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COMPOSITION OF TERBINAFINE HCL POLYMERIC GEL FOR MUCOSAL DRUG DELIVERY

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ABSTRACT

The buccal mucosa provides an attractive route of administration for systemic drug delivery. The buccal mucosa has rich blood supply which provides rapid absorption of drugs directly into the systemic circulation. The Terbinafine Hcl is an antifungal agent used in the treatment of fungal infection where quick onset of action is required. In present investigation, an attempt has been made to develop polymeric mucoadhesive buccal gel of Terbinafine Hcl. Optimization of formulation factor was achieved using Central composite experimental design. The variables selected include HPMC (stabilizer), PEG400 (permeation enhancer). The buccal gel of Terbinafine Hcl was prepared with HPMC as a stabilizer and PEG 400 as permeation enhancer using solid dispersion method. The prepared gel was evaluated for physical properties viz; drug content, in-vitro release, ex-vivo release, rheology etc. The infrared, spectral, thermal, X-Ray diffraction characterization were performed. The in-vitro permeation study of optimized gel showed prolonged release, due to the addition of permeation enhancer. The in-vitro drug release of gel with 40% of HPMC as a stabilizer, 10% of PEG 400 as a permeation enhancer and 1% of DMSO concentration showed maximum drug release (91.77% ±1.35) in 0.1N HCL at 120 minutes. Thus the buccal gel of Terbinafine Hcl was successfully formulated to achieve a safe, rapid and effective dosage form and rapid Antifungal therapy.

Keywords: Terbinafine Hcl, Polymeric gel, Mucoadhesive buccal drug delivery

INTRODUCTION

The oral mucosa has rich blood supply and relatively greater permeability. Among the various transmucosal routes the mucosal lining of the oral cavity (buccal route) shows some distinct advantages over the other transmucosal routes as richly vascularized and more accessible for administration as well as removal of the dosage forms in case of toxicity [1-3]. The buccal route has been studied as a favorable site for the local and systemic delivery of drugs [4]. Because of the rich blood supply and direct access to systemic circulation, the oral mucosa suitable for drugs, which are susceptible to acid hydrolysis in the stomach are extensively metabolized in the liver [5]. The continuous secretions of saliva results in rapid removal of released drug and hence the oral cavity should be restricted to the delivery of drugs, which have a short systemic circulation. The buccal and gingival areas are associated with a smaller flow of saliva, thus the duration of adhesion of the delivery system would be longer at these areas than the sublingual region. The buccal or gingival membrane, with their accessible, smooth surface offers a platform for prolong delivery of drugs [6-8].

Rapidly dissolving or quick dissolving dosage forms have great importance to treat the emergency conditions like hypertension and various allergic reactions. The rapidly dissolving formulations disintegrate or dissolve within several minutes when placed in the mouth. There is no need of water to swallow or to chew the dosage form. These dosage forms are meant for local as well as systemic action. The fast dissolving dosage forms when placed in the mouth it gets rapidly disintegrate without use of water or chewing and release the medicaments for oromucosal absorption by avoiding the first pass metabolism of the drug. The dosage forms provides fast onset of action with improved bioavailability [9-11]. The various rapidly disintegrating formulations are rapidly disintegrating tablets, fast dissolving patches or films and oral wafers, Gels. Among these formulations the buccal Gel acquired great importance over the other dosage forms. Oral bioadhesive polymeric buccal gels are preferred over tablets in terms of comfort and easy application to the buccal cavity [11].

Terbinafine Hydrochloride (T-HCL) [(E)-N,6, 6-trimethyl-N-(naphthalen-1-ylmethyl) hept-2-en-4-yn-1-amine;hydrochloride] is a new potent antifungal agent of allylamine class which selectively inhibits fungal squale ne expoxidase. Candida species are opportunistic fungus species invading

mucus membrane and deep tissues.Although T-HCL is mostly used in the treatment of dermatophytes infection [12]. It has also been shown that it demonstrated a high in vitro activity against aspergillus and other filamentousv fungi. Terbinafine Hcl is a structurally related to naftifine, antifungal T HCL blocks ergosterol biosynthesis by inhibition of squalene expoxidase, part of the sterol synthesis pathway for the fungal cell membrane. Highly lipophilic, it tends to accumulate in skin, nails, and fatty tissues. Terbinafine Hcl is active against dermatophytes [13].

The present study is aimed to formulate and characterize buccal gel of Terbinafine Hcl for rapid dissolution and absorption which may produce the rapid onset of action in the treatment of fungal infection and also to improve the bioavailability of the Terbinafine Hcl.

