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DESIGN AND CHARACTERIZATION OF SOLID DISPERSED FEXOFENADINE HYDROCHLORIDE BUCCAL FILM BY CENTRAL COMPOSITE DESIGN

Utakarsh U Goankar, U B Bolmal* and A P Gadad

Department of Pharmaceutics, KLE's College of Pharmacy, Belagavi, Karnataka, India.

Keywords:

Fexofenadine Hydrochloride (FHCl), 2-Hydroxypropyl β cyclodextrin (2HPβCD), HPMC E5, HPMC K4M, Solid dispersed buccal films

Correspondence to Author:
Mr. U. B. Bolmal

Asst. Professor
Department of Pharmaceutics
KLE's College Of Pharmacy, JNMC Campus Nehrunagar Belagavi-590010, Karnataka, India.

Email: udaybolmal@yahoo.co.in

ABSTRACT: Fexofenadine Hydrochloride (FHCl) is a second generation antihistaminic drug which is used in the treatment of allergic rhinitis and urticaria. It is a BCS class II drug and has high first pass metabolism leading to low oral bioavailability. Drug-inclusion complex with 2HPβCD was prepared by kneading method and characterized for solubility study, FTIR study and *in vitro* dissolution study. Nine different combinations of polymers to be added were generated by Central Composite Design was used to evaluate dependent parameters by varying the independent variables, HPMC E5 and HPMC K4M and responses were tensile strength, mucoadhesive strength and *in vitro* diffusion. Films were prepared and evaluated for different parameters and found to be in acceptable limits. Optimized formulation F10 generated from the design showed good tensile strength and mucoadhesive strength and optimum *in vitro* diffusion results. Drug permeation through porcine oral mucosa at the end of 120 mins was 85.59%. Short term stability studies revealed that formulation was stable after storage for 1 month.

INTRODUCTION: Buccal films are dosage forms that employ a water soluble polymer which allows the dosage form to quickly hydrate, adhere and dissolve when placed between cheek and gum resulting in systemic drug delivery and combat the disadvantages of conventional dosage forms.

The rich vascularisation of the buccal mucosa and the direct access through the jugular vein to the systemic circulation is making it an attractive option in the current drug development and drug delivery process. Owing to the merits of this route presently buccal drug delivery is considered as the best alternative for many drugs.[1, 2]

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Fexofenadine hydrochloride is a BCS class II drug having low bioavailability of 30-40% and a half life of 14 hours. It undergoes hepatic first pass metabolism.[3] The present study is an attempt to prepare solid dispersion of Fexofenadine Hydrochloride and incorporate into a buccal film to enhancement of solubility, bioavailability thereby reducing the dose size and side effects.

MATERIALS AND METHODS: Fexofenadine Hydrochloride was a gift sample from Sanofi Aventis Pvt. Ltd. Ankleshwar. HPMC E5, HPMC K4M and Ethyl Cellulose were gift samples from Colorcon Pvt. Ltd., Verna Goa. All chemicals and reagents were of analytical and pharmacopieal grade.

Preformulation studies:

1. Identification tests:

a) Determination of melting point of the drug: Melting point of Fexofenadine Hydrochloride was

determined by open capillary method using Thiele's tube apparatus.

b) FTIR spectroscopy:
FTIR spectral measurements of the drug sample were recorded using IR Spectrophotometer. The FTIR spectrum of the sample drug was compared with the standard FTIR spectrum of the pure drug to ascertain any significant changes in the sample drug.

c) Solubility analysis:
Solubility studies were carried out by preparing saturated solutions of drug by adding excess of drug into non-volatile solvents and sonicating them for specific time period under constant stirring, analysing spectrophotometrically at λ_{max} 220nm. Fexofenadine Hydrochloride was dissolved in selected solvents like distilled water, phosphate buffer pH 6.8 and ethanol.

d) Determination of absorption maxima (λ_{max}) of the drug:
Stock solution of the drug was prepared using phosphate buffer of pH 6.8 to give concentration of 100µg/ml. 1ml from above solution was diluted up to 10ml in a volumetric flask to give concentration of (10 µg/ml). Wavelength scan from 400-200nm was done to find absorbance maxima.

2. Compatibility studies:
a) By FTIR spectroscopy:
The FTIR spectrum of Fexofenadine Hydrochloride and a physical mixture of Fexofenadine Hydrochloride with HPMC E5 and HPMC K4M were recorded by using FTIR (IRAffinity-1, Shimadzu, Kyoto, Japan).

II. Standard Calibration Curve of Fexofenadine Hydrochloride in phosphate buffer pH 6.8:
10 mg of drug was dissolved in 5ml ethanol and the volume was adjusted to 100ml using phosphate buffer pH 6.8 to get stock solution of concentration 100µg/ml. Serial dilutions were done in Beer's range of 10-50 µg/ml. The absorbencies were recorded at λ_{max} 220nm using UV visible spectrophotometer. The graph of absorbance v/s concentration (µg/ml) was plotted.

III. Preparation and characterization of inclusion complex of Fexofenadine Hydrochloride and 2 Hydroxy Propyl β Cyclodextrin (2HPβCD):

a) Preparation of inclusion complex by kneading method:
Weighed quantities of Fexofenadine Hydrochloride and 2-HPβC in 1:1 equimolar ratio [taking molecular weights of drug and cyclodextrin 538 and 1193 respectively] were taken**.** Drug and 2-HPβC was slowly added to solvent (Ethanol: distilled water 1:1) and triturated to obtain a homogenous paste. The paste was dried at 40ºC for 24 hours and passed through sieve no 40.[4, 5]

b) Characterization of inclusion complexes:
i. Drug content of inclusion complexes:
10mg of complex was diluted with phosphate buffer pH 6.8 upto 100ml. sonicated for 15 mins to dissolve.1 ml of this solution was transferred into volumetric flask and volume made upto 10ml. After suitable dilutions absorbance was taken in a UV spectrophotometer at λ_{max} 220nm. The obtained absorbance was used for calculating the drug content.

ii. FTIR spectroscopy:
The FTIR spectrum of Fexofenadine Hydrochloride, 2-Hydroxy Propyl β Cyclodextrin and the inclusion complex were recorded using FTIR instrument (IRAffinity-1, Shimadzu, Kyoto, Japan). Scanning was done from 4000 cm^{-1} to 400 cm^{-1}.

iii. Differential Scanning Calorimetry:
The DSC thermograms of Fexofenadine Hydrochloride and inclusion complex were obtained and observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks.

iv. *In -vitro* dissolution studies:
The quantity of inclusion complex equivalent to 100 mg of drug was taken and dissolution study was conducted using USP type I dissolution apparatus in 900 ml of phosphate buffer of pH 6.8 at 37±0.5ºC and at 50 rpm. Aliquots of 5 ml were withdrawn at predetermined time interval up to 60 minutes. The concentration of drug in samples was determined by measuring

absorbance at λ_{max} 220 nm by UV-visible spectrophotometer.

IV. Design of Experiment: [6]

Central composite design set up using software Design Expert 9.0.6.2 consisting of 2 factors and 3 levels was used to study the effect of independent variables/factors: the polymers used HPMC E5 and HPMC K4M on the product quality attributes: responses like Tensile strength, Mucoadhesive strength and *In vitro* diffusion.

