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FORMULATION AND EVALUATION OF ORAL DISSOLVING FILMS OF FEXOFENADINE

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ABSTRACT

The main objective of the present work was to develop the oral dissolving films of Fexofenadine. Total 12 formulations were prepared by using different viscosity grades of HPMC such as E3, E6 and E15 by solvent casting method. The films were characterized for various physicochemical parameters such as weight variation, thickness, folding endurance, % drug content, *In vitro* disintegration time and *In vitro* dissolution time. The results of quality control tests were found to be within the acceptable limits. The thickness of the films was found to be in the range of 0.12 mm to 0.24 mm. The folding endurance was found to be more than 300. The *In vitro* disintegration time of the films was found to be between 18-62 sec. The invitro dissolution time of the films was found to be between 15-30mins in most of the formulations. FTIR and DSC study revealed that there is no drug – polymer interactions. SEM study showed that films were clear, transparent and had a smooth surface texture. It was concluded that fexofenadine oral dissolving films can be prepared by using different viscosity grades HPMC with good commercial success.

KEYWORDS: Fexofenadine, HPMC, oral dissolving film, solvent casting technique.

INTRODUCTION

Oral drug delivery is the most popular route of administration for most of the therapeutic agents to produce systemic effects. They are easy to manufacture and are patient compliant.[1,2] There has been tremendous demand in the manufacture of more patient-friendly dosage forms from the past decade which resulted in the development of several new technologies.[3] However conventional dosage forms cannot be administered successfully to children, elderly, patients who are uncooperative, mentally retarded, nauseated and on reduced liquid-intake diets as they suffer from difficulty in swallowing. Those who are in traveling or do not have access to water were also similarly affected.[4,5,6]

Quick dissolving or fast dissolving dosage forms have gained great importance in the pharmaceutical industry due to their unique properties and advantages. They have some advantages like ease of administration and can be taken without the need of water.[7,8,9] Oral mucosa has high blood flow and permeability. When ODF is placed in the mouth they undergo fast disintegration in the salivary fluids and release the drug in the oral cavity followed by quick absorption and instant bioavailability of drugs.[10,11,12] The fast dissolving films are referred as mouth dissolving, quick disintegrating and orally disintegrating films.[13] They were developed in the late in 1970 as an alternate dosage forms to capsules, tablets and syrups for the patients who have difficulties in swallowing and chewing.[14,15,16] They are thin, elegant and shows improved patient compliance.[17,18] Fexofenadine is the 2nd and 3rd generation antihistamine drug used to treat hay fever and allergic symptoms. It does not readily pass through the blood-brain barrier so it causes less drowsiness than first-generation histamine-receptor antagonists. The mechanism of action includes, it competes with free histamine to bind at H1-receptors in the large blood vessels, GI tract and bronchial smooth muscle. They block the action of endogenous histamine, which subsequently provides temporary relief from negative symptoms such as nasal congestion and watery eyes brought by histamines. It is reported that it does not exhibit any antidopaminergic, anticholinergic, cardio toxic effects and alpha1-adrenergic or beta-adrenergic-receptor blocking effects.[19-23]

MATERIALS AND METHOD

Materials

Fexofenadine was obtained as gift sample from Aurobindo Pharma Labs. HPMC E3, E6 and E15 grades were obtained from Colorcon Asia Pvt. Ltd. Methanol was obtained from Merck Specialties Pvt. Ltd., Dichloromethane, Poly ethylene glycol was obtained from S.D. Fine

Chem Ltd. Acesulfame potassium was obtained from Shanghai Brightol. Orange flavor was obtained from Pentagon trading company. All other excipients used in the study were of fine grade.

Method

The oral dissolving films (ODF) of fexofenadine were prepared using different viscosity of HPMC such as E3, E6 and E15 in the ratios of 1:0.5, 1:1, 1:1.5 and 1:2 drug to polymer ratio. The polymeric solution was prepared by dissolving the HPMC in methanol and dichloromethane. It was kept aside for about 5 to 6 hrs for complete swelling of the polymer. Fexofenadine drug solution was prepared by dissolving the drug in measured quantity of solvents. This drug solution was added to the above polymeric solution. Finally plasticizer PEG 400, sweetener and flavors were added to the above solution. Uniformity of drug content is achieved by mixing the solution in cyclo mixer for about 20 minutes. The solution was cast on a petridish and kept aside for air drying. The film was carefully removed from the petridish, checked for surface imperfections and cut into the required size (2 × 2 cm2) to deliver the equivalent dose per strip.

