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Formulation development of oral disintegrating film of fexofenadine hydrochloride

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ABSTRACT

The present study aimed to develop an oral disintegrating film of fexofenadine hydrochloride for the immediate management of allergies and related symptoms. The formulation of fast dissolving oral film was carried out by solvent casting method using two different grades of hydroxy propyl methyl cellulose, polyvinyl pyrrolidone, polyvinyl acetate, and pullulan as polymers and different plasticizers. Six such films were produced. The films were evaluated for their physicochemical and mechanical properties. Compatibility and thermal studies were carried out. The surface morphology of the films was studied. All six formulations were evaluated for surface pH, disintegration, and drug release study in simulated saliva. The best films were taken for stability studies. Formulations prepared with all the polymers in different proportions of plasticizers could produce a non-sticky stable film. The thermal studies revealed the uniform dispersion of the drug in the polymer matrix. Films prepared with pullulan showed better flexibility and dissolution behavior. Stability studies of the pullulan films highlighted that the films were stable and could retain their physical and mechanical properties. Hence, it can be concluded that pullulan can be successfully employed to prepare fast dissolving oral films of fexofenadine hydrochloride.

Keywords: Fexofenadine hydrochloride, Oral disintegrating film, Plasticizers, Mechanical properties, pullulan.

INTRODUCTION

Oral disintegrating films are a new type of dosage form that is particularly well

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suited to juvenile and geriatric patients. These are the thin strips that are largely transparent, biodegradable, and contain hydrophilic polymers when simply placed on the patient's tongue they disintegrate and dissolve quickly in the oral cavity when exposed to saliva, and no additional water is required for drug administration and release of the drug[1]. This type of delivery has the potential to increase patient compliance, especially for the pediatric population and for people suffering from mental illnesses, dysphagia, or emesis. Absorption of the drug by oral mucosa into the systemic circulation is an interesting approach, the drug absorbs directly into the systemic circulation, bypassing the first-pass metabolism in the liver[2].

Fexofenadine hydrochloride (FXD), an H1 antagonist is used to ease seasonal allergic rhinitis and hives. Conventional oral dosage form of FXD includes tablets and liquid oral which suffer from the drawback of slow onset of action and variable absorption on food intake. Approximately 80% of the ingested drug is eliminated primarily by biliary and renal secretion[3].

FXD belongs to class III of the Biopharmaceutical Classification System and shows variable absorption with oral bioavailability of 35%[4]. The adult daily dose of FXD is limited to 180mg, whereas the child dose is limited to 30 mg per day[5].

The present research work proposes a formulation of oral disintegrating films of FXD to provide a rapid onset of action and improvement of bioavailability. They can be administered without water, and are ideal for children. They are flexible and easy to carry[6].

The ability of the oral films primarily depends on the water solubility and film-forming ability of the polymer used. The critical parameter is the polymer to plasticizer ratio that provides the mechanical strength of the films.

Garsuch V. et al. reported the film-forming ability of hydroxypropyl methylcellulose[7]. Jantrawut P. et al. investigated and reported the effect of different plasticizers like PEG 400, glycerin, and propylene glycol on the mechanical properties of the film[8]. In another study, Pezik E. et al. commented-on pullulan as a good film-forming agent for rapid action of drugs from an orally disintegrating film[9]. The use of a combination of polymer of polyvinyl pyrrolidone and polyvinyl acetate in the formulation of fast dissolving films was reported by Chaklan N. et al[10].

Hence the present study explores the combination of different types of polymers and plasticizers to formulate oral disintegrating films of FXD and observed the effect of the variation in polymer and plasticizer content on the physicochemical and mechanical properties of the film.

METHODOLOGY

FXD was purchased from Yarrow chemicals, Mumbai, Maharashtra. Pullulan was procured from Gangwal chemicals, Mumbai, Maharashtra. Hydroxypropyl methylcellulose (HPMC) 15cp and 5 cp, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), sodium starch glycollate (SSG), polyethylene glycol 400 (PEG 400), glycerine, propylene glycol, ethanol, and mannitol were procured from SD fine chemicals, Bangalore, India.

Fourier transform infrared (FTIR) spectroscopy study

The compatibility study of the FXD with different polymers in a physical mixture of 1:2 was carried out by Fourier transform infrared (FTIR) spectroscopy Shimadzu, Tokyo, Japan. The IR spectra of the samples were obtained using the KBr pellet method in the range between 400 to 4,000cm^{-1} at ambient temperature [11].