TABLE 1: FACTORS AND CORRESPONDING LEVELS AS PER CENTRAL COMPOSITE DESIGN

Factors	Levels		
	-1	0	+1
A: HPMC E5	3%	4%	5%
B: HPMC K4M	0.5%	1.5%	2.5%

TABLE 2: AMOUNT OF X_1 AND X_2 GENERATED BY THE SOFTWARE TO BE ADDED IN THE 9 FORMULATIONS

RUN	Amount of HPMC E5 (%)	Amount of HPMC K4M (%)
1	4	1.5
2	5	1.5
3	3	2.5
4	4	0.5
5	3	1.5
6	4	2.5
7	5	2.5
8	3	0.5
9	5	0.5

3. Formulation of Fexofenadine Hydrochloride inclusion complex loaded buccal films:

Solid dispersed buccal films of Fexofenadine Hydrochloride were prepared by solvent casting method using hydrophilic polymers HPMC E5 and HPMC K4M in combination generated by the Design Expert 9.0.6.2 software. Propylene glycol was used as a plasticizer and sodium saccharin as sweetener. Formulation ingredients are shown in the **Table 3**.

Procedure:

Film: The weighed quantities of polymers were soaked overnight containing 5ml of distilled water. The polymeric solution was stirred for 30mins on a stirrer to get homogenous solution. Plasticizer 10% w/w of the polymer concentration was added to the polymeric solution with continuous stirring. In another beaker weighed quantities of Fexofenadine Hydrochloride-2-HPβC complex and sodium saccharin were dissolved in sufficient quantity of solvent (Ethanol: distilled water 1:1) The solution was continuously stirred for 6 hrs. Then the polymeric solution and the drug solution with other excipients was mixed together to get homogenous solution. The pre lubricated petri plate was kept overnight for drying in an oven at a temperature of 40ºC. The films were carefully removed after drying and cut into 2×2 centimeter square size and stored at room temperature with butter paper wrapped.

Backing layer:

5% of Ethyl cellulose was dissolved in isopropyl alcohol- acetone solvent mixture in the ratio (3:1) and kept for stirring for 6 hrs. Amaranth solution (1%) was added to impart colour to the backing layer. The petri plate was kept overnight for drying in an oven at a temperature of 50ºC. The backing layer formed was cut into 3x3 centimeter square size and it was stored at room temperature butter paper wrapped.

TABLE 3: FORMULATION CHART OF FEXOFENADINE HYDROCHLORIDE BUCCAL FILMS

Formulation Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Complex Equivalent To 20mg OF FHCl mg	744	744	744	744	744	744	744	744	744
HPMC E5 %	4	5	3	4	3	4	5	3	5
HPMC K4M %	1.5	1.5	2.5	0.5	1.5	2.5	2.5	0.5	0.5
Propylene Glycol %	10	10	10	10	10	10	10	10	10
Sodium Saccharin %	0.	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Distilled Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

The response variables tensile strength, mucoadhesive strength and % *in vitro* diffusion were obtained experimentally. Experimental values were compared with software generated predicted values. Response variables were subjected to one way ANOVA at 0.05. Based on optimization

results, software generates optimized solutions for independent variables X_1 and X_2 and also for response variables Y_1, Y_2 and Y_3. Finally, a check-point batch F10 (optimized formulation) using optimized values is prepared to prove the validity of evolved method.

VI. Evaluation of buccal films:

1. Physical appearance and Surface texture:

Visual inspection of films for visible imperfections was carried out and surface texture of film was analyzed by feel or touch.

2. Thickness of films:

Thickness was measured using Vernier Callipers by folding the film multiple times and average was taken by dividing the measured value with number of folds. This study indicates the uniformity of thickness in the film and proper dose of the film.[7]

3. Uniformity of weight:

Films of size 2 x 2 cm^2 were cut at 3 different places on the casted petri-plate film. Individual film was weighed on an analytical balance weight were recorded. This study determines whether there is proper amount of drug and excipients in each film.[7]

4. Folding endurance:

Folding endurance of the films was determined by repeatedly folding a small strip of the films (2x2 cm^2) at the same place till it breaks. The number of times film could be folded at the same place, till it breaks gives the value of folding endurance. This test ensures if the film has endurance to withstand repeated folding and brittleness.[7]

5. Surface pH:

Three patches of each formulation are allowed to swell by keeping in contact with 0.5ml 0f distilled water (pH 6.5 ± 0.5) for one hr at room temperature. The pH was determined by bringing the electrode in contact with the buccal film and allowing it to equilibrate for one min.[7]

6. Tensile strength:

Film of dimension 2 x 2 cm^2 was placed between two clamps at a distance of 3 cm apart. During the measurement the bottom clamp pulled the film by addition of weights in the pan till the film breaks. The load when the film breaks was measured by equation.[7]

$$\text{Tensile strength} = \frac{\text{force at break}}{\text{Initial cross sectional area of film}}$$

7. Drug content uniformity:

Film of size 2 x 2 cm^2 was dissolved in 100ml of phosphate buffer pH 6.8, stirred and sonication for 24 hours. 1ml of filtered solution was transferred and diluted with phosphate buffer pH 6.8, the absorbance was measured at λ_{max} 220 nm using UV spectrophotometer.[8]

8. Percent moisture absorption:

Films were accurately weighed and placed in a desiccator containing saturated solution of Calcium chloride (79.5% relative humidity) for 3 days. The patches were reweighed and percentage moisture absorbed was calculated using the formula.[9]

$$\text{Percentage moisture absorption} = \frac{\text{final weight} - \text{initial weight}}{\text{Final weight}} \times 100$$

9. Percent moisture loss:

The prepared films were accurately weighed and placed in a desiccator containing anhydrous calcium chloride for 3 days. After 3 days again the films were reweighed and percentage moisture loss was calculated using the following formula.[9]

$$\text{Percentage moisture loss} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

10. Mucoadhesive strength:

The mucoadhesive strength was measured using an analytical balance. Both the ends were tied to glass plates. Buccal patch was placed onto the slide by placing one drop of water on the slide. Weight was added slowly to the left hand pan until the glass slide got detached from the patch placed. Weight required to detach the patch from the glass slide is measure of mucoadhesive strength.[7]

11. Percent Elongation:

Film of dimension 2 x 2 cm^2 was placed between two clamps at a distance of 3 cm apart. During the measurement the bottom clamp pulled the film by

addition of weights in the pan till the film breaks. The length of the film when the patch breaks by application of stress is measured by equation: [10]

$$\textbf{Elongation at break} = \frac{l_b - l_o}{l_o} \times 100$$

Where, l_o = original length of the patch and l_b = length of the patch at break when stress is applied.

12. Swelling index:

Swelling index was determined by placing film of dimension 2 x 2 cm2 preweighed on a wire mesh into a petri plate filled with 15 ml of phosphate buffer pH 6.8. Weight of the film was measured at regular intervals till the weight remained constant and average of 3 films was taken. Swelling index was calculated by following formula: [11]

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

Where W_t is weight of the film after time t and W_0 is weight of the film at time 0

13. Drug release from the backing layer:

To evaluate the performance of the backing layer this study was conducted using Franz diffusion cell in phosphate buffer pH 6.8 as a medium. The film with the backing layer was placed between the donor and receptor compartment over the cellophane membrane. Temperature was maintained to 37ºC at 50 rpm using magnetic bead stirrer. 1ml of sample was withdrawn from the receptor compartment at predetermined intervals of 15, 30, 45, 60, 90 and 120mins and was replaced with phosphate buffer pH 6.8. Samples were measured for absorbance at λ_{max} 220nm using UV visible spectrophotometer.

