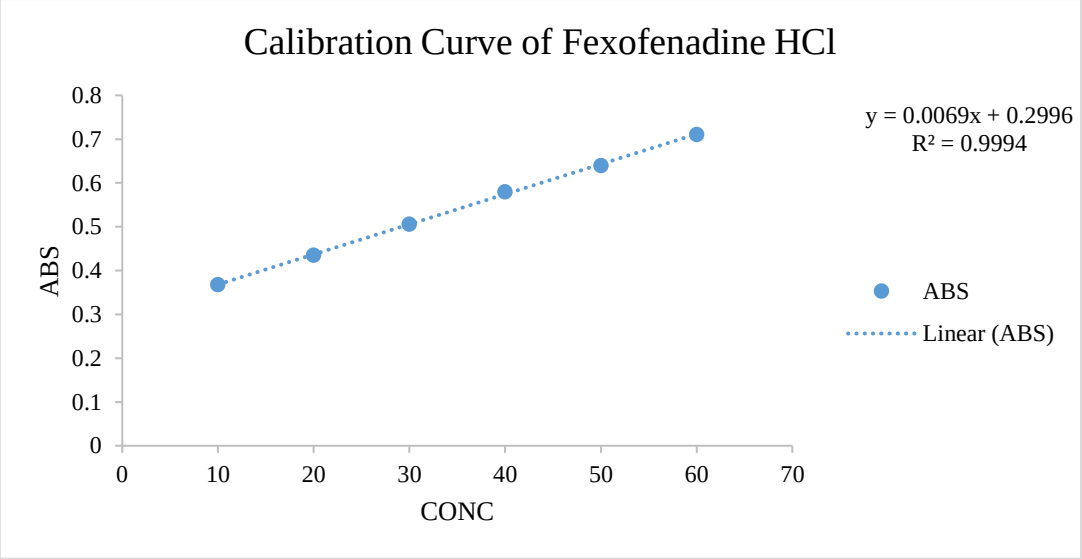
The films were tested for content uniformity. Films of size one square inch were cut, placed in 100 ml volumetric flask and dissolved in phosphate buffer pH 6.8, volume was made up to 100 ml with phosphate buffer pH 6.8. The solution was suitably diluted. The absorbance of the solution was measured at 220nm.

In-vitro drug release in T80%

The dissolution studies of the commercially available antihistaminic drug Fexofenadine HCl ODF were carried out using USP II type apparatus as per the specifications in EP for ODF, using 900ml of 0.1N HCl and 0.2% Tween80. The studies were conducted at 37 ± 0.5°C for 30 minutes. 5ml samples were withdrawn from the test mixture at 5-minute intervals and the same amount of medium was replaced after the test. The method was repeated for triplicate tests. The dissolution studies were carried out using a Dissolution Tester DS 14000 (Lab India) and Shimadzu UV-1800 spectrophotometer to estimate the drugs released at 220nm and 254nm with appropriate dilutions.[21]

RESULTS:

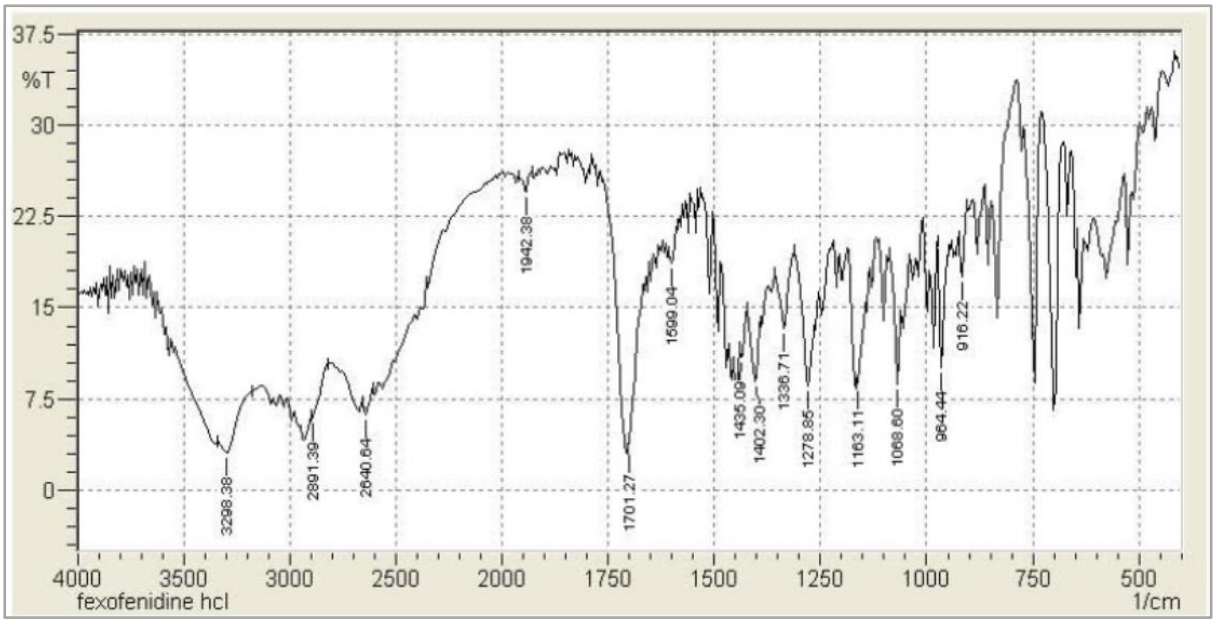
Physical characterization of Fexofenadine HCl is obtained as a white to off-white crystalline powder. The melting point was found 143 ^oC and confirmed with reference.



Graph 1: Calibration curve of Fexofenadine hydrochloride

FTIR Spectroscopy

The FTIR spectra of fexofenadine HCl were captured and analyzed. The drug sample showed the expected IR absorption peaks, confirming the fexofenadine HCl purity.



Graph 2:FTIR spectra of pure fexofenadine HCl

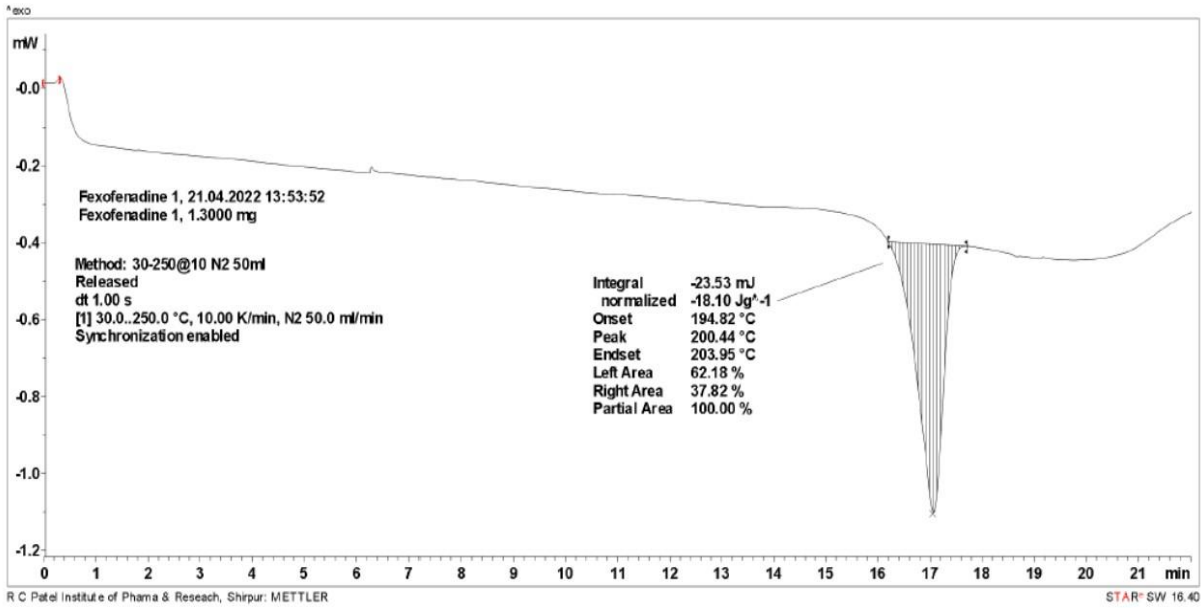
Table 4: Principal peaks obtained in fexofenadine HCl pure drug

