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DESIGN AND CHARACTERIZATION OF FAST DISSOLVING BUCCAL FILMS OF KETOTIFEN FUMARATE"

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ABSTRACT

Anti-histaminic drugs are pharmacological agents that are used to treat Major Allergic Reactions. The aim of the present study is to Design and Characterization of Fast dissolving buccal films Ketotifen fumarate films were prepared by using different polymers like HPMC E15, PVA, PVP and Glycerol as Plasticizer and Saccharin as a Sweetening agent and Vanillin as a Flavoring agent. Buccal films were prepared using Solvent casting technique. The major problem with Ketotifen fumarate was it belongs to class Ⅱ in BCS classification and have low solubility in biological fluids. In order to enhance the solubility of Ketotifen fumarate Solid dispersion of Ketotifen fumarate were prepared by melting technique at different drug carrier (PEG 4000) weight ratios and evaluated. No interaction was found between the drug and the polymers by the FTIR studies. The buccal films were evaluated for Folding endurance, Weight variation, Drug content, Thickness, Permeation study and In-vitro drug release study. Dissolution profile as studied in USP dissolution apparatus type 1 using pH 6.8 Simulated Saliva. The influence of variable like polymer type, concentration, of Ketotifen fumarate release profile was studied. The formulation was optimized on the basis of various evaluation parameters like Drug content and In-vitro drug release. Formulation F3 successfully sustained the release of drug within 12min. stability studies were as per ICH guidelines and result indicated that the selected formulation was stable.

KEYWORDS: Ketotifen fumarate, HPMC E15, PVA, PVP, PEG 4000, Solvent casting method.

INTRODUCTION

According to WHO, Ketotifen fumarate is the fumarate salt of Ketotifen, a Cycloheptatriene derivative with Anti Allergic activity. Ketotifen selectively blocks Histamine (H1) receptors and prevents the typical symptoms caused by Histamine release. In its oral form, it is used to prevent asthma attacks or anaphylaxis as well as various mast cell, allergic type disorders.

However, the fear of taking solid tablets and the risk of choking for certain patient population still exist despite their short dissolution/disintegration time. Recent development in novel drug delivery system aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration. One such approach is rapidly dissolving film. It consists of a very thin Buccal strip, which releases the active ingredient immediately after uptake into the Buccal cavity. Rapid film combines all the advantages of tablets (precise dosage, easy application).

Advantages of Buccal films

- No fear of Obstruction or Chocking.
- No need of water during film administration.
- Reduction in dose of the drug.
- Taste masking
- Improved Patient Compliance.
- Enhanced Stability

MATERIALS AND METHODS

Ketotifen fumarate, Hydroxypropyl methyl cellulose (HPMC E15), Polyvinyl alcohol (PVP), Polyvinyl pyrrolidone (PVP), from Yarrow chemicals. All other chemicals used were of analytical grade.

Standard Curve of Ketotifen fumarate

Ketotifen fumarate is a white fine powder which was soluble in Simulated saliva pH 6.8. Though several methods are reported for its estimation, the UV spectrophotometric method was employed in the study. Ketotifen fumarate shows maximum absorbance at 300 nm in simulated saliva pH 6.8. Based on this information, a Standard graph was constructed (Figure No.1).

Drug-polymer interaction study of films

There is always a possibility of drug-excipients interaction in any formulation due to their intimate

contact. The technique employed in this study to know drug- excipients interactions is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug Ketotifen fumarate and formulations were scanned by using FTIR, by a thin film method.

Evaluation of Ketotifen fumarate buccal films

a) Physical appearance and surface texture of films

This parameter was analyzed simply with visual inspection of films and evaluation of texture by feel or touch.

b) Weight uniformity of films

3 films of the size 2×2 cm was weighed individually using digital balance and the average weights were calculated.

c) Thickness of films

Thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

d) Folding endurance of patches

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately 2x2 cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

e) Drug content uniformity of films

The films were tested for drug content uniformity by UV Spectrophotometric method. Films of 2×2 cm size were cut from three different places from the casted films. Each film was placed in 100 mL volumetric flask and dissolved in simulated saliva pH 6.8 and 5 mL is taken and diluted with water up to 10 ml. The absorbance of the solution was measured at λ max 300 nm using UV/ visible spectrophotometer (Shimadzu). The percentage drug content was determined.