Table 1: Formulation development of oral dissolving films of fexofenadine using different viscosity grades of HPMC.

INGREDIENTS	Formulation codes (Quantity in mg)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Fexofenadine	450	450	450	450	450	450	450	450	450	450	450	450
HPMC E3	225	450	650	900	-	-	-	-	-	-	-	-
HPMC E6	-	-	-	-	225	450	650	900	-	-	-	-
HPMC E15	-	-	-	-	-	-	-	-	225	450	650	900
Dichloro methane *	12	12	12	12	12	12	12	12	12	12	12	12
Methanol *	8	8	8	8	8	8	8	8	8	8	8	8
PEG 400	58	58	58	58	58	58	58	58	58	58	58	58
Acesulfame Potassium	15	15	15	15	15	15	15	15	15	15	15	15
Orange flavor	2	2	2	2	2	2	2	2	2	2	2	2

*Processing solvent (ml) in the preparation of films.

EVALUATION OF FILMS

Weight variation

The films were weighed individually from the randomly selected batches. The average of five readings from each batch was calculated and reported.[24, 25]

Thickness

The thickness of the films was measured using calibrated digital Vernier caliper. Three readings from all the batches were taken and mean thickness was calculated and reported.[26]

Folding endurance

The folding endurance was done manually for the films. A strip of film was cut and folded repeatedly at the same place until it was broken. The number of times the film could be folded at the same place without breaking was recorded as the value of folding endurance.[27]

Drug Content

The film of specified area (2×2cm) was cut and placed in a volumetric flask containing 100 ml of 0.1N HCl. The medium was sonicated for 15 min and filtered using Whatman filter paper. The filtrate was suitably diluted and analyzed using UV spectrophotometer against 0.1N HCl as blank at λ max 220 nm.[28, 29]

In vitro disintegration time

In vitro disintegration time of the films was determined visually in a petridish with 25 ml 0.01N HCl and swirling was done for every 10 sec. The time taken by the film to disintegrate was taken as disintegration time.[30]

In-vitro dissolution studies

In vitro Dissolution study was carried out using USP type II (basket type) apparatus with 0.01N HCl as a dissolution medium. The temperature was maintained at 37±0.5^{0}C with 50 rotations per minute. 5ml of aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were analyzed for drug content at λ max 220 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported.[31, 32, 33]

DRUG EXCIPIENT COMPATIBILITY STUDY

Fourier Transform Infrared spectroscopy (FT-IR)

Drug excipient interaction studies were done by using BRUKER FTIR to confirm interactions between the selected drug and polymer. The film was finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and a spectrum was scanned in the wavelength range of 400 and 4000 cm-1.[34]

Differential scanning colorimetric study (DSC)

Thermal properties of pure drug and the formulation were determined by Differential Scanning Colorimetry (DSC) using DSC 200 F3 instrument. The samples were placed in standard aluminium pans and sealed with a lid. Heating scans by 10 k/min were applied with a nitrogen purge of 60 ml/min over a temperature range of 0 to 450 0C. An aluminium pan was used as a reference. A quality equivalent to 2 mg of pure drug was used for the study.[35]

Scanning electron microscopy (SEM)

The surface morphology of the optimized formulations was observed by scanning electron microscopy. The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at 200X, 500X and 1000X magnification.[36]

RESULTS AND DISCUSSION

Evaluation of films

Fexofenadine oral dissolving films were prepared using HPMC E3, E6 and E15 as film forming polymer and PEG 400 as the plasticizer. The prepared films were evaluated for various physico chemical properties like weight variation, folding endurance, thickness, drug content etc. The weight variations in the films were found to be uniform in all the prepared batches. The thickness of the films was found to be in the range of 0.12 mm to 0.24 mm. The folding endurance of the films was found to be more than 300 indicating that the plasticizer concentration was adequate. The films were found to have adequate thickness for handling and use. % Drug content of the films was in between 97±1.5 to 99±1.1, indicating that the drug was uniformly distributed in the films. The disintegration time of films in formulations F1 to F4 was in the range of 18 sec to 36 sec, in F5 to F8 it was in the range of 21 sec to 57 sec, in F9 to F12 it was in the range of 27 sec to 70 sec. It was observed that the disintegrating time was increased as the concentration of polymer was increased.