Preparation of oral film

The solvent casting approach was used to make the oral film. Six such FXD-loaded orally disintegrating films (F1-F6) were prepared using different polymers, and plasticizers as mentioned in table 1.

Table 1. Composition of the oral films of FXD

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Drug (mg)	30	30	30	30	30	30
HPMC 15 cp (%w/v)	20	--	--	--	--	--
HPMC 5 cp (%w/v)	--	20	--	--	--	--
PVP (%w/v)	--	--	10	--	--	--
PVA (%w/v)	--	--	10	--	--	--
Pullulan (%w/v)	--	--	--	20	20	20
PEG400 (%w/v)	3	2	3	2	--	2
Propylene glycol (%w/v)	--	--	--	1	3	--
Glycerine (%w/v)	--	1	--	--	--	1
SSG (%w/v)	3	3	3	3	3	3
Mannitol (%w/v)	1.5	1.5	1.5	1.5	1.5	1.5
DM Water (q.s) (ml)	5	5	5	5	5	5

The drug was dissolved in ethanol. The polymers as per table 1 were dispersed in distilled water under magnetic stirring to which the drug solution was added. To this homogenous solution of polymer and drug, the required quantity of plasticizer, disintegrants, and sweeteners was added. The entire dispersion was continued to stir using a magnetic stirrer at 800rpm for 30min[12,13]. The prepared mixture was set aside for 15min to remove any bubbles before being poured into the fabricated 8cm^2 glass mold. The casted films were dried for 45–50 minutes in a laminar hot-air oven at 60°C. The film was carefully peeled off after drying, packaged in plastic zip pouches (polythene), and stored in a desiccator for further characterization.

Evaluation of the prepared films

Differential scanning calorimetric (DSC) study

Samples weighing approximately 5mg were placed in an Aluminum crucible and heated at a rate of 10/min on a Perkin Elmer STA 8000 series instrument from room temperature to 500°C. The thermograms were recorded for the pure drug and the physical mixture of drug with different polymers[14].

Drug content

Each film of the sample (1cm^2) was dissolved in methanol to extract the drug. The sample was suitably diluted with pH 6.8 buffer and analyzed at 277nm using a UV spectrophotometer (UV-1900i, Shimadzu, Tokyo) against a suitable blank prepared from the non-medicated film. This experimentation was done with three trials for all the formulations (F1-F6) [15,16].

Film Thickness

The thickness of the film (2cm(L) X 8cm (W)) was measured with a digital vernier caliper (Mitutoyo), and the average value was calculated. The thickness was measured at 5 different points throughout the film to ensure uniformity. The estimation was carried out in triplicate for all the prepared films[17].

Moisture loss

To determine the moisture content in the films, the freshly prepared film (4cm^2) of the formulations (F1-F6) was weighed and placed in desiccators containing anhydrous calcium chloride under airtight conditions. The film was reweighed after 3 days to determine the percentage of moisture loss [18].

$$Percentage\ moisure\ loss\ = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Film pH

The film to be tested was moistened with distilled water and stored in a Petri dish for 1h, and the pH of the solution was recorded using the pH meter Digisun electronic system, Model No:2001. The experimentation was carried out thrice for each film [17].

Swelling index

The studies on the swelling index of the films (F1-F6) (2cm(L) X 2cm(W)) were carried out in pH 6.8 phosphate buffer solution. Each film was weighed and placed in a pre-weighed stainless-steel wire sieve. The film was submerged in phosphate buffer pH 6.8 on a Petri dish. At a specified interval (1min), the rise in film weight was measured until a constant weight was recorded. In this test, three films of each formula were employed [19]. The degree of swelling was determined by using the following formula:

$$Swelling\ index = \frac{W_t - W_0}{W_0}$$

Where, is the weight of the film at the time t; is the Weight of film at t = 0

Mechanical properties of the film

Folding endurance

Randomly selected films (2cm(L) X 2cm (W)) from each formulation were folded at the same place until any signs of fracture were visible. Folding endurance was determined for all the films (F1-F6) to observe how many times the films could be folded without breaking or showing noticeable fissures[20]. Each experiment was carried out thrice.