f) *In-vitro* dissolution studies

The release rate of Ketotifen fumarate fast dissolving Buccal films were determined by using magnetic stirrer. The film with 2×2 cm was placed in the 100mL of 6.8 pH simulated saliva as dissolution medium, and temperature was maintained at 37°C.From this dissolution medium, 2 mL of the sample solution was withdrawn at different time intervals. The samples were filtered through Whitman filter paper and absorbance was determined 300nm using double beam UV- Visible spectrophotometer.

g) Permeation study

The prepared Buccal films were placed in the diffusion cell on the upper membrane of the (donor compartment) and the receptor compartment contain a simulated saliva (20 ml) it can be contact with the dialysis membrane upper side of the donor compartment contain a film attach the film of length and width (2×2) cm it contains 10 mg of drug and the receptor compartment it contain a simulated saliva and magnetic bead and this diffusion compartment placed in the magnetic stirrer the drug permeation start through the dialysis membrane and enter in to the receptor compartment the drug to be enter in the receptor compartment and this solution taken 2 ml at regular time intervals and maintain the sink condition by replace the 2ml of simulated saliva in to the receptor compartment and this every interval taken samples analyzed by (Shimadzu) UV-visible spectrophotometer.

h) Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done as per ICH guidelines. The formulated Buccal films were wrapped in aluminum foil and stored at 45 ± 0.5ºC for period of twelve weeks. After the period of three month, films were tested for appearance, drug content and *In-vitro* drug release.

RESULTS AND DISCUSSION

Weight variation

The randomly selected film strips about 2 × 2 cm areas were cut at different places from the casted film and weight was measured. Weight of film strip units varies from 46.21 to 52.05 mg. The proportion of carrier used have reduced the variation and improved the uniformity of the distribution in casted films (Table No.3). It was observed that *in vitro* dissolving/disintegration time varies from 36 to 47 sec for all the formulations (Table No.3). *In vitro* disintegration time of films was affected by polymers viz. HPMC E 15, PVA and PVP. This is due to polymer's high-water absorption and retention capacities.

Drug content

The prepared film formulations were studied for their drug content. The drug was dispersed in the range of 91 % to 97 %. Suggesting that drug was uniformly dispersed in all films.

***In vitro* dissolution studies**

The in-vitro drug release profiles of the formulations in simulated saliva pH 6.8 show differences depending on their composition. The rate of drug release from the HPMC E 15 films was significantly higher than the films containing PVP and PVA (Figure No.6). The formulation F3 films containing a HPMC E 15 showing high percentage of drug release (97.41%) within 12 min compared to that of films containing PVP and PVA as a polymer.

Table 1: Calibration curve of Ketotifen fumarate.

Sl. No	Concentration (µg/mL)	Absorbance at 300 nm
1	2.5	0.101
2	5	0.192
3	10	0.384
4	15	0.570
5	20	0.733
6	25	0.934

Table 2: Formulation details of Ketotifen fumarate (K F) buccal films.

Formulation	Polymer and its composition (mg)				Plasticizer (mL)	Sodium saccharin (mg)	Vanillin (mg)	Distilled. Water (mL)
	Ketotifen Fumarate	HPMC E 15	PVA	PVP				
F1	12	400			0.1	2	2	10
F2	12	450			0.1	2	2	10
F3	12	500			0.1	2	2	10
F4	12		400		0.1	2	2	10
F5	12		450		0.1	2	2	10
F6	12		500		0.1	2	2	10
F7	12	300		100	0.1	2	2	10
F8	12	350		100	0.1	2	2	10
F9	12	400		100	0.1	2	2	10

Table 3: Evaluation data for mucoadhesive buccal films.

Formulation Code	Weight variation(mg)	Thickness(mm)	Folding endurance	% Drug content	Disintegration time (sec)
F1	46.21±0.67	0.15 ± 0.012	344.67 ± 4.64	91.77434457	34.67±1.25
F2	47.83±0.36	0.17 ± 0.012	321.00 ± 2.45	95.61329588	37.33±1.70
F3	49.95±0.43	0.17 ± 0.008	324.33 ± 2.49	92.89794007	46.67±1.25
F4	51.65±0.50	0.21 ± 0.008	344.33 ± 2.05	93.27247191	34.00±2.16
F5	50.96±0.56	0.23 ± 0.008	338.33 ± **1.25**	91.77434457	38.67±2.62
F6	52.05±0.009	0.21 ± 0.012	353.00 ± 3.74	97.43913858	32.67±1.70
F7	48.06±0.21	0.18 ± 0.008	323.67 ± 2.49	95.75374532	42.67±2.05
F8	51.85±1.25	0.18 ± 0.012	316.67 ± 2.62	96.9241573	47.33±1.70
F9	50.31±0.77	0.19 ± 0.012	330.67 ± 1.25	96.9241573	41.67±1.70

Table 4: *In-vitro* release data of various Ketotifen fumarate Mucoadhesive buccal films. Cumulative % drug release from buccal films F1 to F9.