MATERIALS

Analytical grade materials were used for study. The Terbinafine Hydrochloride were received from Cipla Pharmaceuticals Goa, India. HPMCK4M were purchased from Research lab Fine Chem Industries, Mumbai, India. PEG4OO, DMSO, HCL, NaOH, Ethanol and Acetone purchased from, Molychem Mumbai.

METHODS

Preformulation

The Terbinafine HCL and other excipients were received from Cipla Pharmaceuticals, Goa, India. This sample was studied for its preformulation data. The drugs used were USP quality and excipients were 99% purity as confirmed by its FTIR and DSC. No further purification was performed.

Spectrophotometric Analysis: Different aliquots (1.0-7.0 ml) of a standard 100 µg/ml Terbinafine HCL solution were transferred into a series of 10 ml volumetric flasks. Adequate quantity of 0.001% w/v (0.1 N NaOH)) was then added to fill the flasks. The amount of Terbinafine HCL was determined by measuring the drug absorbance at 223 nm using UV-visible spectrophotometer (UV-1800, Shimadzu, Japan) [14].

Solubility of Terbinafine HCL: An excess amount of Terbinafine HCL was added to 10 mL of each solvent (in Methanol, Ethanol, Methylene chloride, DMSO, Benzyl alcohol and Ethyl acetate) in 30 mL screw-capped vials and the whole mixture was mixed by vortexing. The vials were then shaken at 37°C for 72 h at 100 rpm in a thermostatically controlled water bath shaker. Then, the supernatant layer was separated and subjected to centrifugation at 3,000 rpm for 5 min in order to remove the undissolved drug. Samples of these solutions were then collected and the drug concentration was determined

spectrophotometrically at 223 nm against a suitable blank using an ultraviolet visible spectrophotometer (UV-1800, Shimadzu, Japan) [15-16].

Drug excipient interactions

Interactions between the Terbinafine HCL and excipients were studied by spectral and thermodynamic changes.

Infra-red spectral analysis: The Possibility of Drug Excipient interaction was investigated by Fourier Transform Infra red spectroscopy (Cary-60 ATR, Agilent). The FTIR spectra of Terbinafine HCL and drug excipient mixtures were recorded. FTIR spectrometer in the range of 4000- 400cm^{1-}, study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients [17].

Differential Scanning calorimetry: Thermo grams of pure Terbinafine HCL were taken for DSC study. An empty aluminum pan was used as a reference. DSC measurements were performed at a heating rate of 5^0C/min from 50 to 400^0C using aluminium sealed pan. The sample size was 5 mg of pure drug and 5 mg of physical mixture for measurements. During the measurement, the sample cell was purged with nitrogen gas at 40 ml/min [18].

X-ray powder diffraction: To verify the physical state of Terbinafine HCL in excipients, X-ray powder scattering measurements were carried out with an X'Pert PRO diffractometer (PAN analytical, the Netherlands). A voltage of 40 kV and a current of 40 mA for the generator were applied with Cu as the tube anode material. The solids were exposed to a Cu–K radiation, over a range of 2h angles from 5°- 40°, at an angular speed of 2° (2h)/min [19].

Formulation of mucoadhesive polymeric gel of Terbinafine HCL

The buccal gel of Terbinafine hydrochloride was prepared using Solid Dispersion Method. The HPMCK4M mixture was prepared by dissolving the HPMCK4M into the distilled water. The solution was allowed to stir for 2-3 hours. While stirring the PEG400 and DMSO was added in the above mixture. After stirring the above mixture was kept aside for 24 hrs to remove air entrapment and form a clear swollen mixture. Furthermore the Terbinafine HCL was dissolved in Ethanol. Both the mixture were mixed and stirred for 1 h on magnetic stirrer [20-21]. The final solution was allowed to stand for another 1 h to remove all air bubbles.

Design of Experiment

Central-composite experimental design: The objective functions for the present study was selected as maximizing the permeability while controlling the viscosity as responses depending on two Independent variables HPMCK4M (stabilizer) and

PEG400 (permeability enhancer) ratio at three different levels. Hence, a Central-composite statistical design with 2 factors, 3 levels and 13 runs was selected to statistically optimize the formulation parameters and evaluate the linear, interaction and quadratic effects of the formulation ingredients on the permeability and viscosity of mucoadhesive polymeric gel. 2-factor, 3-level design was used to explore the quadratic response surfaces and for constructing polynomial models thus helping in optimizing a process using a small number of experimental runs [22-24]. Statistical analysis of the Central-composite design batches was performed by multiple regression analysis using Design Expert DOE. The contribution of each factor with different levels to the response was evaluated with two-way analysis of variance (ANOVA). The models were evaluated in terms of statistically significant coefficients and R^2 values. The experimental design consists of a set of points lying at the midpoint of each edge and the replicated centre point of the multidimensional cube [25].