14. *In vitro* drug release:

In vitro dissolution studies were conducted using USP type I (Basket type) dissolution test apparatus containing 250 ml of phosphate buffer of pH 6.8 as dissolution medium. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment with 50 rpm. 1ml samples were withdrawn at time intervals of 15, 30, and 60 mins and replaced the same with fresh dissolution medium to maintain sink conditions. Drug content was analysed spectrophotometrically at λ_{max} 220nm by using UV-visible spectrophotometer.[7]

15. *In vitro* diffusion studies:

In vitro diffusion study was performed by using modified Franz diffusion cell across cellophane membrane of molecular size 12,000-14,000D and pore size 2.4nm (HiMedia Pvt. Ltd.) using phosphate buffer solution pH 6.8 as a medium. 2x2cm^2 patch was placed on the membrane, placed between donor and receptor compartment of Franz diffusion cell. Cellophane membrane was brought in contact with Phosphate buffer of pH 6.8 filled in receptor compartment. Temperature was maintained at 37ºC at 50rpm using magnetic stirrer. 1ml of sample was withdrawn from receptor compartment at pre-determined interval of 15, 30, 45, 60, 90 and 120 mins and was replaced with fresh Phosphate buffer of pH 6.8. With suitable dilution, samples were analysed for absorbance at λ_{max} 220nm using UV visible spectrophotometer.[7]

16. *Ex-vivo* permeation studies:

Ex-vivo permeation studies were carried out using modified Franz diffusion cell using phosphate buffer pH 6.8. (35ml) as a medium. Mini magnetic bead was placed in the receptor compartment for agitating the buffer solution. Porcine oral mucosa was used as the model membrane, obtained from local sluttery house Optimized film of dimensions 2×2cm^2 was cut and placed over the porcine oral mucosal membrane. The donor compartment was then placed and fixed over it with the help of rubber bandages and clamps. The donor compartment was filled with 1 ml of phosphate buffer of pH 6.8. The whole assembly was placed on a magnetic stirrer, and the solution in the receptor compartment was continuously stirred. The temperature was maintained at 37±2ºC. Samples of 1 ml were withdrawn at predetermined time intervals of 15, 30, 60 90 and 120 minutes and were analyzed at λ_{max} 220nm spectrophotometrically by using UV-visible spectrophotometer to determine the amount of drug permeated.[12]

17. Stability studies:

Stability studies were performed in accordance with ICH guidelines. Patches (2x2 cm^2) were

wrapped individually in aluminium foil and maintained at room temperature 25ºC and 60% RH and temperature 40ºC and 75% RH for a period of 1 month. Changes in the appearance, drug content, tensile strength and *in vitro* drug release of the stored patches were investigated after 15 days and 30 days.[13]

RESULTS:

I. Preformulation studies:

1. Identification tests:

a) Determination of melting point of the drug:

Melting point of Fexofenadine Hydrochloride (FHCl) was found to be 196 ºC and it complies with the IP standard thus indicating purity of the drug sample.

b) FTIR spectroscopy:

The IR spectrum of pure drug was found to be similar to the reference standard IR spectrum of Fexofenadine Hydrochloride.

c) Solubility Studies:

Fexofenadine Hydrochloride was found to be slightly soluble in distilled water and phosphate buffer pH 6.8, freely soluble in ethanol.

d) Determination of absorption maxima (λ_{max}) of the drug:

Wavelength scan from 400-200 nm was performed to find absorption maxima. Maximum absorption was found at 220 nm.

2. Compatibility studies

a) By FTIR spectroscopy:

The IR spectra of drug and physical mixture show similar characteristic peaks indicating compatibility of drug and film forming polymers.

II. Standard calibration curve of Fexofenadine Hydrochloride:

The standard calibration curve of Fexofenadine Hydrochloride was obtained by plotting concentration v/s absorbance. The curve was found to be linear in the concentration range of 10 – 50 µg/ml at λ_{max} 220 nm. The correlation coefficient (R^2) obtained was 0.9986 and equation was y = 0.0302x + 0.0246 as shown in **Fig.1**

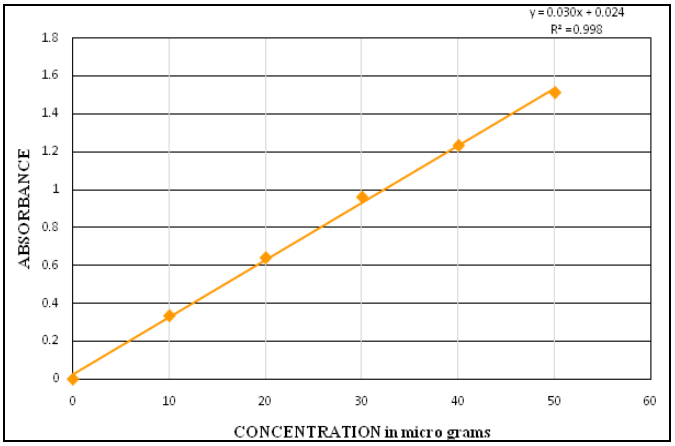


FIG. 1: STANDARD CALIBRATION CURVE OF FEXOFENADINE HYDROCHLORIDE IN pH 6.8 PHOSPHATE BUFFER

III) Characterization of inclusion complex of Fexofenadine Hydrochloride with 2 hydroxy propyl β cyclodextrin:

1) Drug content of inclusion complexes:

From 100mg of drug complex contains 29.98mg.drug. Thus the ratio of drug and complex is 1:1.4

ii) Fourier transformer infrared spectroscopy (FTIR) of inclusion complex:

Analysis of IR spectra of inclusion complexes revealed that the intensity and shape of all bands changed dramatically for the inclusion complex as compared to those for Fexofenadine Hydrochloride. These indicated that the vibrating and bending of the guest molecule Fexofenadine Hydrochloride was restricted due to the formation of an inclusion complex.

iii) Differential Scanning Calorimetry:

The thermal curve of the FHCl obtained indicated its crystalline anhydrous state, exhibiting a sharp endothermic peak at 198°C shown in **Fig.2**.

The DSC thermogram of Fexofenadine Hydrochloride / 2-HPβC inclusion complex prepared by kneading method display a broad endothermic band due to the dehydration of the complex. This explains the amorphous solid dispersion and the molecular encapsulation of FHCl into the HPβCD cavity.