Tensile strength, percentage elongation, and young's modulus

The tensile strength of films, F1 to F6 was measured to estimate the resistance of the film against the applied forces from breaking down. The tensile strength was measured using a tensiometer by holding a film (an area approximately 2cm × 2cm) longitudinally in it and drawn against an increasing load at a rate of 10mm/min. Tensile strength is calculated mathematically by the equation illustrated below[21,22].

$$\sigma_{TS} = \frac{F_{max}}{A}$$

where, is the tensile strength of the film, is the maximum load applied on the film till it breaks, and A is the initial cross-sectional area of the sample.

During the process of estimating tensile strength, the length elongation was measured for each film.

The increase in the length of the film was used to determine percentage elongation (%E) using the formula [23].

$$\%\varepsilon = \frac{\Delta L}{L_0} \times 100$$

Where percent ε is elongation at break, ΔL is the increase in length, and L_o is the sample's initial length.

The hardness of the oral disintegrating film was measured by calculating the young modulus as per the following formula.

$$E = \frac{F}{A} \times \frac{1}{\varepsilon}$$

Where, E is elastic modulus, which is Young's modulus, F is the force at the corresponding strain, *A* is the sample's initial cross-sectional area, and ε is the corresponding strain[24].

Disintegration time

The disintegration time of each film (8cm^2) was measured by placing a unit dose of the formulated film in a petri-dish containing distilled water and the time taken for the film to complete breakdown was noted[25,26].

In vitro dissolution study

The *in vitro* dissolution study was carried out by using USP dissolution apparatus type-II with 900ml of simulated salivary fluid of pH 6.8 at 37±0.5°C at 100rpm. A film size of 8cm^2 was used as dose size. In the dissolution apparatus, the film was attached with adhesive tape on a glass disk and placed at the center of the vessel[27]. At specified intervals, specific volumes of samples were collected for 60min and replaced with an equivalent volume of the blank dissolution media. The blank of each formulation was subjected to dissolution at the same condition and used as a blank to negate the effect of excipients in the determination of drug spectrophotometrically. The filtered samples were analyzed at a wavelength of 277nm for drug concentration, and the percentage (%) of drug dissolved or released was calculated. The drug release study of all the films (F1-F6) was compared with a popular commercial tablet available in India.

Scanning Electron Microscope study (SEM)

SEM study was carried out using Zeiss, ultra 55 (GEMINI® technology), to study the surface morphology of the films. The film was adhered to the stubs with adhesive carbon and then sputter-coated with a thin gold-palladium layer. The coated samples were scanned at 5kV[18].

Statistical analysis

All the six formulations were subjected to Dunnett's multiple comparison test using graph pad prism software V5, considering the parameters of disintegration time, drug release at the earliest, and the mechanical strength of the films. The ANOVA study was carried out at a significance level of $p<0.05$.

Stability testing

Stability testing was carried out for the best formulations (F4, F5, and F6). The films were stored in the aluminum package at 40 ±5°C and 75±5%RH for 28 days. The films were tested for physicochemical and mechanical properties at a specific interval of time[9].

RESULTS and DISCUSSION

FTIR study

The FTIR spectra showed the characteristics peak of the pure drug at 1704. 1470. 1278 and 1167cm^{-1} for the major functional groups like carbonyl stretching, aromatic stretching, and C-O stretching of tertiary alcohol respectively, the same peaks were preserved in the combinations of drug and different polymers used in the oral films. Major functional groups were retained in all the combinations as shown in figure 1, which indicated the absence of any interactions between the drug and polymers[28].

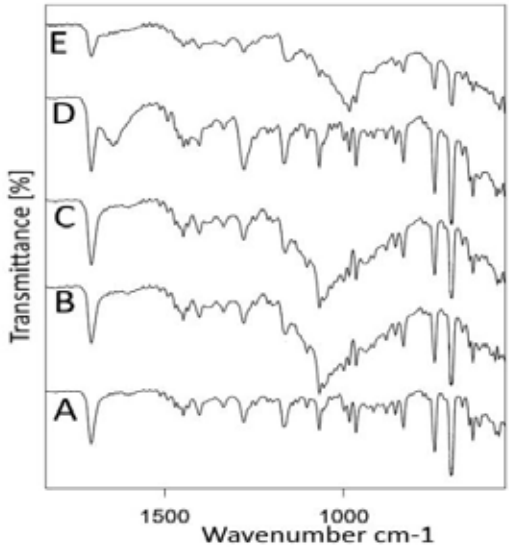

Figure 1. FTIR spectra of Pure drug FXD (A), FXD and HPMC 15cp(B), FXD and HPMC 5cp(C), FXD and PVP+PVA(D), FXD and Pullulan(E).