Characterization of mucoadhesive polymeric gel of Terbinafine HCL

Infra red spectral analysis: Infrared spectra's of mucoadhesive polymeric gel of Terbinafine HCL was obtained using FTIR spectrometer (Cary 630 FTIR, Agilent Techn.). About 3-4 mg sample was directly placed on the stage of spectrometer and scanned from 4000-400 cm^{-1}[26]

Thermal analyses: Thermal analysis of the prepared mucoadhesive gel and pure Terbinafine HCL were carried out using a differential scanning calorimeter (Mettler Toledo, Giessen, Germany). The samples were placed in sealed aluminum pans with pierced lids and heated at a scanning rate of 10°C/min between 25 and 300°C in nitrogen atmosphere.[27]

Powder X - Ray diffraction (PXRD): Physical state of the drugs within the drug-loaded gel was estimated using a performed busing a D/Max X-ray fluorescence spectrophotometer with a CuKa line as the source of radiation. Standard runs were carried out using a voltage of 56 kV, a current of 182 mA and a scanning rate of 2^0 min^{-1} over a 2-theta range of $5\text{-}50^o$. [27-28]

Rheology

The rheological property of the mucoadhesion gel was investigated (C75-1 spindle plate-plate a Brookfield R/S-CPS+ Rheometer, Germany) at 25±2°C. About 2 g of prepared mucoadhesion gel was placed at the centre of lower and upper plate. Flow properties were investigated using the dynamic viscosity (n,pa/s) as a function of time 150 sec in addition to measurement of viscosity as a function of share rate [11,12](ranging from 1-100 $sec^{-1)}$ [29-30].

Flow Type: The flow type was determined using, increased shear rate (1-100 sec^{-1}) linearly for 150 seconds. The measured viscosity vs. shear rate curve indicates the flow type of mucoadhesion gel [30].

Thixotropy: The dynamic viscosity of anhydrous emulsion was studied for resolute the thixotropic behavior of sample. The process parameters embrace the increased and decreased shear rate from 1-100 sec^{-1} and 100-1 sec^{-1} for 150 seconds[31].

Viscosity: The viscosity of prepared gel was measured at changing shear rates from 1-100sec^{-1} and 100^{-1} sec^{-1} with equal stray [31].

In vitro dissolution/release

The in vitro drug transport through the artificial cellulose acetate membrane (molecular weight cut off 1000 Da) was carried out using a vertically static type Franz diffusion cell. Franz diffusion cells are characterized by an effective diffusion surface area of 4.9 cm^2 and a receptor cell volume of 30 mL. The receptor cell was filled with 30 mL simulated salivary fluid (pH 6.8) and was stirred with a small magnetic bar at a speed of 100 rpm for uniform mixing. The receptor compartment was maintained at 37 ± 0.5°C and prepared gel containing 10 mg of Terbinafine HCL were placed on the cellulose membrane surface facing the donor compartment and 1ml samples were withdrawn from the receptor compartment at predetermined time points of 5, 10, 20 and 30 min. The 1 ml sample withdrawn was replaced by fresh simulated salivary fluid (pH 6.2) and maintained at 37 ± 0.5°C. The drug content in the collected samples was determined at 223 nm (UV/visible spectrophotometer, Shimadzu-120, Japan) [32-36].

Permeability coefficient: The permeability coefficient through the membrane (Kp) was determined according to the following equation:

Permeability coefficient (Kp) = (Jss.H)/C0

Where H is the thickness of membrane and, C0 is the initial drug concentration.

Steady-state flux: Flux is defined as the rate of diffusion or transport of a substance across a permeable membrane. After drug permeation has reached steady state, the steady-state flux was calculated:

Steady state flux (Jss) = dM/S.Dt

Where dM is the amount of drug that permeates through a unit cross section area, S, per unit time, t. The slope of the steady-state portion of the permeation curve created by plotting the cumulative amount of drug permeated in micrograms versus time in hours is the flux [37-40].