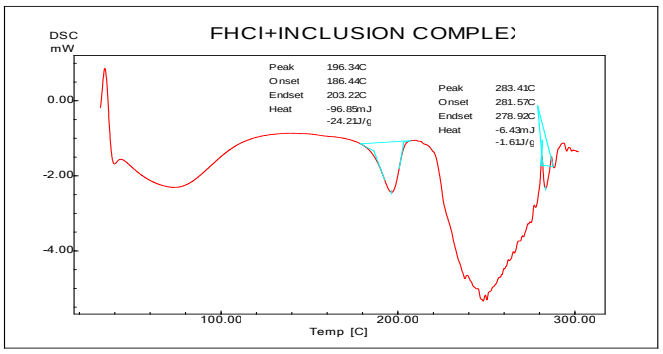


FIG. 2: DSC THERMOGRAM OF FEXOFENADINE HYDROCHLORIDE AND 2- HPβCD COMPLEX

iv) *In vitro* dissolution studies:

In vitro drug release of the pure drug the end of 60 mins was 27% as compared to release of inclusion complex is 90% as shown in **Fig. 3**. This showed that dissolution rate of pure Fexofenadine Hydrochloride was enhanced by forming an inclusion complex with 2- Hydroxy propyl β cyclodextrin.

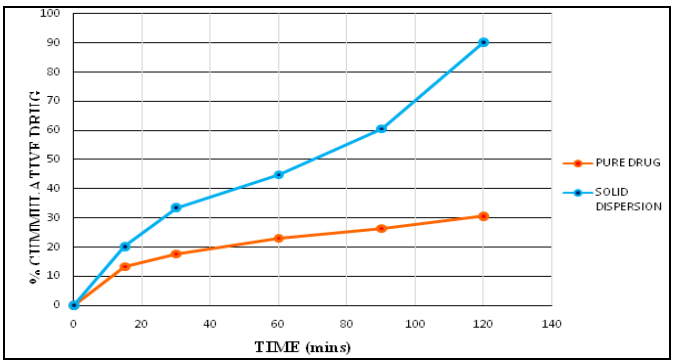


FIG. 3: COMPARISON OF *IN-VITRO* DISSOLUTION PROFILES OF PURE DRUG AND DRUG INCLUSION COMPLEX

IV) Formulation of FHCl Buccal Films:

Films formed were homogenous with no cracks. They were cream white in colour with good physical properties.

V) Evaluation Parameters of Prepared Buccal Films:

1. Physical appearance and Surface texture:

All the films were cream white, smooth and elegant in appearance.

2. Thickness of films:

The average thickness of the films ranged from 0.073mm to 0.167mm shown in **Fig.4**. Formulation F8 had lowest thickness, formulation F7 had highest thickness value.

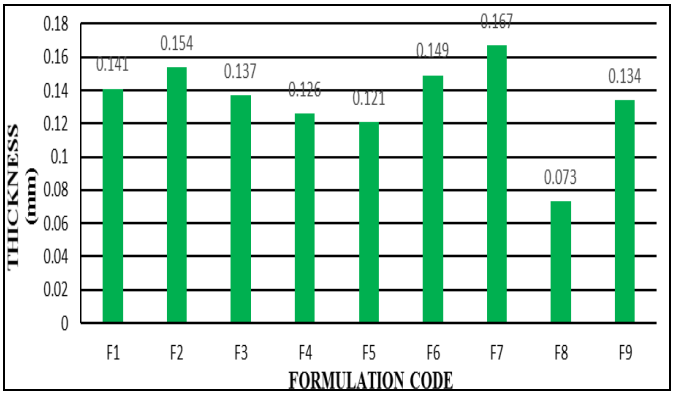


FIG. 4: COMPARATIVE BAR GRAPH OF THICKNESS OF FORMULATIONS F1-F9

3. Weight of the films:

The mean weight of all films ranged from 58mg to 81mg shown in **Fig. 5**. Formulation F8 weighed 59mg whereas formulation F7 weighed 81mg.

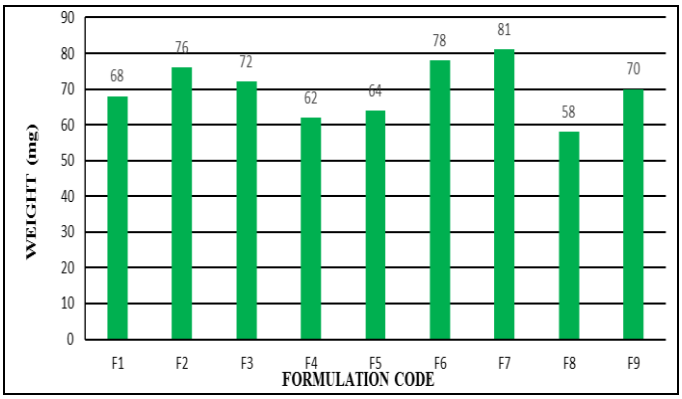


FIG. 5: COMPARATIVE BAR GRAPH OF WEIGHT OF FORMULATIONS F1-F9

4. Folding endurance of films:

The folding endurance values of all the formulations was found to be in the range of 165 to 198 shown in **Fig. 6**. Formulation F8 showed highest folding endurance value whereas formulation F7 showed lowest value.

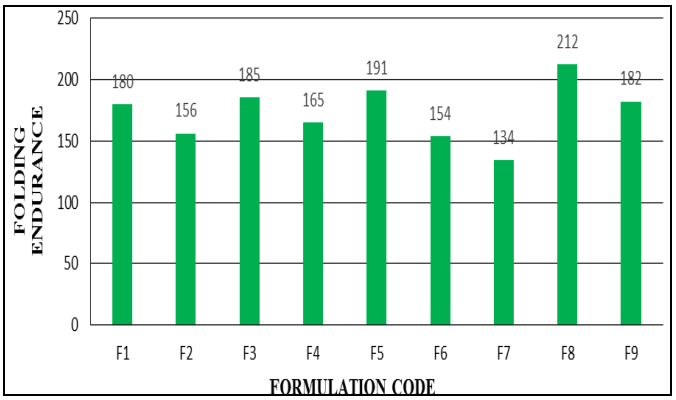


FIG. 6: COMPARATIVE BAR GRAPH OF FOLDING ENDURANCE OF FORMULATIONS F1-F9

5. Surface pH of films:

Surface pH gives an indication of alkalinity and acidity of the films because the acidic or alkaline pH of films may cause irritation to the oral mucosa. Surface pH of films prepared by using different polymers was found to be in the range of 6.57 to 6.84 shown in **Fig.7**, which was close to the neutral pH.

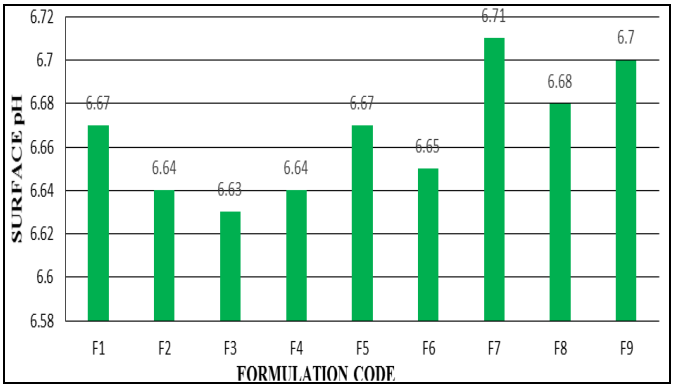


FIG.7: COMPARATIVE BAR GRAPHS OF SURFACE pH OF FORMULATIONS F1-F9

6. Tensile strength:

Tensile strength of prepared films varies from 37.45 to 65.5 gm/cm^2 shown in **Fig. 8** revealing that the films had good mechanical strength and flexibility. Formulation F8 showed lowest tensile strength whereas formulation F7 showed highest tensile strength.