DSC Study

The DSC thermograms showed a sharp endothermic peak of the pure drug at 192°C[29]. The drug dispersion in the various polymer mixture showed a reduction of the peak intensities to a great extent. The reduced intensity of the endothermic peaks of the pure drug represented the conversion of crystalline to the amorphous state of the drug as shown in figure 2.

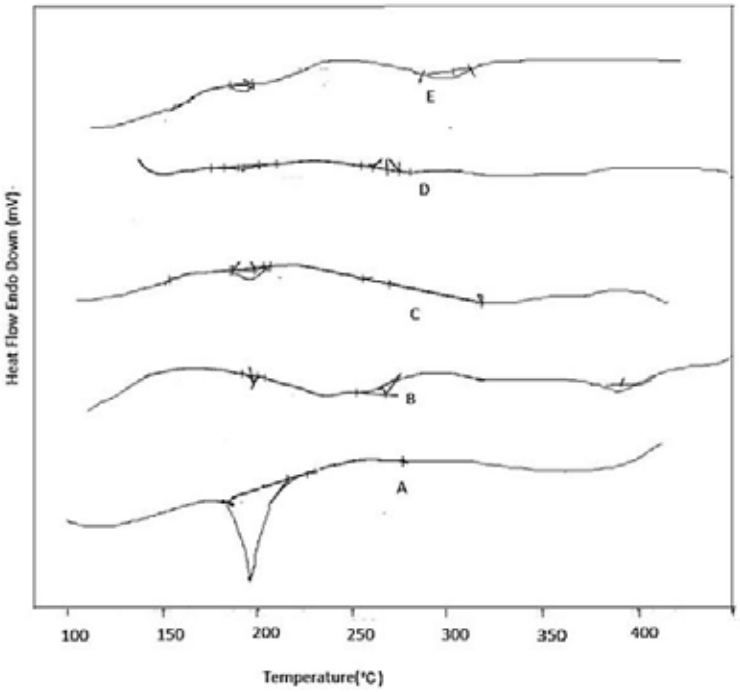

Figure 2. DSC thermograms of Pure drug FXD(A) and films of different polymers (B-HPMC 15 cps, C- HPMC 5 cps, D-PVP and PVA, E-Pullulan)

This is an indication of the dispersion of the drug in different polymer matrices. Hence it can be concluded that the drug was molecularly dispersed in the polymer matrices. Miscibility of the drug with the polymers confirms the formation of miscible dispersion. Therefore, all the selected polymers were found to be suitable for the formulation of the oral disintegrating film of FXD. The glass transition temperature of the prepared films was found to be greater than the temperature of the buccal cavity and environment, which proves the stability of the film during manufacturing, and storage.

Physicochemical evaluation of the prepared films

The prepared six films were found to be smooth and opaque with a uniform dispersion of drug in the films. The physical characteristics of the films are summarized in table 2.

Table 2. Evaluation of the oral disintegrating films of fexofenadine hydrochloride

Formulation	Drug Content (%)	Thickness (mm)	Weight (mg)	pH	Moisture content(%)	Swelling index
F1	98.78±0.01	0.032±0.01	66.3±0.03	6.8	0.85±0.85	1.76±4.70
F2	99.12±0.023	0.035±0.02	64.3±0.02	6.4	0.87±0.69	2.79±1.01
F3	99.05±0.04	0.027±0.02	57.6±0.05	6.6	0.45±0.09	6.12±2.90
F4	99.44±0.02	0.025±0.03	56.6±0.01	5.5	0.88±0.21	1.73±1.04
F5	99.61±0.12	0.021±0.02	60.5±0.04	5.6	0.83±0.68	1.77±1.94
F6	99.75±0.05	0.023±0.01	58.5±0.04	5.5	0.84±0.74	1.33±1.93

The drug content of the films was found to be more than 98%, which indicated that the drug was distributed homogeneously in the polymer matrix. The drug content of all the films was found to be in the acceptable pharmacopeial range for standard oral solids.