Bioadhesion

Rat buccal tissue was obtained from a freshly killed Rat . After removal the tissue was stored in 0.1N HCL. and used within 3

hours. The epithelium was separated from the underlying connective tissue with a surgical technique making sure that the basal membrane was still present and the membrane was allowed to equilibrate for one hour in receptor fluid to regain lost elasticity. Slice thickness range from 1 to 2 mm [37,41].

RESULTS AND DISCUSSION

PREFORMULATION

The Terbinafine HCL and other excipients were received from Cipla Pharmaceuticals, Goa, India. This sample was studied for its preformulation data. The drugs used were USP quality and excipients were 99% purity as confirmed by its FTIR and DSC. No further purification was performed.

Spectrophotometric Analysis: The maximum absorption value of Terbinafine Hcl was found to be 0.4962 at 222 nm wavelength (Figure 1). Therefore 222 were recorded as λ max of the pure drug Terbinafine Hcl.

Solubility of Terbinafine HCL: The observed practical solubility of *Terbinafine HCL indicated that, drug was practically insoluble in distilled water.*

Fourier Transform Infrared Spectroscopy: The FTIR spectrum (Figure 2) of the Terbinafine Hcl showed similar characteristics peaks to that of reported spectra of Terbinafine hydrochloride.

X-Ray Diffractometry (XRD): The X-Ray diffraction patterns of Terbinafine Hcl were illustrated (Figure 4) for the crystalline nature of drug powder. The characteristic peaks of Terbinafine Hcl appeared at a diffraction angle of 24.16^0 and maximum intensity of 1543 and several sharp diffraction peaks suggesting that the drug is present in crystalline form.

Differential Scanning Calorimetry (DSC): The DSC curves obtained for Terbinafine Hcl (4.5 mg) (Figure 6) showed a sharp melting endotherm at (212.59°C).

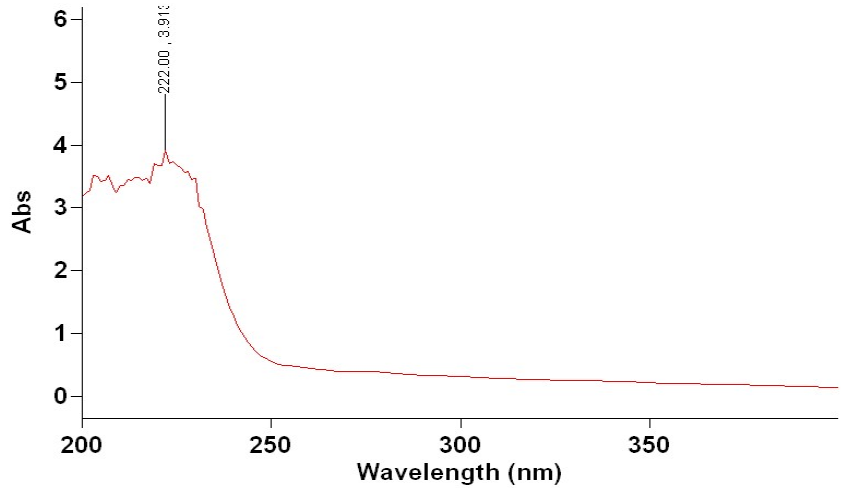

Figure 1: UV Spectrum pure Terbinafine HCl

DRUG EXCIPIENTS INTERACTION

Fourier Transform Infrared Spectroscopy:

In FTIR spectrum of pure Terbinafine HCL and the mucoadhesive polymeric gel of Terbinafine HCL containing higher proportion of the above excipients were almost in the same region of wave number ranging from 3443cm-1to 621.10 cm-1 and characteristic bands were observed (Figure 3) at 2116 (C≡C Stretching), 3266 (N-H Stretching), 1637 (C=O Stretching) and 1081 (CO Stretching).

From the structures of HPMCK4M and Terbinafine HCL it can be assume that possible interaction could occur between C=O group of the ester or amide function of Avicel and N-H (amide) or the C=O (amide) groups of Terbinafine HCL. Generally, hydrogen bonding leads to a shift of original peak maxima towards lower wavelength and/or there is increase in peak width.

The results proved that there were no significant interactions between the drug and all excipients. The FTIR spectra's of the mucoadhesive polymeric gel has not shown any significant shift in the peaks of Terbinafine HCL.