FORMULATION CODE	F1	F2	F3	F4	F5	F6	F7	F8	F9
2 min	45.92	42.92	50.92	38.00	41.92	35.00	26.00	21.00	23.00
4 min	64.24	58.21	66.25	51.18	57.21	50.17	31.16	26.13	29.15
6min	73.29	70.27	76.30	59.22	66.25	57.21	40.12	36.18	35.18
8min	81.33	83.34	83.34	66.25	72.28	68.26	53.19	43.14	46.15
10min	86.35	88.36	91.38	75.30	82.33	76.30	63.24	51.18	55.20
12min	92.38	93.39	97.41	82.33	87.36	84.34	70.27	63.24	66.25
14min				89.37	93.39	87.36	78.31	71.28	75.30
16min				94.39		91.38	84.34	79.32	83.34
18min							90.37	86.35	88.36
20min								91.38	93.39

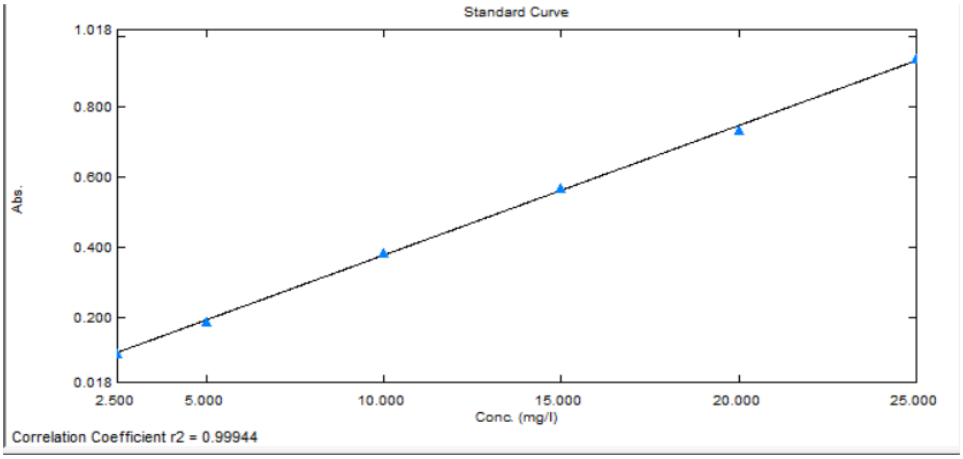

Figure 1: The standard graph of Ketotifen fumarate using simulated saliva buffer of pH 6.8.

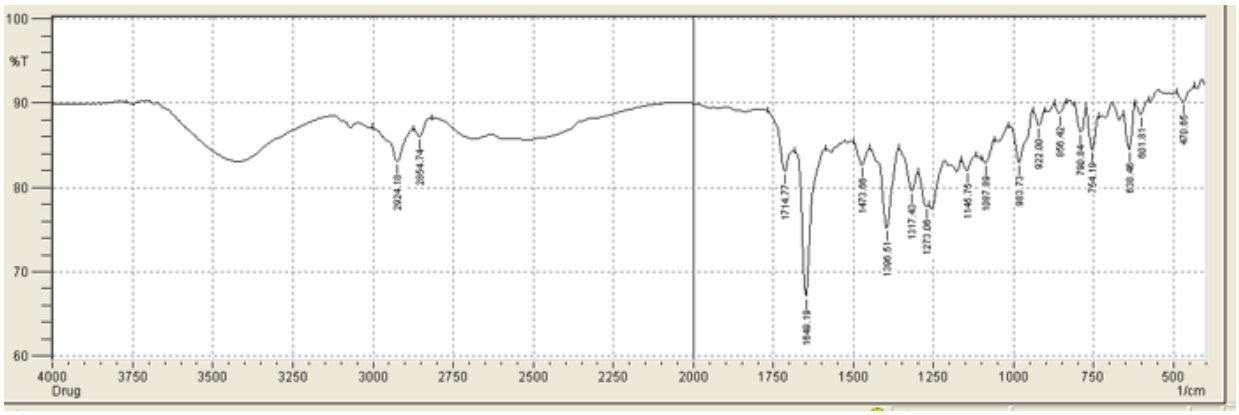

Figure 2: FTIR Spectrum of pure drug (Ketotifen fumarate).