***In vitro* drug release study Fexofenadine oral dissolving films**

In vitro dissolution study of fexofenadine oral dissolving films prepared with HPMC E3, F1 to F4 showed faster drug release at initial 5 minutes and found to be between 70 -79%. F1 showed complete drug release in 20mins. The drug release from the films prepared with HPMC E6, F5 to F8 showed drug release of 65 – 73% in initial 5 minutes and F5 showed complete drug release in 25 mins. In vitro drug release of the films prepared with E15, the formulation F9 -F10 showed 62- 70% of drug release in 5 mins. Formulations F11 and F12

showed the drug release up to 99% and 89% in 30 mins. It was found that; dissolution rate was slower as the polymer concentration was increased.

Table 2: Physicochemical parameters and in vitro disintegrating data of fexofenadine ODF with different ratios of polymer HPMC.

Parameters evaluated	Formulation codes											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Theoretical Weight(mg)	50	65	80	95	50	65	80	95	50	65	80	95
Actual Assay	97	96	98	96	98	99	99	98	96	98	99	99
Actual Weight	52.6	67	82	85	52.6	67	82	85	52.6	67	82	85
Thickness(mm)	0.12	0.16	0.18	0.24	0.13	0.14	0.22	0.24	0.13	0.14	0.22	0.24
Folding Endurance	>300	>300	>300	>300	>300	>300	>300	>300	>300	>300	>300	>300
In vitro Disintegration time(sec)	18	23	27	36	21	28	34	57	27	30	48	70
Assay (%)	97	99	98	99	99	99	98	99	99	99	98	99

Table 3: *In Vitro* drug release study fexofenadine oral dissolving films.

Time (mins)	Formulation codes											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	79	75	73	70	73	70	68	65	70	68	64	62
10	90	86	78	74	85	76	74	71	78	72	70	68
15	94	90	85	79	91	84	79	75	87	81	74	71
20	99	95	89	84	96	90	82	80	91	84	79	76
25	99	99	93	90	99	94	91	86	97	89	85	82
30	99	99	99	97	99	99	95	93	99	96	92	89

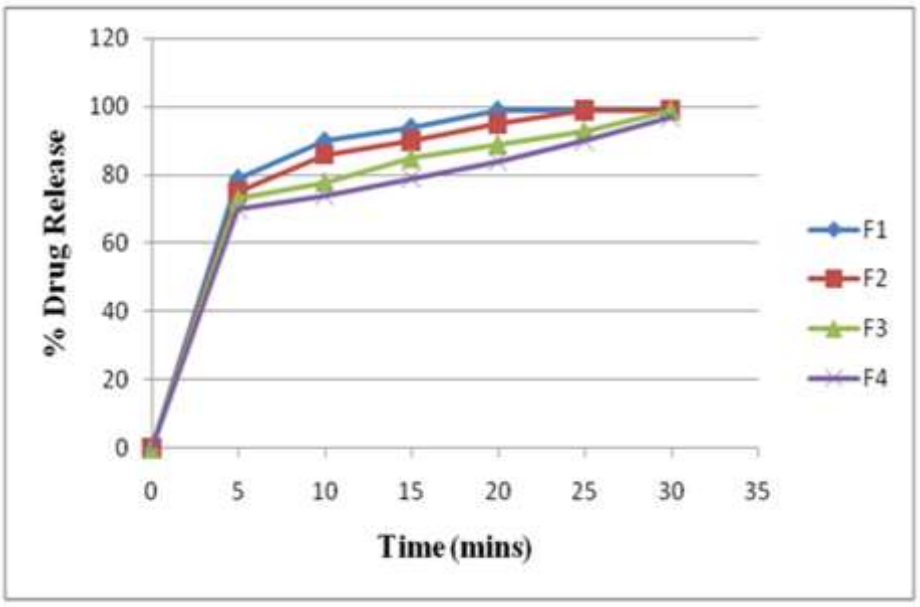

Fig 1: *In vitro* drug release profile of fexofenadine oral dissolving films prepared with HPMC E3.