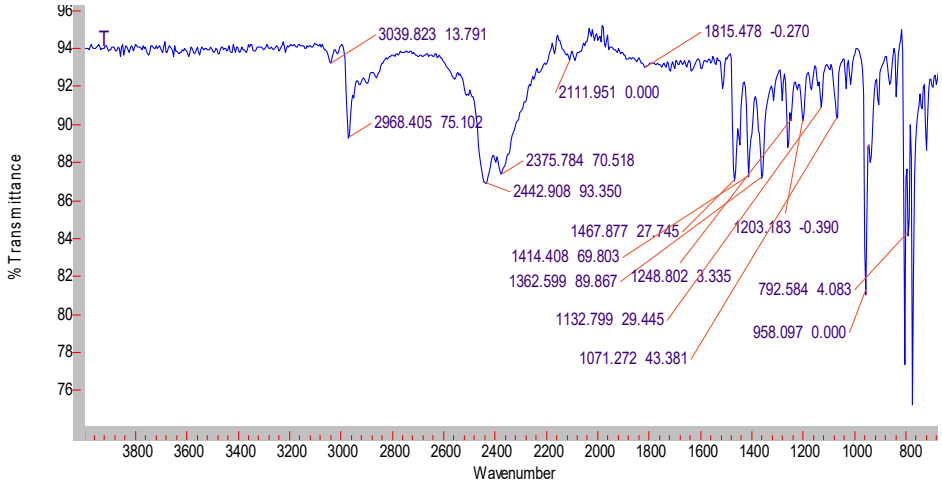

Figure 2: FTIR spectra of pure Terbinafine HCl

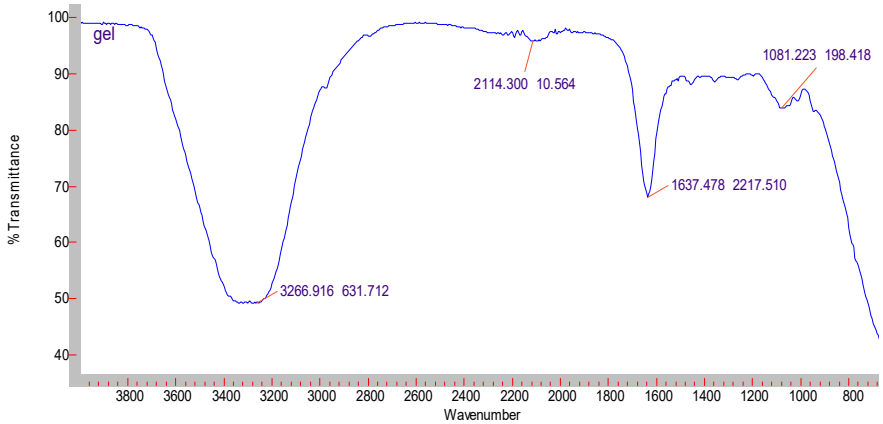

Figure 3: FTIR spectra of optimized mucoadhesive polymeric gel of Terbinafine HCL

X-Ray Diffractometry (XRD)

For the conformation of crystalline nature of Terbinafine HCl X-ray diffraction analysis was performed (Figure 5). Existence of high intensity suggesting that Terbinafine HCl is purely crystalline in nature. optimized mucoadhesive polymeric gel of Terbinafine HCL has shown less intense and wide diffraction peaks, which can be attributed to partial amorphization of Terbinafine HCL.