Sr. No	Standard peak(cm-1)	Observed peak (cm-1)	Interpretation
1.	1200–1020	1068.60	C-OH stretching (carboxylic acid)
2.	3600–2500	3298.38	O-H stretching (carboxylic acid)
3.	2960–2850	2891.39	C-H stretching (aldehyde)

4.	1600–1400	1402.30	C=C stretching
5.	1250–1050	1163.11	C-O-C stretching

Differential Scanning Calorimetry (DSC)

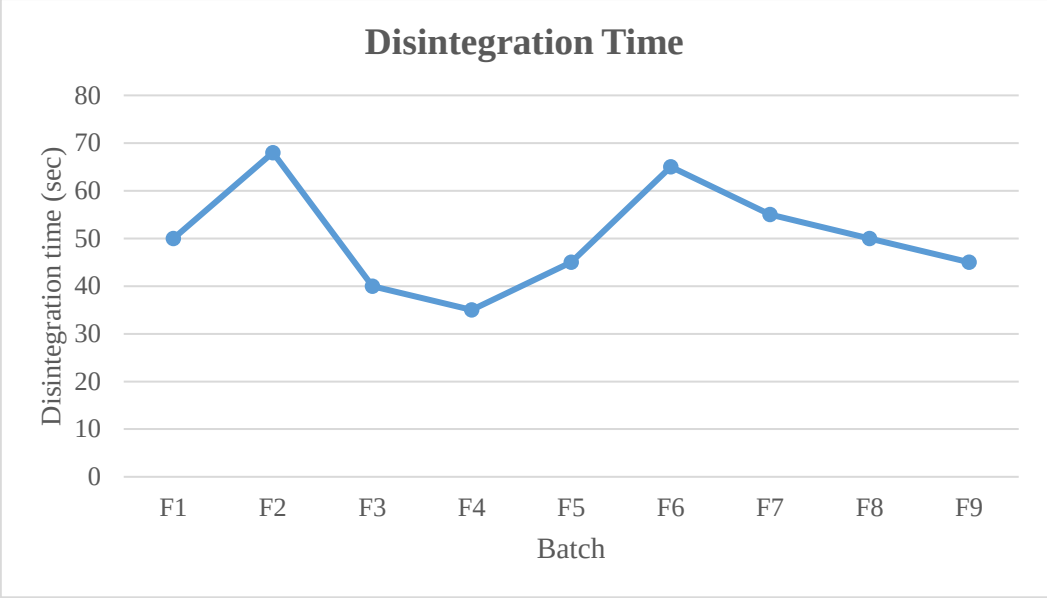
The fexofenadine HCl DSC curve exhibits an endothermic peak at 200.44°C.