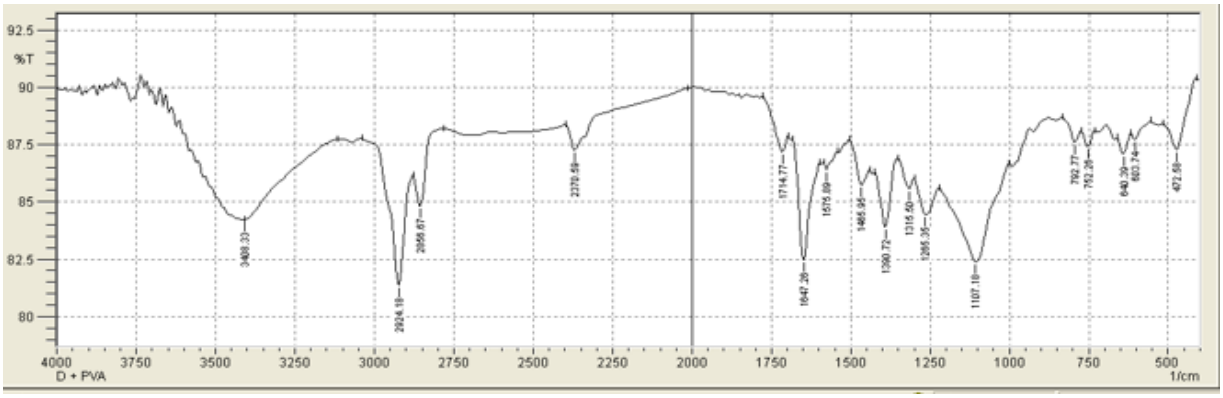

Figure 3: FTIR Spectrum of Ketotifen fumarate + PVA.