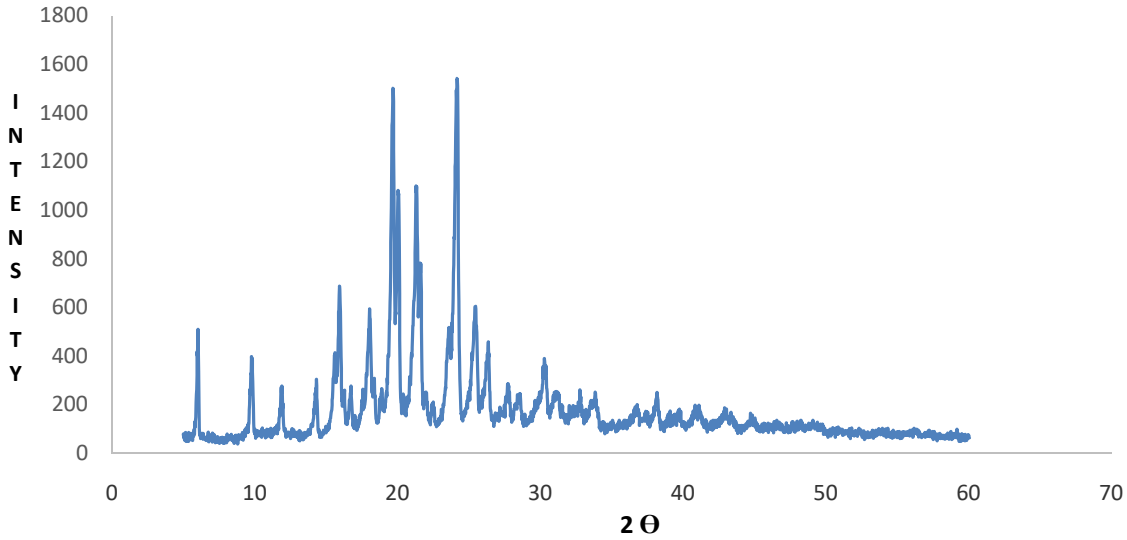

Figure 4: XRD Pattern of pure Terbinafine HCl

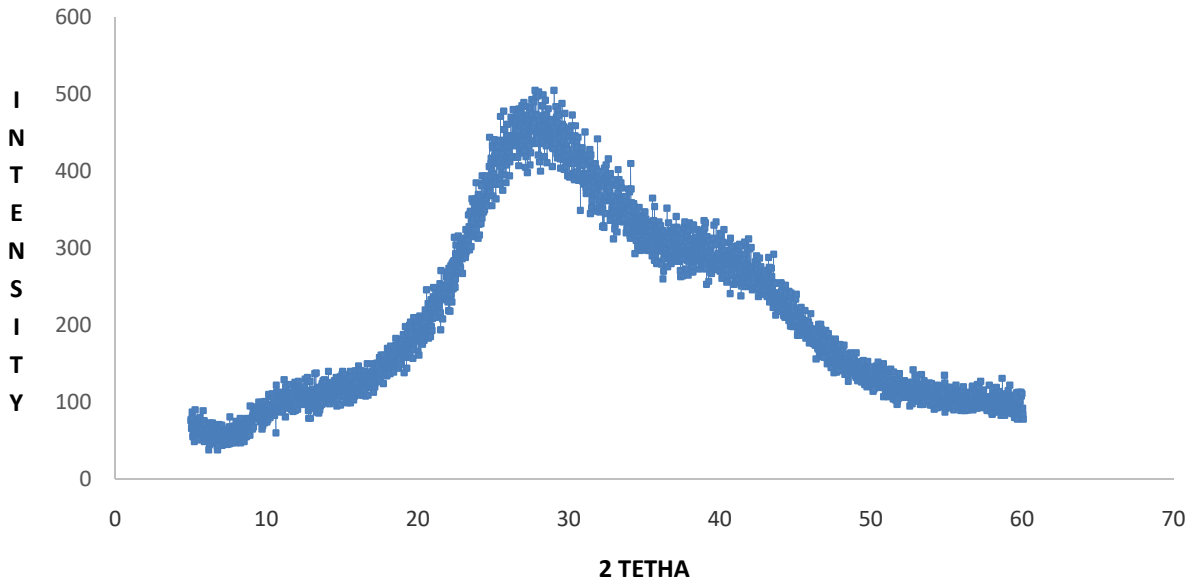

Figure 5: XRD Pattern of optimized mucoadhesive polymeric gel of Terbinafine HCL

Differential Scanning Calorimetry

DSC curves of Terbinafine Hcl and physical mixture of gel (4.5mg) (HPMCK4M, PEG 400 and DMSO) were obtained (calorimeter (Mettler Toledo, Giessen, Germany). Pure Terbinafine hydrochloride showed a sharp melting endotherm at 212.59°C attributed to the melting of the active substance. DSC thermograms of physical mixture of drug and excipients showed the melting peak of the drug at 90.3°C. Physical mixture of all above ingredients showed their identical peaks at defined temperature range (Figure 7). The shifting of melting endotherm was may be due to higher concentration of excipient in samples and lower concentration of the Terbinafine Hcl. Presence of all peaks indicates that all ingredients are compatible with drug means there is no incompatibility between selected ingredients.