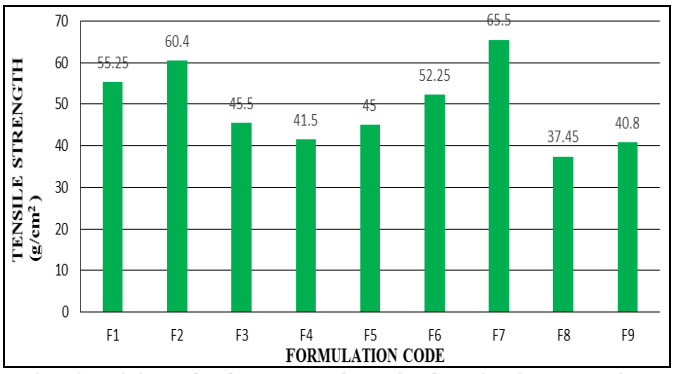


FIG. 8: COMPARATIVE BAR GRAPHS OF TENSILE STRENGTH OF FORMULATIONS F1-F9

7. Percent Elongation:

Percent elongation study was carried out to test the strength and ability of the films. Percent elongation values arranged between 110 to 156% shown in **Fig 9.** Formulation F7 showed lowest percentage elongation whereas formulation F8 showed highest percentage elongation.

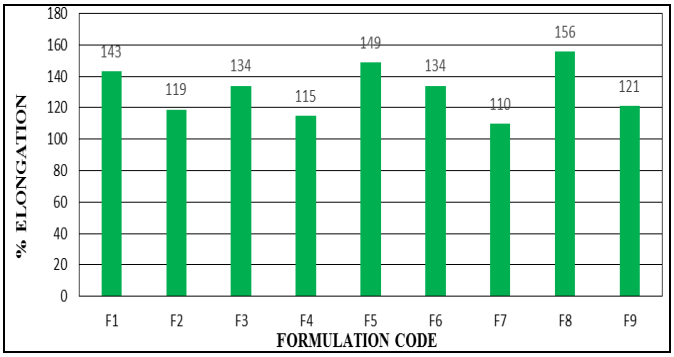


FIG. 9: COMPARATIVE BAR GRAPH OF % ELONGATION OF FORMULATION F1-F9

8. Drug Content Uniformity:

The drug content uniformity test was performed to ensure uniform distribution of drug. The percentage drug content of all the formulations was found to be in the range of 94% to 97.3% shown in **Fig 10**. The results indicated that the drug was uniformly distributed in all the formulations.

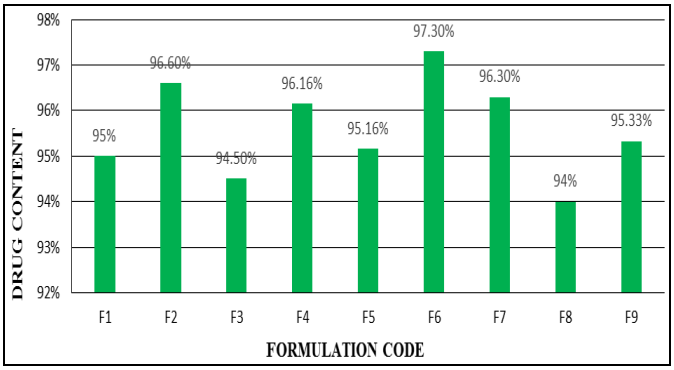


FIG. 10: COMPARATIVE BAR GRAPH OF DRUG CONTENT OF FORMULATIONS F1-F9

9. Swelling index:

Swelling behaviour of all formulations was assessed. The swelling index values of films ranged from 20.6 to 35.6% shown in **Fig.** 11. Formulation F7 showed high swelling index whereas formulation F8 showed low swelling index.

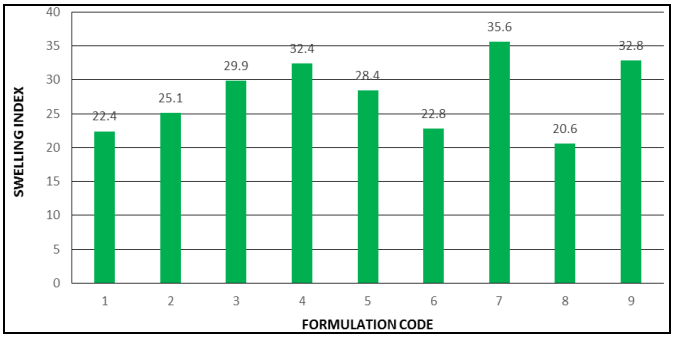


FIG. 11: COMPARATIVE BAR GRAPH OF SWELLING INDEXES OF FORMULATIONS F1-F9

10. Mucoadhesive strength:

The values ranged from 4.5 to 8.2 grams shown in **Fig.12.** Formulation F8 showed lower mucoadhesiveness whereas formulation F7 showed higher mucoadhesiveness.

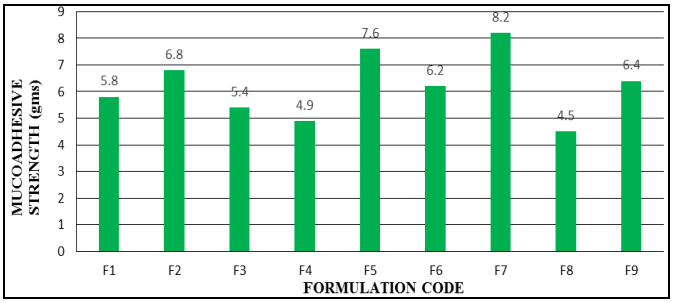


FIG. 12: COMPARATIVE BAR GRAPH OF MUCOADHESIVE STRENGTH OF FORMULATION F1-F9

11. Moisture absorption:

Moisture absorption studies were carried out to assess the physical stability of films in humid conditions. The results varied from 2.58 to 5.65% shown in **Fig.13**. Formulation F7 showed higher moisture absorption, formulation F8 showed lower moisture absorption.

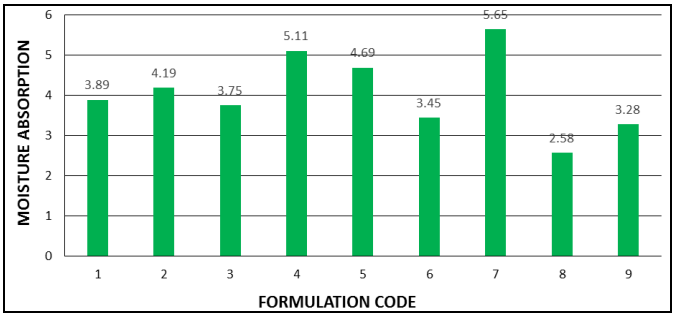


FIG.13: COMPARATIVE BAR GRAPH OF % MOISTURE ABSORPTION FORMULATION F1-F9

12. Moisture Loss:

Moisture loss values ranged from 1 to 2.2% shown in **Fig.14**. Formulation F7 showed lower moisture loss value, formulation F8 showed higher moisture loss value.