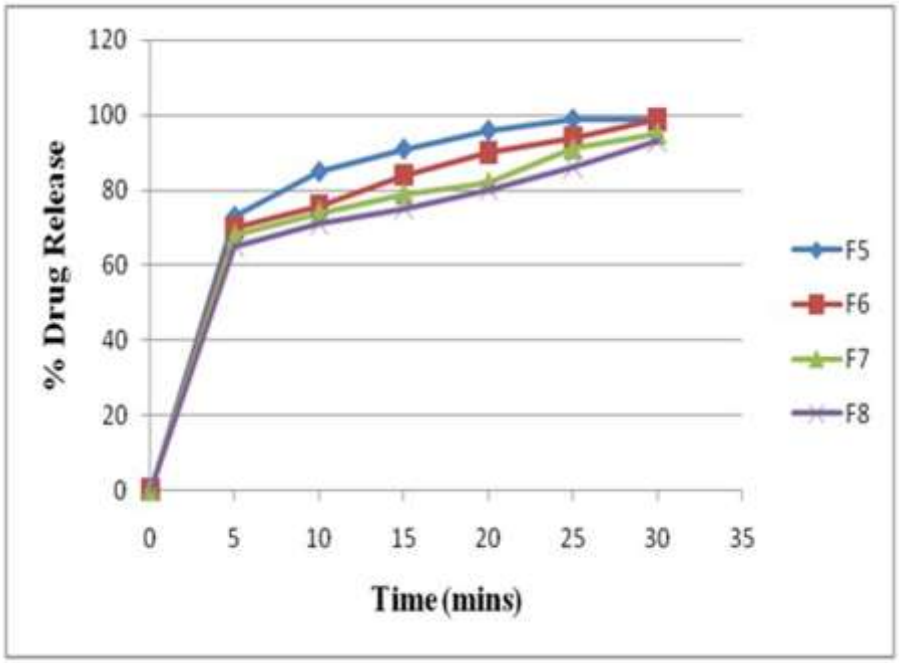

Fig 2: *In vitro* drug release profile of fexofenadine oral dissolving films prepared with HPMC E6.

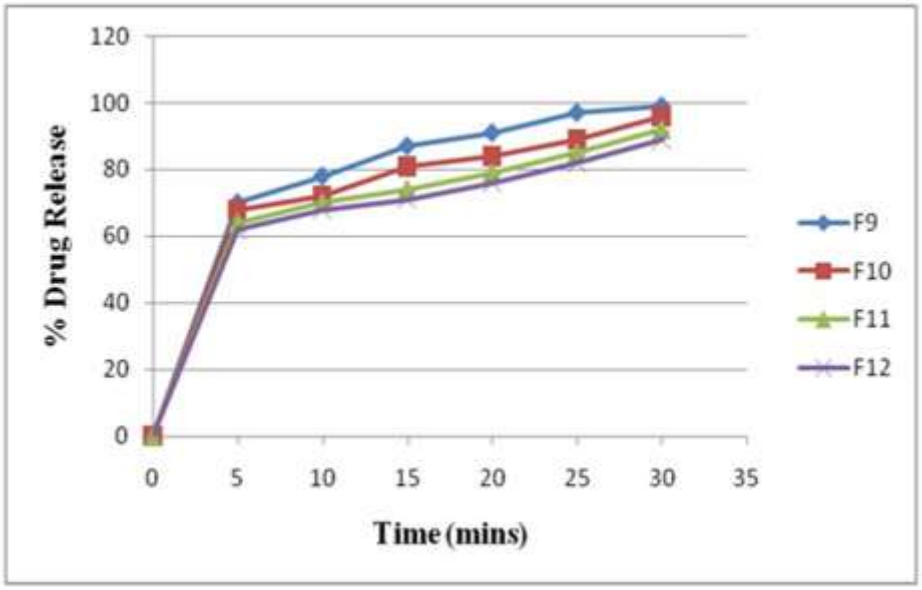

Fig 3: *In Vitro* drug release profile of fexofenadine oral dissolving films prepared with HPMC E15.

DRUG AND EXCIPIENT COMPATIBILITY STUDY

Differential Scanning Calorimetric (DSC) study

Selected formulations of Fexofenadine films were characterized for DSC study. Formulations prepared with E3 and E6 were selected for compatibility study. The pure drug Fexofenadine

showed a sharp exothermic peak at 198.7 0C. Similar exothermic peaks were observed at similar temperature in the prepared films at 196.9 0C for HPMC E3, 197.8 0C for HPMC E6. The study indicated that there is no interaction between drug and selected polymers.