Graph 3: Differential scanning calorimetric thermogram of Fexofenadine HCl

Table 5: Result of Evaluation Test

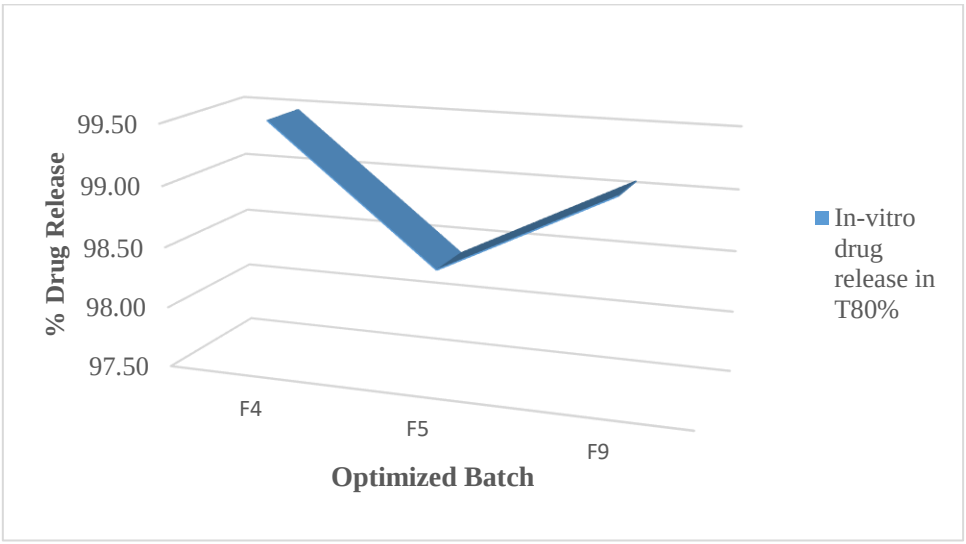
Batch	Parameter	Weight variation(mg)	Thickness of film(mm)	Tensile strength	Folding endurance	Disintegration time(sec)
F1		165±0.08	0.81±0.06	214	240	50±1.2
F2		165±0.07	0.82±0.04	218	268	68±1.1
F3		166±0.05	0.83±0.08	216	280	40±1.2
F4		167±0.06	0.82±0.04	220	305	35±1.2
F5		167±0.07	0.84±0.04	222	301	45±1.4
F6		166±0.07	0.83±0.08	215	280	65±1.4
F7		164±0.08	0.83±0.06	218	290	55±1.3
F8		168±0.05	0.88±0.07	228	310	50±1.2
F9		166±0.07	0.83±0.06	215	305	45±1.3



Graph 4: Disintegration Time of all Batches

Table 6: Result of Optimized Batches

	In-vitrodisintegration time	**In-vitro drug release in T80%**
F4	**35±1.2**	**99.5%**
F5	45±1.4	98.4%
F9	45±1.3	99.1%



Graph 5:% Drug release in T80

DISCUSSION

Nine formulations were prepared by changing the concentration of polymer and plasticizer. The ODF was prepared by film casting technique. The film thickness, weight, and content

uniformity were evaluated. The mechanical properties of the film were analyzed. The standard ratio content uniformity was 98-100%. The mechanical properties of the orodispersible films were measured. F4 orodispersible film formulation was the best formulation based on the physical properties and requested attributes of the orodispersible film.

CONCLUSION

Non-sedating antihistamine, fexofenadine HCl, is often administered to treat many forms of allergies, such as hay fever, allergy to pet dander, skin allergies, urticaria, and other respiratory allergies. Since gels and patches containing fexofenadine HClare known to be allergenic, an orodispersible film containing fexofenadine HCl was prepared for use in the oral cavity. Upon prolonged contact with the mucous membrane, the film dissolved rapidly in saliva, yielding a clear fexofenadine HCl oral solution that might be swallowed or absorbed through the oral mucosa. The film was prepared to have excellent tensile strength, disintegration time, thickness, and drug release.

The solvent casting method successfully resulted in the development of an orodispersible film that contains fexofenadine hydrochloride. Out of the polymers used, HPMC and HPC proved to be the most effective in creating the film. The fexofenadine drug maintained its initial crystallinity and physical and chemical properties in the formulated ODF. By adding a surfactant and plasticizer, the tensile strength of the oral strip increased. This optimized the oral strips to have sufficient tensile strength for stability and distribution of the film. Additionally, the ODF's excellent thickness contributed to its ability to mask unpleasant taste. Since we measure disintegration time, it is possible that the fexofenadine suspension can be absorbed directly upon contact with oral mucosal tissue, particularly the buccal membrane.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ODF	Orodispersible film
ARIA	Allergic Rhinitis and its Impact on Asthma
SAR	Seasonal Allergic Rhinitis
FTIR	
UV	
HPMC	Hydroxypropyl methylcellulose
CPS	Centipoises
TEC	Triethyl Citrate
HPC	Hydroxypropyl Cellulose
HCl	Hydrochloric Acid

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