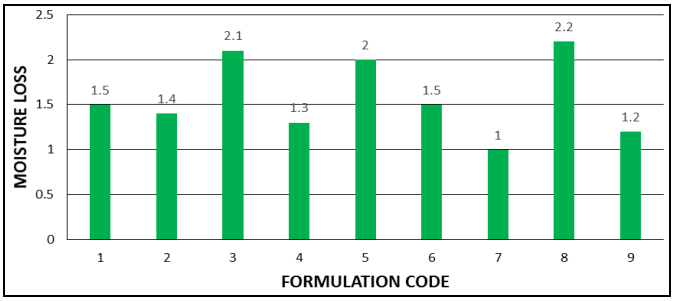


FIG.14: COMPARATIVE BAR GRAPH OF % MOISTURE LOSS FORMULATION F1-F9

13. Drug release from the backing layer:

At the end of 120 mins no drug was released in the receptor compartment of the diffusion cell. This indicated that ethyl cellulose membrane is impermeable to drug Fexofenadine Hydrochloride and swelling of mucoadhesive layer does not affect the integrity of the backing layer.

14. *In vitro* drug release studies:

At the end of the 60 minutes formulations showed drug release between 89.55 to 95.5 % shown in **Fig. 15**. Formulation F8 showed highest drug release at the end of 120mins, F7 showed lowest drug release.

Kinetic study of *in vitro* drug release data:

The release of drug followed Peppas model but only F1 and F6 follows matrix release pattern. The drug release of the rest of the formulations shows Kosmeyer peppas as the best fit model. None of the formulation follows fickian diffusion but follows non fickian (anamolous) behaviour. The optimized formulation F10 shows the peppas as the best fit model with non-fickian anamolous behaviour with n value of 0.9831.

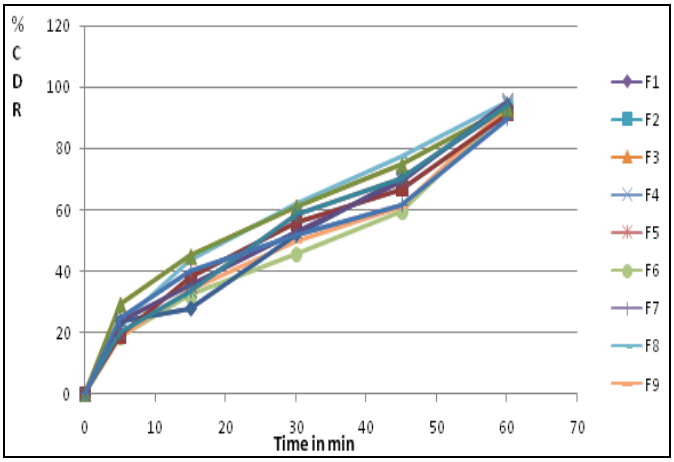


FIG.15: COMPARATIVE *IN VITRO* DRUG RELEASE PROFILE OF FORMULATION F1-F9

15. *In vitro* drug diffusion studies:

Percent drug permeated through all formulations ranged between 90.06 to 96.34% shown in **Fig. 16**. Formulation F8 with lowest concentration of polymers showed highest drug permeation (96.34%), F7 with highest concentration of polymers showed lowest drug permeation (90.06%).

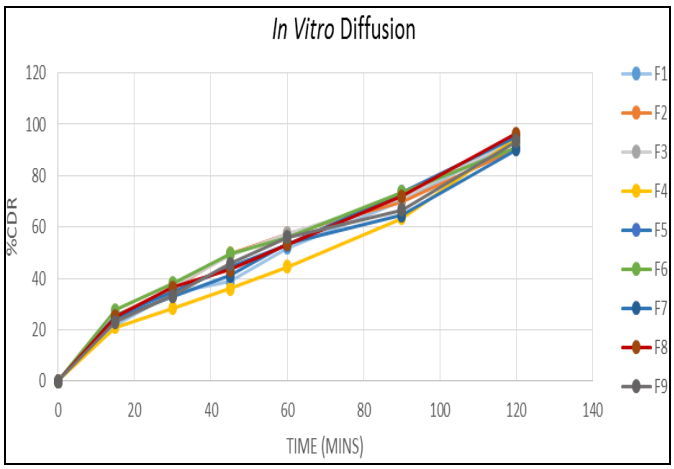


FIG. 16: COMPARATIVE *IN VITRO* DIFFUSION PROFILE OF FORMULATION F1-F9

Optimization:

The regression analysis of quadratic model fit revealed that tensile strength, mucoadhesive strength and % *in vitro* diffusion were 97% correlated with active factors X_1, X_2. Based on the optimization results, ANOVA ($p< 0.05$) and desirability = 1, one solution was predicted by the software for independent variables X_1 and X_2 with desired responses Y_1, Y_2, Y_3.

Finally, a check-point batch F10 (optimized formulation) (**Table 5**) using optimized values is formulated to prove the validity of evolved method. The results of evaluation parameters for optimized formulations F10 were found to be uniform and within the permissible limit as shown in **Table 6.**

TABLE 4: PREDICTED SOLUTIONS (OPTIMIZED) BY THE SOFTWARE: FACTORS AND RESPONSES

Factors		Response		
X_1 (%)	X_2(%)	Y_1(gm/cm2)	Y_2(gms)	Y_3(%)
4.5%	1.25%	63.45	7.4	93.67

TABLE 5: OPTIMISED FORMULATION F10

Formulation ingredients	Quantities
Complex Equivalent to 20mg of Fexofenadine Hydrochloride	744 mg
HPMC E5	4.5%
HPMC K4M	1.25%
Propylene Glycol	10%
Sodium Saccharin	0.1%
Distilled Water	q.s

TABLE 6: EVALUATION PARAMETERS OF OPTIMISED FORMULATION F10

Physical Appearance	Smooth, homogenous and white
Drug Content	96.3 ± 0.89 %
Swelling Index	23.3 ± 1.22%
Surface pH	6.3 ± 0.34
Tensile Strength	65.50 ± 1.03 gm/cm^2
Mucoadhesive Strength	7.2 ± 0.95gms
In vitro Diffusion at the end of 120mins	94.42 ± 0.87%
In vitro drug release at the end of 120mins	96.34 ± 0.93%
Kinetic Release Model	Peppas R^2= 0.9831

TABLE 7: COMPARISON BETWEEN EXPERIMENTED VALUES (E) AND PREDICTED VALUES (P) FOR THE OPTIMIZED FORMULAE

Response variables	Experimented values	Predicted values	% Error
Y_1 Tensile strength (gms)	65.50	63.45	+ 3.23
Y_2 Mucoadhesive strength (gm/cm2)	7.2	7.5	- 4
Y_3 *In vitro* drug diffusion (%)	94.42	93.67	+ 0.8