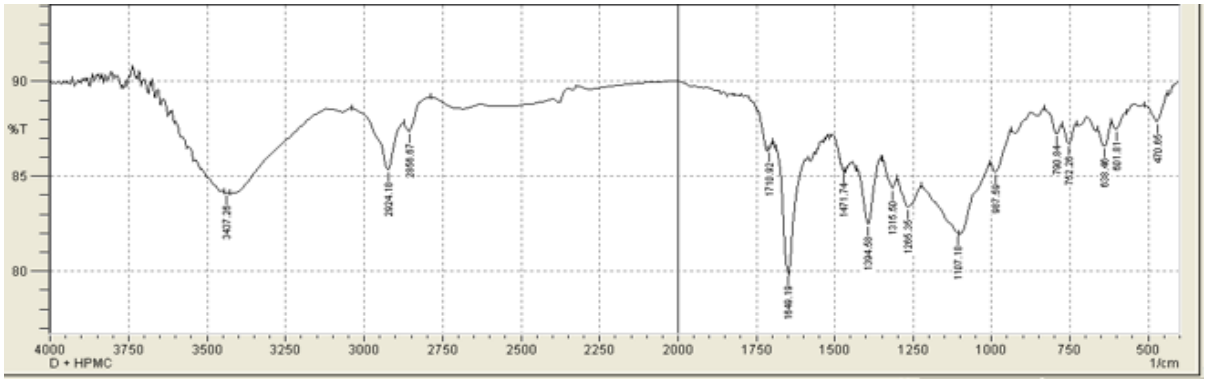

Figure: 4: FTIR Spectrum of Ketotifen Fumarate+ HPMC E15

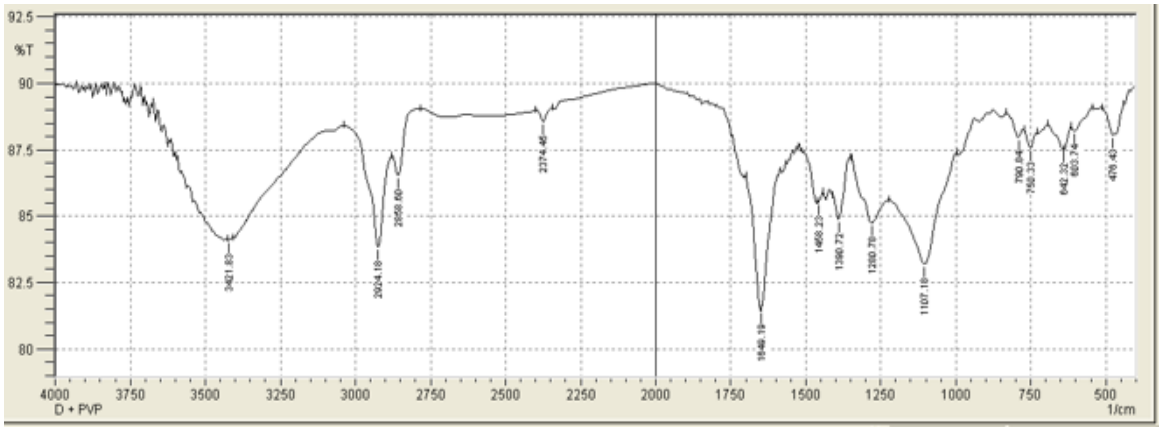

Figure 5: FTIR Spectrum of Ketotifen Fumarate+ PVP

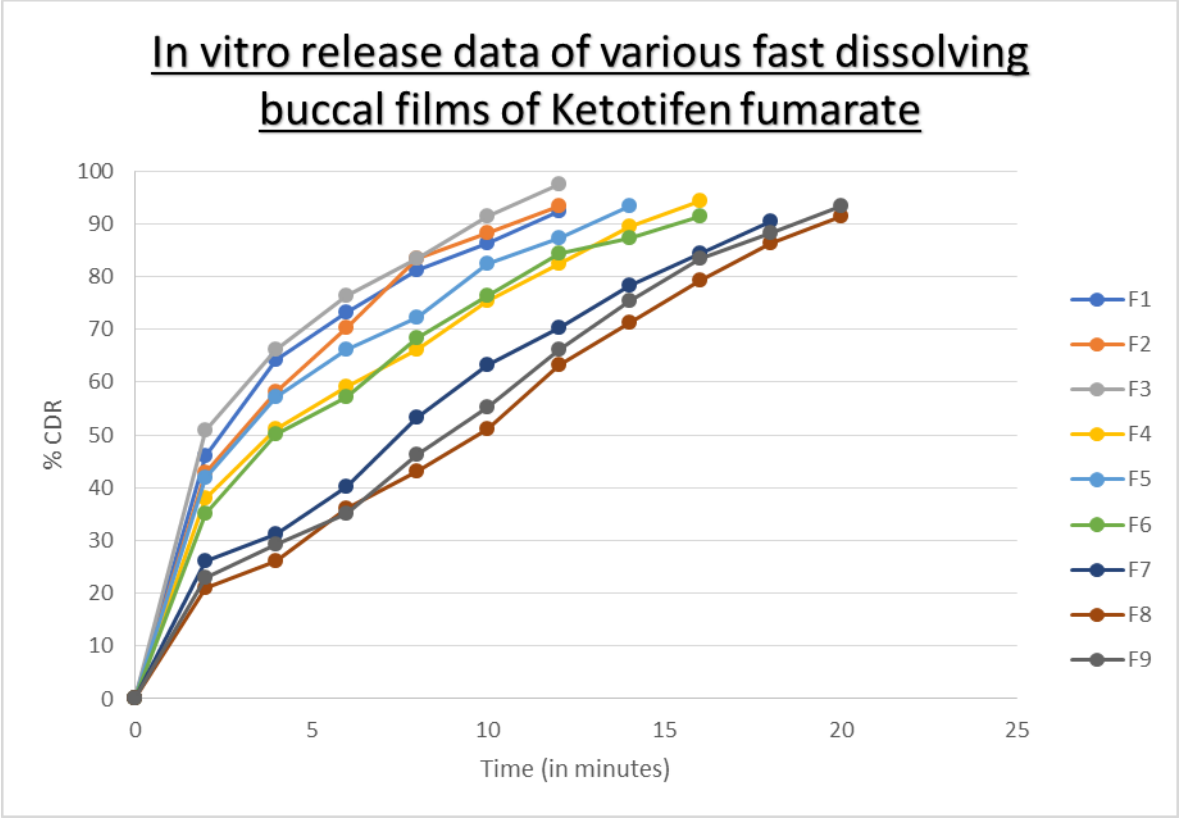

Figure 6: In-vitro drug release profile of formulations F1-F9.

CONCLUSION

All the formulation showed acceptable quality control property formulation F3 having polymer concentration HPMC E 15 showed better drug release rate over period of 12min thus formulation F3 was found to be the most promising formulation on the basis of acceptable evaluation property and the *In-vitro* drug release rate of 97.41%. Based on the FTIR studies appear to be no possibility of interaction between the Ketotifen Fumarate and polymers of other excipients used in the films.

Stability studies were conducted for the optimized formulation as per ICH guidelines for a period of 90 days which revealed that the formulation were stable. The result suggests that the developed mucoadhesive buccal film of Ketotifen Fumarate could perform the better than conventional dosage form leading to improved efficacy and better patient compliance.

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