The thickness of the films was measured at 5 different points of the prepared films and found that the standard deviation was less than 0.05, which indicated the thickness of all the films was uniform. It also revealed that the prepared drug-polymer dispersion had optimum viscosity to be spread over the fabricated dish uniformly by solvent casting method. For an oral film, the thickness should be 12 to 100μm[4]. The thickness of the film was found to be high for the films prepared by HPMC polymers (F1 and F2). Rest all the films prepared had a thickness varied from 0.021 to 0.027mm. This variation in thickness might be due to the difference in composition of the films which resulted in various viscosity and the spreadability of the dispersion over the petri dish. The average weight of the films was slightly high for the films made with HPMC. The pH of all the films was found to be in the range of 5.5-6.8. The surface pH of the films indicated the non-irritability of the films for oral mucosa. The mechanical properties of the films are greatly affected by the moisture content. This quality control parameter enables to detect the protection of the films against drying out during storage. All the formulations showed a moderate moisture content to retain the plasticizing effect of the films. Formulation F3 containing PVP and PVA was found to be brittle on storage as indicated by the moisture content and folding endurance. The swelling index for the films varied widely because of the composition of the films. A high swelling index is an indication of high viscosity on the absorption of moisture and thereby a slow release. Formulation F3 showed a very high swelling index compare to the other formulations. Folding endurance was found to be the best for films containing

HPMC (F1 and F2), it is due to the comparatively high thickness and weight, and moisture content of the films. Films prepared with pullulan (F4, F5, and F6) were also found to be good for arresting the breakage during folding[30]. But the films prepared with PVP and PVA (F3) are not found to be satisfactory in durability as indicated by the low value of folding endurance.

Mechanical Properties

The deformation of a film under applied stress determines the mechanical strength of the film. Mechanical strength is an ideal property of an orally disintegrating film. The mechanical strength of oral disintegrating films is estimated by the determination of folding endurance, tensile strength, percentage elongation, and young modulus. The folding endurance of all the films was found to be more than 110 except for formulation F3. Higher folding endurance was indicative of high mechanical strength of the films. The elongation of the film increases as the plasticizer content rises. The use of a mixture of plasticizers was found to be good in formulations F4, F5, and F6. An optimum elongation was obtained from each formulation. Young's modulus, also known as elastic modulus, is a measurement of the film's stiffness and a correlation between applied stress to strain. An ideal film is characterized by higher folding endurance and tensile strength, and low elastic modulus[31]. The films produced by HPMC (F1 and F2) and Pullulan (F4, F5, and F6) were quite strong compared to films produced by PVP and PVA (F3) as shown in table 3.

Table 3. Mechanical properties of the prepared oral films of fexofenadine hydrochloride.

Formulation code	Folding endurance	Tensile strength (dyne/cm^2)	% Elongation	Young modulus (Pascal)
F1	120±2.13	5	22.33	0.224
F2	110±1.16	4.5	22.12	0.203
F3	89±1.67	3	20.21	0.148
F4	115±1.78	4.5	21.03	0.214
F5	114±2.34	3.75	20.59	0.182
F6	118±2.50	4.5	21.76	0.207

Disintegration time

The oral films should disintegrate quickly in the mouth and should be able to release the drug immediately for instant therapeutic action. The composition and the physicochemical property of the polymer play an important role. All the polymers used in the present study showed good film-forming properties.

But the disintegration time of the films becomes critical to identify the best polymer for the proposed hypothesis. Hence in the present study, the formulation with different polymers was prepared to identify the best polymer for the oral disintegrating films of FXD, the disintegration time was found to be the least for films prepared with pullulan (F4, F5, and F6) as shown in table 4. According to European pharmacopeia, the oral disintegrating tablets should disintegrate within 3min, and in the present study all the films were disintegrated below 1min and that satisfies the limit prescribed by the pharmacopeia[32].

Table 4. Disintegration time of the films

Formulation code	Disintegration time (sec)
F1	35±0.05
F2	43±0.01
F3	65±0.02
F4	29±0.65
F5	29±0.05
F6	26±0.03

In vitro Dissolution profile

The dissolution of all the oral films of FXD was carried out in simulated salivary fluid at pH 6.8 for 60min. The dissolution profile of all the films is expressed in figure 3. The maximum release was exhibited by formulation F6 in 30min. The marketed formulation exhibited 75% release in 30min.