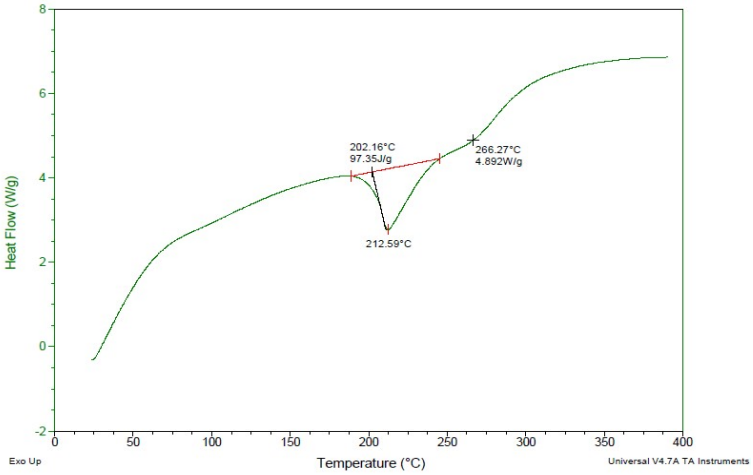

Figure 6: DSC thermogram of pure Terbinafine HCl

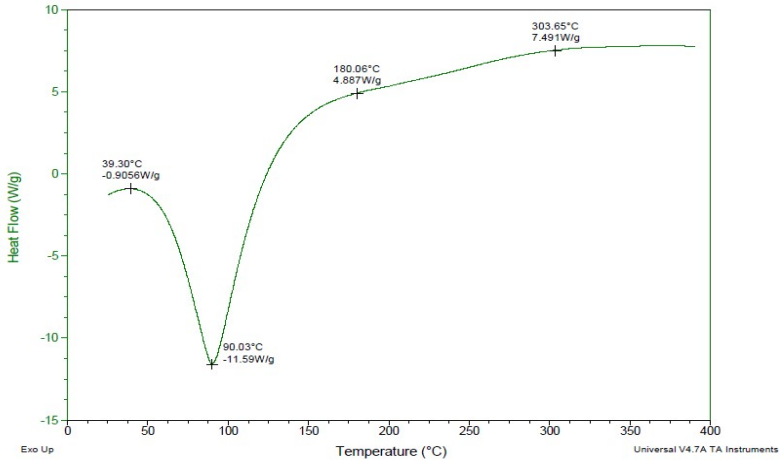

Figure 7: DSC thermogram of mucoadhesive polymeric gel of Terbinafine HCl

FORMULATION OF MUCOADHESIVE POLYMERIC GEL OF TERBINAFINE HCL

The buccal gel of Terbinafine hydrochloride was prepared using Solid Dispersion Method. The HPMCK4M mixture was prepared by dissolving the HPMCK4M into the distilled water. The solution was allowed to stir for 2-3 hours. The final solution was allowed to stand for another 1 h to remove all air bubbles

Design of Experiment:

Central composite experimental design: The traditional approach to developing a formulation is to change one variable at a time. By this method it is difficult to develop an optimized formulation, as the method reveals nothing about the interactions among the variables. The use of experimental design allows for testing a large number of factors simultaneously and precludes the use of a huge number of independent runs when the traditional step-by-step approach is used. Systematic optimization procedures are carried out by selecting an objective function, finding the most important or contributing factors and investigating the relationship between responses and factors by the so called response surface methodology.

Data analysis: A Central composite statistical design with 2 factors, 3 levels and 13 runs was selected to study the effects on dependant variables. All the batches of prepared gel within the experimental design yielded gel and these were evaluated for drug permeation. A Central composite experimental design has the advantages of requiring fewer experiments (13 batches) than would a 3^2 full factorial design (27 batches). Transformed values of all the batches were shown in table 5.9 Formulations 11 have the optimize drug permeation. The observed and predicted values with residuals error of responses for all the batches. The all selected dependent variables obtained at various levels of the 2 independent variables (X1, and X2) were subjected to multiple regression to yield a second order polynomial equation.

$$Y1 = 52.13 - 4.95X_1 - 5.50X_2 + 3.29X_1X_2 + 5.78X_1^2 + 4.89X_2^2$$

Effect of formulation variables: The results clearly indicate that the permeation value is strongly affected by the variables selected for the study. This is also affected by the wide range of values for coefficients of the terms of polynomial equation for Y1. The main effects of X1 and X2 represent the average result of changing one variable from its low level to its high level. The interaction terms (X_1X_2, X_{12}, and X_{22}) shows how the permeation changes when remained variables are simultaneously

changed. The negative coefficients for all 3 independent variables indicate an unfavorable effect on permeation, while the positive coefficients for the interactions between 2 variables indicate a favorable effect on the permeation. Y1, value measured for the different batches showed wide variation (values ranged from 48.23%- 91.77%) which clearly indicate that the Y1 values is strongly affected by the variables selected for the study. This is also affected by the variables selected for the study. This is also reflected by the wide range of values for coefficients of the terms in equations. The main effects of X1 and X2 represent the average result of changing one variable at a time from its low level to its high level. The negative sign for the coefficients in polynomial equation indicates a negative effect on responses, while the positive sign indicate a positive effect.