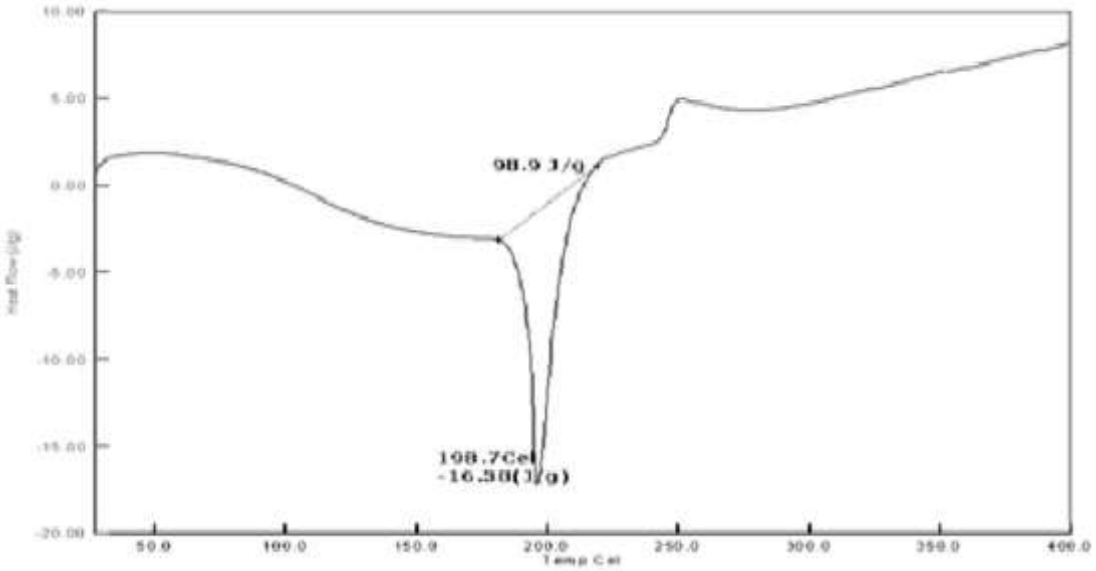

Fig 4: DSC thermogram of fexofenadine pure drug.

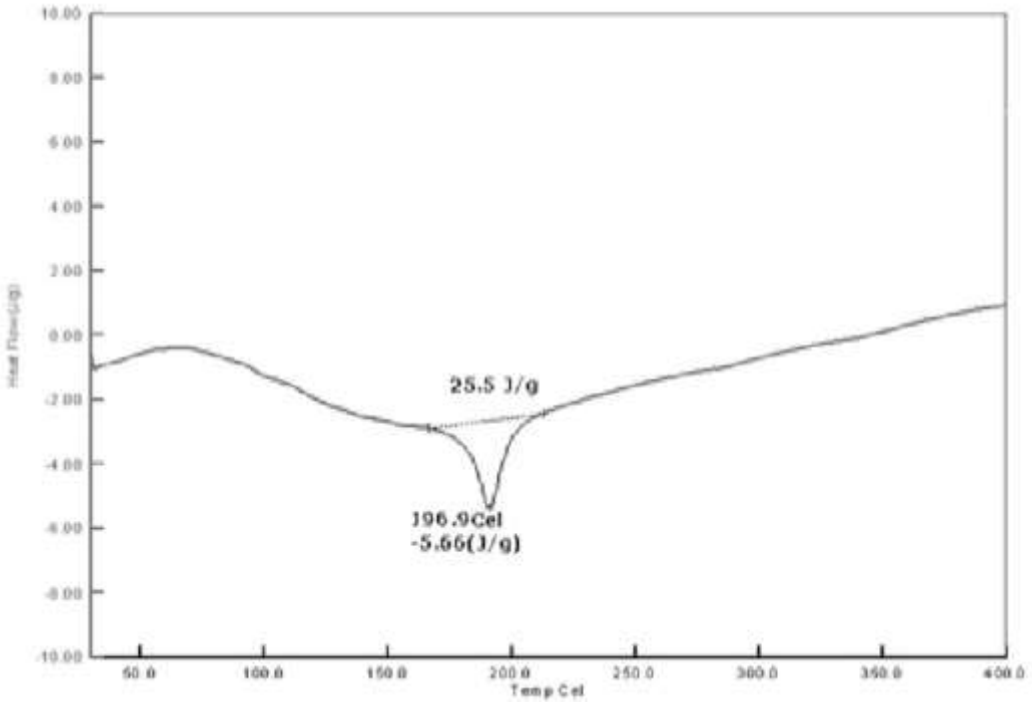

Fig 5: DSC thermogram of fexofenadine oral dissolving oral films prepared with HPMC E3.