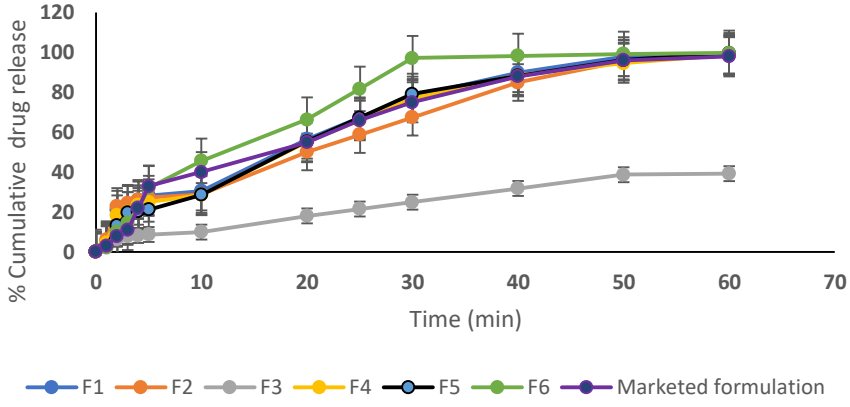

Figure 3. *In vitro* dissolution of the prepared oral films of fexofenadine hydrochloride.

The *in vitro* release data was analysed for release kinetics and found that all the formulations except F3 followed first-order kinetics. The release of the drug from formulation F3 was slow it might be due to the high swelling of the film resulting in high viscosity, hence retarded the drug release. The regression analysis of rate kinetics of dissolution is shown in table

Table 5. Regression analysis for release data

Formulation code	R_1	R_0	R_{HG}	R_{KM}
F1	0.968	0.960	0.956	0.922
F2	0.959	0.962	0.949	0.910
F3	0.983	0.985	0.977	0.950
F4	0.975	0.963	0.959	0.938
F5	0.984	0.966	0.969	0.928
F6	0.986	0.899	0.968	0.967

R_1- Correlation coefficient for first order kinetics, R_0- Correlation coefficient for zero order kinetics, R_{HG}- Correlation coefficient for Higuchi model, R_{KM}- Correlation coefficient for Korsemeyer Peppas model.

SEM Study

The SEM photographs (figure 4) for all the formulations revealed the uniform texture of the prepared film upon dispersion of the drug in the polymer matrix. The films F4, F5, and F6 showed a smooth surface with lesser cracks indicating good mechanical strength of the films prepared by pullulan and different plasticizers. Films prepared by HPMC 15cps (F1) and 5CPs (F2) had comparatively lesser cracks than films prepared by PVP and PVA(F3). Hence the surface morphology also indicated films prepared with pullulans were the best in mechanical strength[14].