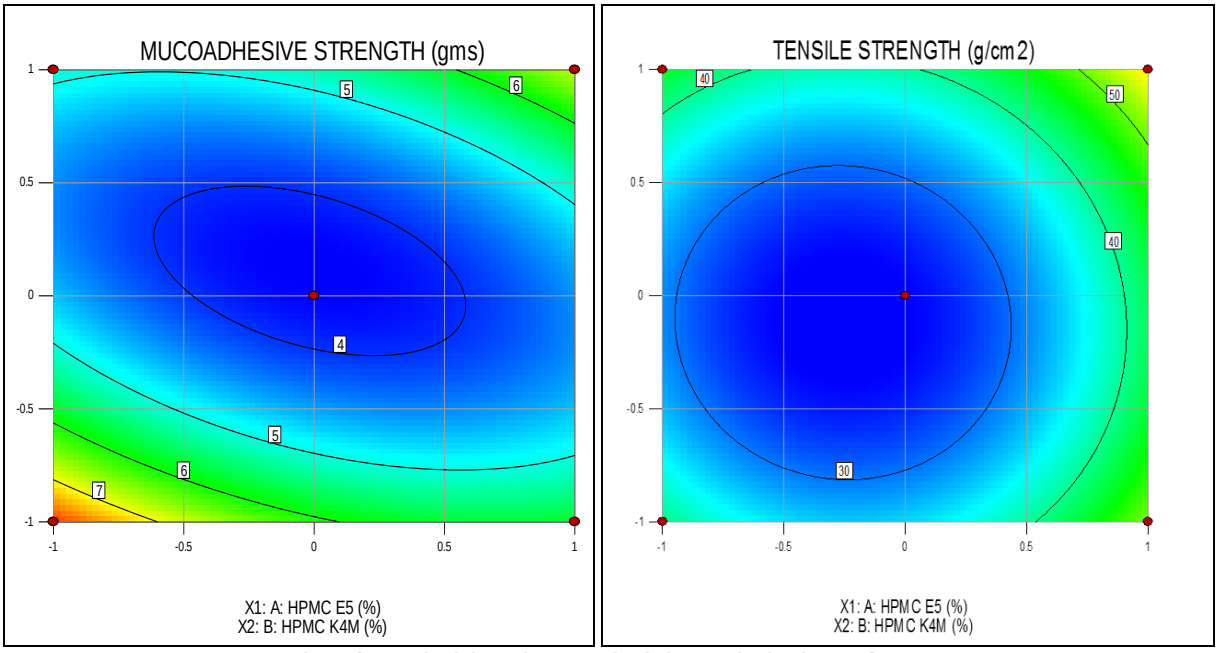


FIG.17 AND 18: CONTOUR PLOTS OF RESPONSE Y_1 AND Y_2

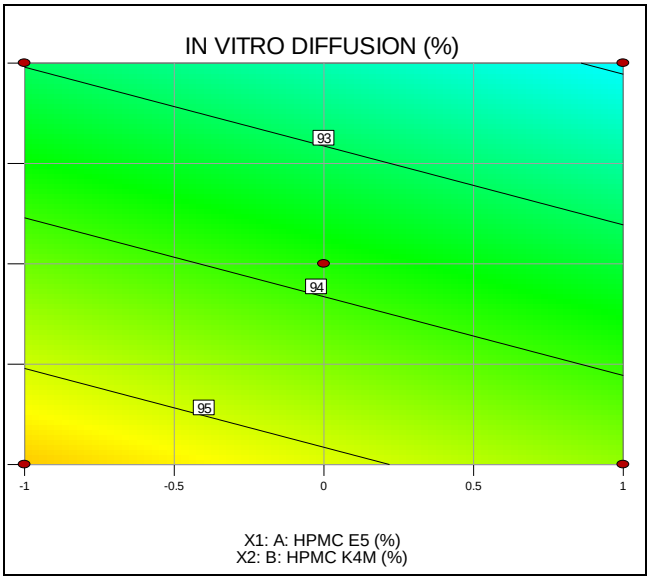
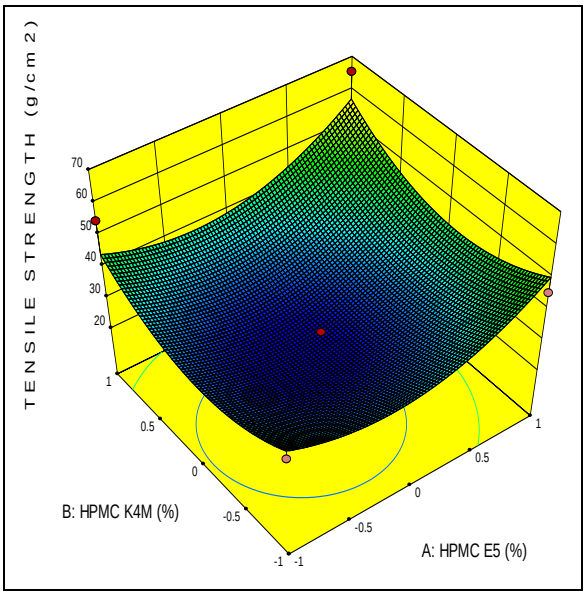


FIG. 19: CONTOUR PLOT OF RESPONSE Y_3



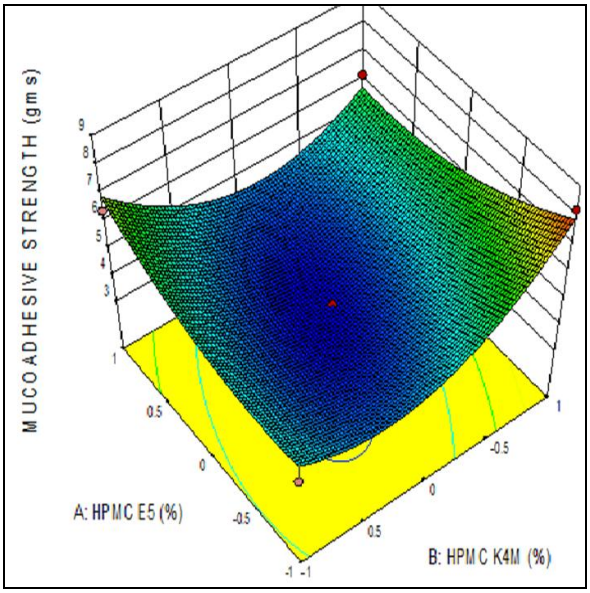


FIG. 20 AND 21: 3D RESPONSE SURFACE PLOTS OF RESPONSE Y_1 AND Y_2

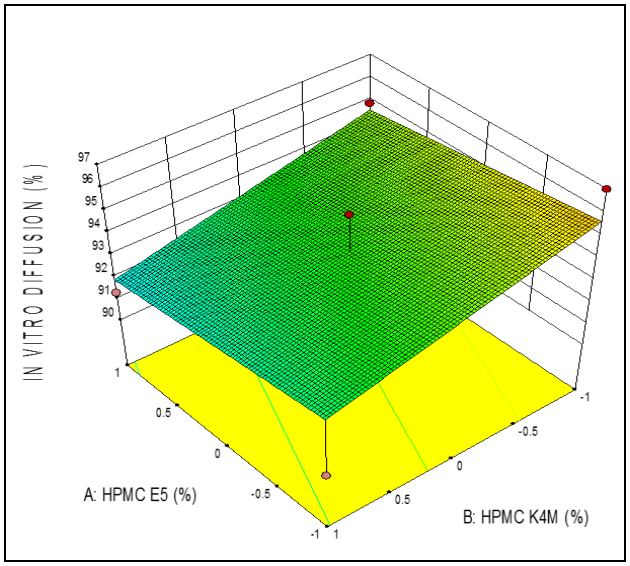


FIG.22: 3D RESPONSE SURFACE PLOT OF RESPONSE Y_3

16. *Ex vivo* permeation studies:

Ex vivo permeation study of optimized formulation F10 was carried out through porcine oral mucosa using modified Franz diffusion cell apparatus. The optimized oral film F10 showed 85.89 % of drug permeation through the mucosa at the end of 2 hours. The percentage of drug permeated was calculated and plotted against time as shown in **Fig. 23**

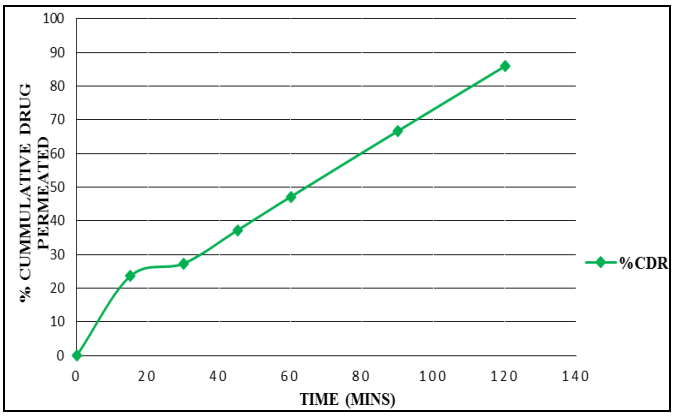


FIG. 23: *EX VIVO* PERMEATION OF OPTIMIZED FORMULATION F10

17. Stability studies:

The optimized formulation F10 was selected for short term stability studies at temperature 25^0C ±2.0^0C/ 60% RH% ±5.0% and accelerated stability studies were carried out at 40^0C±2.0^0C/ 75% RH% ±5.0%. For 15 days and 30 days, the films were analysed for tensile strength, *in vitro* drug release and drug content. There was minor decrease in all the evaluated parameters.

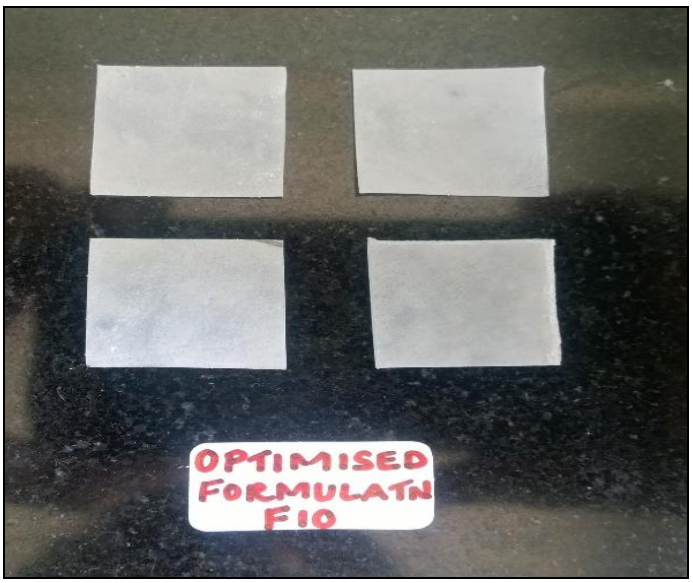


FIG.24: FILMS OF OPTIMIZED FORMULATION F10 OF 2×2 CM^2

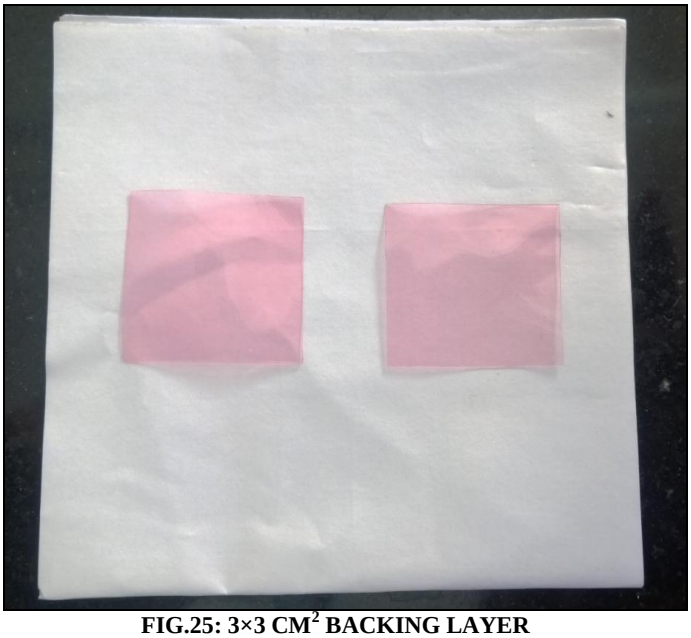


FIG.25: 3×3 CM^2 BACKING LAYER

DISCUSSIONS: The FTIR study and DSC study revealed that there was no interaction between the drug and the polymers used and confirmed the formation of the inclusion complex. The inclusion complex of the FHCl showed enhancement in its solubility and dissolution rate.

All films appeared to be smooth, translucent and uniform in texture. The pH of all formulations was within limits of the normal physiological pH range. The weight and thickness of all the films was found to be uniform. Folding endurance, mucoadhesive strength and tensile strength were in acceptable range. *In vitro* drug release studies at the end of two hours showed maximum release of 95.5% and maximum drug permeation observed at the end of 120 minutes was 96.3%. Kinetic release studies revealed that all formulations show non fickian diffusion following release from peppas and matrix model.

Optimised formulation F10 showed good tensile strength, mucoadhesive strength and optimum *in vitro* diffusion result. Kinetic release studies indicated it follows Korsmeyer Peppas model showing non fickian diffusion. Drug permeation through porcine mucosa at the end of 120 minutes was 85.89%. It was also subjected to stability studies as per ICH storage conditions at room temperature 25^0C ±2^0C (60% ± 5%RH) and accelerated conditions at 40^0C ± 2^0C (75% ±

5%RH) for 30 days. Stability studies revealed that formulation was stable for 1 month.

CONCLUSIONS: Drug and polymers were found to be compatible. Complexation with 2-HPβCD improved the solubility of Fexofenadine Hydrochloride two folds as compared to pure drug. FTIR spectra of inclusion complex and DSC studies showed formation of inclusion complex between FHCl and 2-HPβCD. The effect of HPMC E5 and HPMC K4M was successfully studied on selected responses tensile strength, mucoadhesive strength and *in vitro* diffusion using central composite design.

Prepared films were creamy white, smooth in appearance with good physical and mechanical properties and good results were obtained for evaluated parameters. Regression analysis was fitted to the model to ascertain its validity. Optimised formulation F10 gave optimum results for selected responses i.e experimental values and the predicted values were having no much differences.

Stability studies revealed that formulation F10 was stable without any deviations for evaluated parameters. Optimized film F10 showed 85.89% of drug permeation in *ex vivo* permeation study. Therefore it can be concluded that Fexofenadine Hydrochloride solid dispersed buccal films can be a promising formulation for the effective treatment of allergic rhinitis and urticaria, wth reduced dose size.

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CONFLICTS OF INTEREST: There are no conflicts of interest.

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