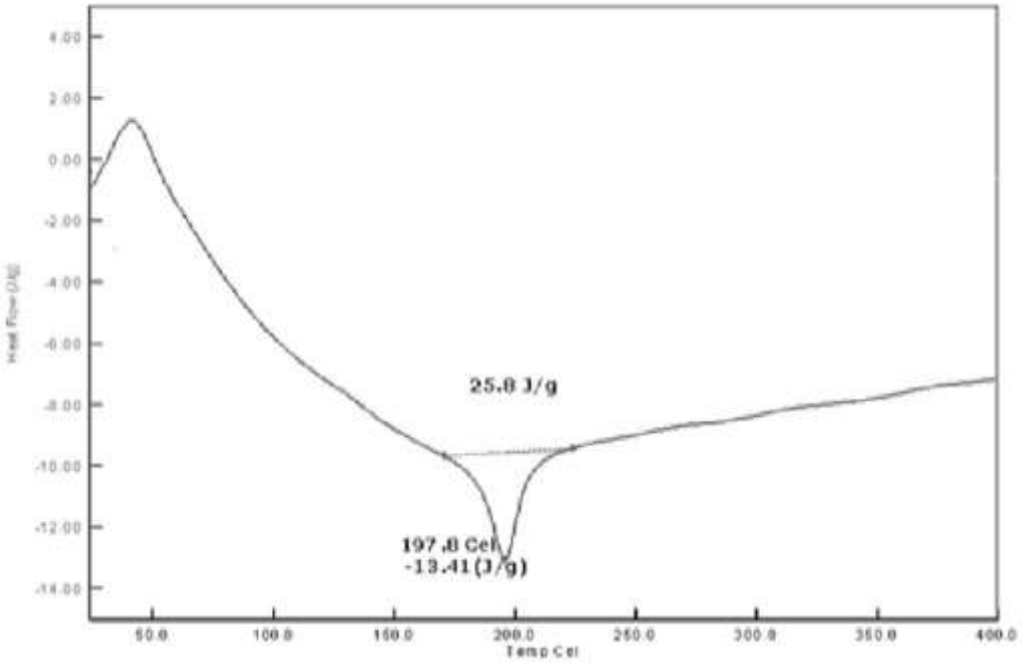

Fig 6: DSC Thermogram of fexofenadine oral dissolving oral films prepared with HPMC E6.

Fourier Transform Infrared Spectroscopy (FT-IR) study

The compatibility between the drug and polymers was established through FTIR study. FTIR study was conducted on the selected formulations prepared with combination of different polymers such as HPMC E3 and E6. The spectrum peak points of the formulation were similar with that of the pure Fexofenadine clearly indicating that there is no drug-polymer interaction.