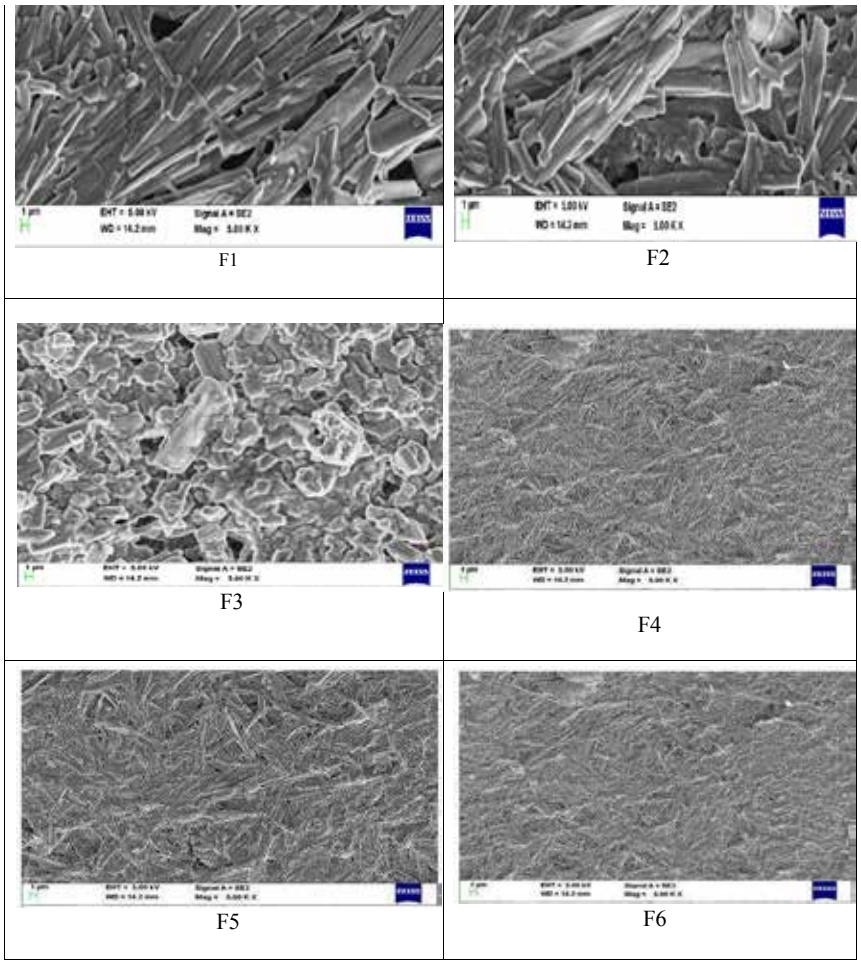

Figure 4. SEM of the different oral films(F1-F6) of Fexofenadine hydrochloride.

Statistical analysis

Dunnett's multiple comparison tests for all the formulations were carried out considering the main characteristics of an oral film like fast disintegration, fast release, and high mechanical strength of the films. A random scaling of 1-5 was assigned for the evaluation of the important characteristics, 5 being the highest, and 1 being the lowest. The low disintegration, rapid dissolution at the earliest, and high mechanical properties were assigned with the highest score. An ANOVA study at a significance level, $p<0.05$ was conducted and it revealed that the characteristics of the formulation F6 were significantly better than F1, F2, and F3 statistically. The formulations F4 and F5 were almost equivalent to F6 and did not show any significant statistical differences. The statistical analysis is listed in Table 6.

Table 6. Dunnett's Multiple Comparison Test

Dunnett's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary
F6 vs F2	1.500	3.464	Yes	*
F6 vs F3	3.250	7.506	Yes	***
F6 vs F4	0.5000	1.155	No	ns
F6 vs F5	0.0000	0.0000	No	ns
F6 vs F1	1.000	2.325	Yes	*

Hence, it can be concluded that the formulations F4, F5, and F6 have the desired properties of an orally disintegrating film. All the films made up of polymer Pullulan have good characteristics to deliver drug immediately from an oral film, irrespective of the type of plasticizer in the film. Therefore, these formulations were taken for stability studies.

Stability study

The selected films were packed in an aluminium package and stored at 40 ±5°C and 75±5% RH for 28 days. The short-term stability data are presented in table 7.

Table 7. Short-term stability study

Properties evaluated	F4		F5		F6	
	14th Day	28th Day	14th Day	28th Day	14th Day	28th Day
Drug content (%)	99.14±0.01	98.64±0.03	99.6±0.02	99.54±0.05	99.69±0.02	99.64±0.03
Thickness (mm)	0.026±0.01	0.0256±0.09	0.023±0.03	0.022±0.09	0.025±0.06	0.0248±0.01
Moisture content (%)	0.91±0.11	0.89±0.19	0.84±0.21	0.82±0.90	0.845±0.44	0.840±0.12
Folding endurance	110±1.08	108±0.23	116±1.30	114±0.92	113±1.05	113±0.07
Young modulus (Pascal)	0.210	0.207	0.178	0.176	0.206	0.205
Disintegration time (sec)	30±0.15	32±0.55	28±0.15	31±0.0.70	26±0.07	27±0.05

Short-term stability studies revealed that the films prepared with pullulans (F4, F5, and F6) were stable, there were no significant changes in the properties of the films ($P>0.05$). Under accelerated conditions, the change in moisture content in the films was found to be minimum. Hence it can be concluded that oral disintegrating films of FXD made with polymer pullulan and different plasticizers were found to be stable and retained their mechanical and pharmaceutical properties.

The current research concentrated on the formulation development of oral disintegrating film of FXD for immediate control of the symptoms of allergy. The study screened a variety of polymers and plasticizers to evaluate their effect on the mechanical property and dissolution behaviour of the drug. Among all the polymers used the polymer pullulan was found to be the best to achieve the desired characteristics of the fast-dissolving film of FXD. The films disintegrated in less than 30 seconds and showed a high drug release at 30 min. The formulations F4, F5, and F6 were found to be stable. The formulation showed good mechanical properties and drug release and could retain flexibility, and strength even after a short-term stability study for 4 weeks. Hence it can be concluded that a fast-dissolving film of FXD with pullulans could be a promising combination to achieve the objective of the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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