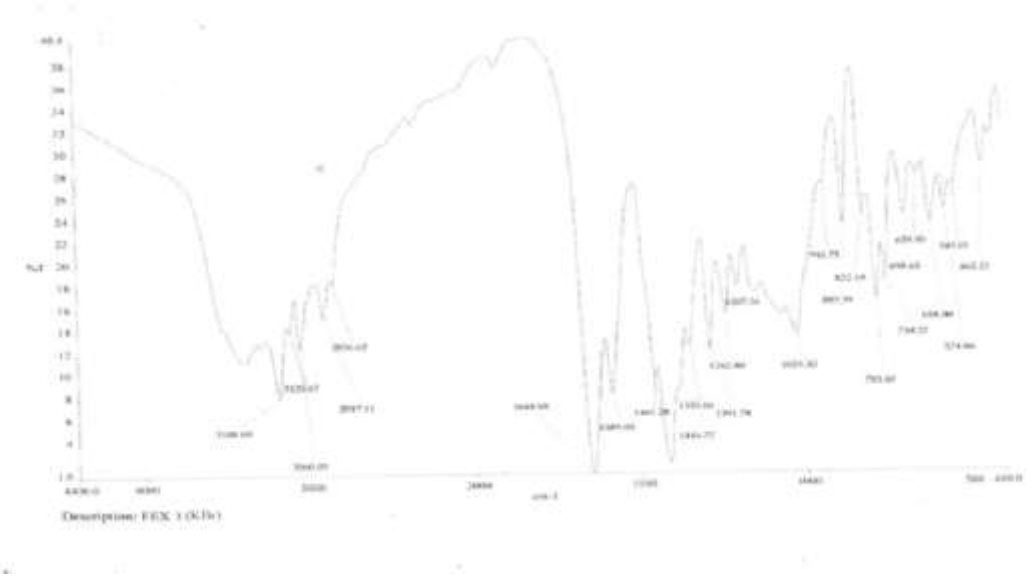

Fig 7: FTIR spectra of fexofenadine pure drug.

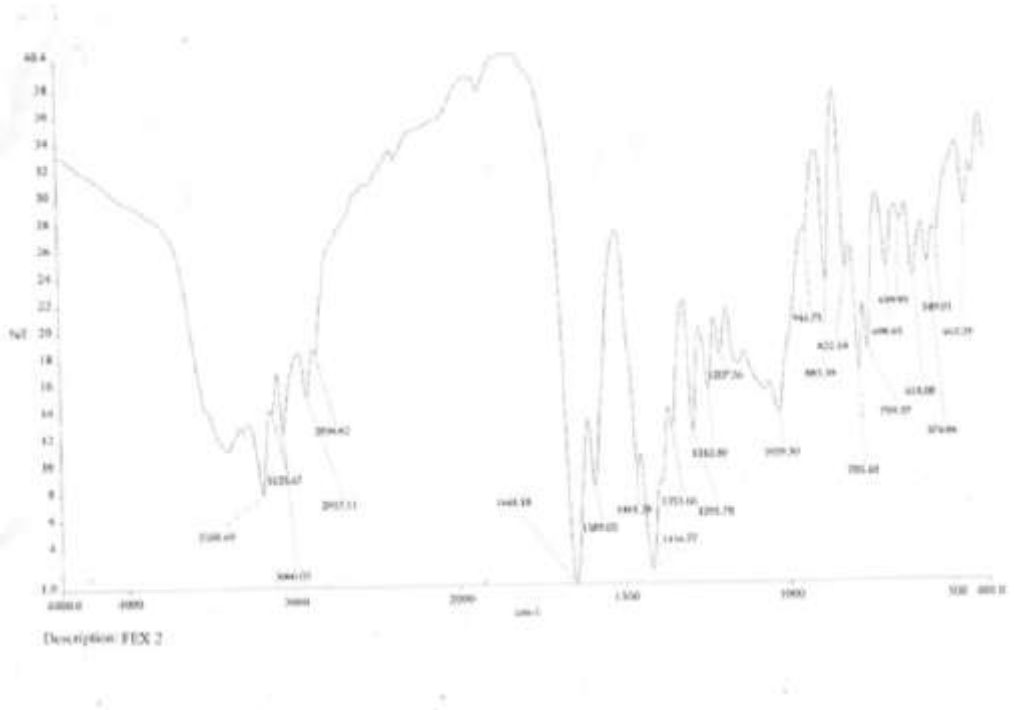

Fig 8: FTIR spectra of fexofenadine oral dissolving oral films prepared with HPMC E3.

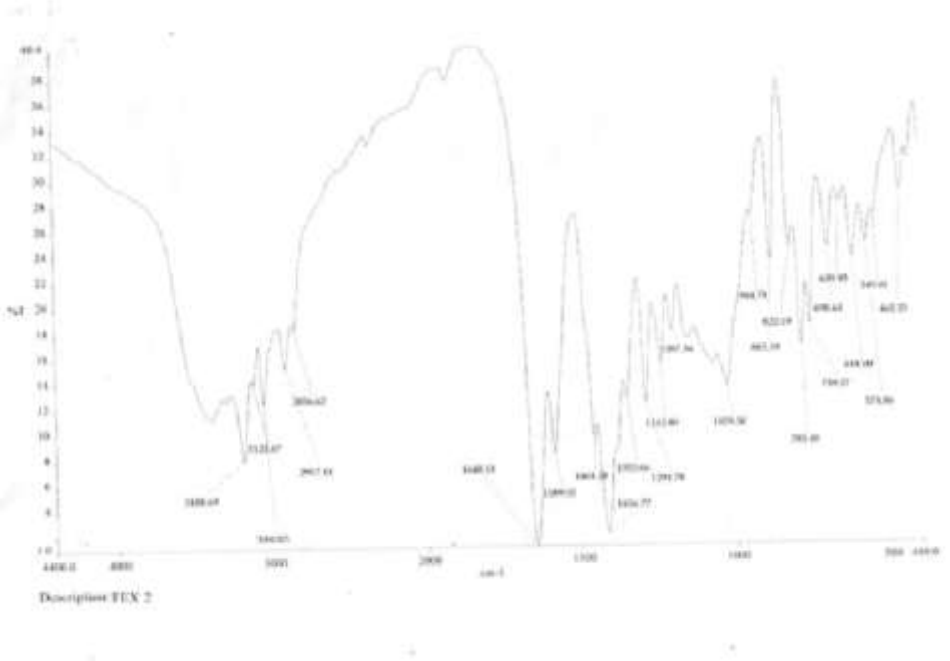

Fig 9: FTIR spectra of fexofenadine oral dissolving oral films prepared with HPMC E6.

Scanning Electron Microscopy (SEM) Study

The surface morphology of the best formulation was observed with scanning electron microscopy. The films were found to be clear, transparent and had a smooth surface texture.

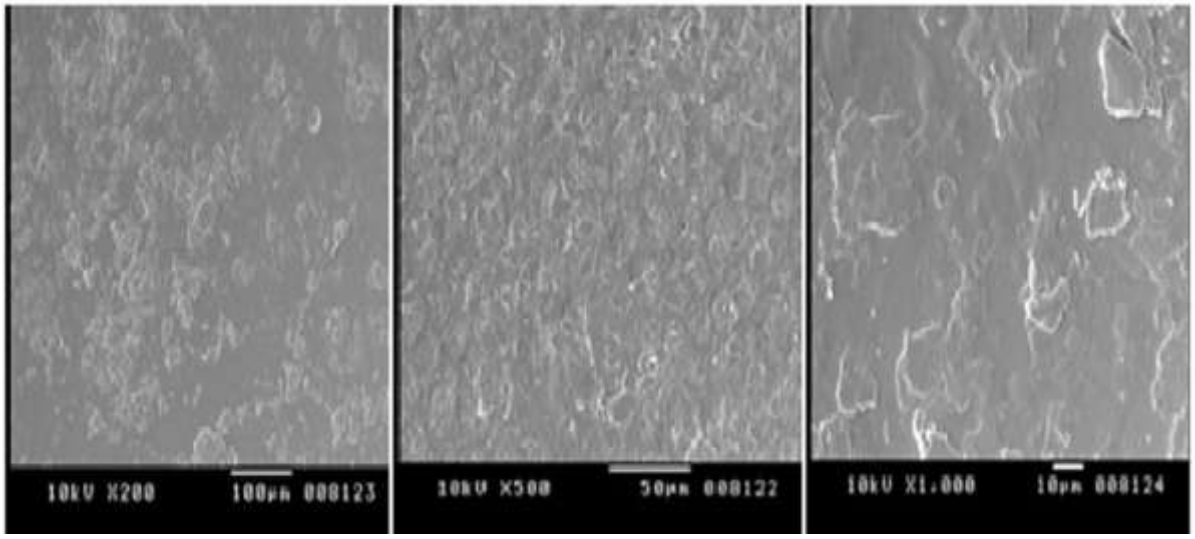

Fig 10: Scanning electron microscopy of fexofenadine oral dissolving oral films at 200x, 500x and 1000x.

CONCLUSION

In the present study, Fexofenadine oral dissolving films were prepared by using different viscosity grades of HPMC like E3, E6 and E15 by solvent casting method. The quality control tests results were within the acceptable limits. The invitro disintegration time of the films was found to be between 18-62 sec. The invitro dissolution time of the films was found to be between 15-30 mins in most of the formulations. It was observed that concentration of polymer effects the formation of film and dissolution time of the formulations. In this study best formulation was chosen from each polymer based on release parameters. FTIR and DSC study indicated that there is no interaction between the drug and excipients.

CONFLICT OF INTERESTS

We declare that we have no conflict of interest.

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