Table 1: Formulation of mucoadhesive polymeric gel of Terbinafine HCL using Central composite design approach

Batch No.	Independent Variables			
	HPMCK4M (mg) (X1)	PEG400 (ml)(X2)		
F1	0	0		
F2	1	-1		
F3	-1.4142	0		
F4	1	1		
F5	0	0		
F6	0	0		
F7	0	0		
F8	1.4142	0		
F9	0	0		
F10	0	-1.4142		
F11	-1	-1		
F12	-1	1		
F13	0	1.4142		
Independent variables		LOW	MEDIUM	HIGH
A. HPMCK4M% w/w		40	45	50
B. PEG400% w/w		10	15	20
Dependent variables (Factors)		Y1 Drug permeation%		

The standardized effect of the independent variables and their interaction on the dependent variable was investigated by preparing a pareto chart (Figure 8), which

depicts the main effect of the independent variables and interactions with their relative significance on the Y1. The length of each bar in the chart indicates the standardized effect of that factor in the responses. Factors remains inside the reference line indicate that these terms contribute the least in prediction of responses.

Probability plots: Probability explains the whether the residuals follow a normal distribution, in which case the points will follow a straight line. Except some scatter even with normal data. Look only for definite patterns like an "S-shaped" curve, which indicates that a transformation of the response may provide a better analysis (Figure 9). In case of normal probability distribution the blue spots indicates non significant effect on variable which red dots indicates significant effect distributed around straight line. (Figure 9) helps to detect a value, which is not easily predicated by the model. The split is straight line if all the actual values are same that of predicated values in figure 5.11 seen that all the data points almost goes through straight line indicating less is residual values.

Interaction matrix

Interaction matrix shows effect of change in concentration of dependant variables on response it easy to interpret two factor interaction from the plot; It will appear with two non-parallel lines, indicating that the effect of one factor depends on the level of other factor and for the drug permeability (Figure 10).

Response surface analysis: Two dimensional contour plots and three dimensional response surface plots (Figure 11, 12) are very useful to study the interaction effects of the factors on the responses. These types of plots are useful in study of the effects of two factors on the response at one time. All the relationships among the three variables are non linear, the effects of X1 and X2 with their interaction on permeability were 76.16%. The plots were found to be linear upto 75% permeability, but above this value, the plots were found to be non linear indicating a non linear relationship between X1 and X2. Similarly all values for remained dependent variables.

It was determined from the contour plot that a higher value of permeability could be obtained with and X1 level range from 55% to 75% (Figure 12). When the coefficients values of two key variables, X1 and X2 were compared, the value for variable X2 was found to be higher, indicating that it contributes the most to predicting the permeability.

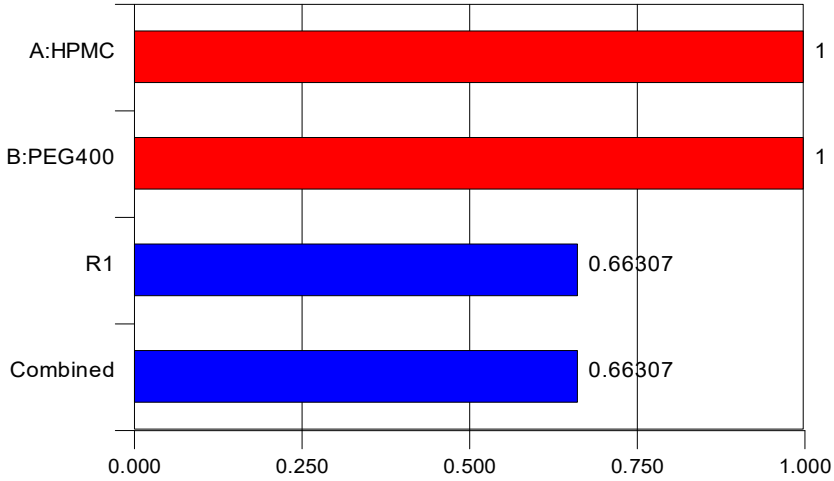

Figure 8: Pareto chart showing the standardized effect of independent variables and their interaction on permeation.

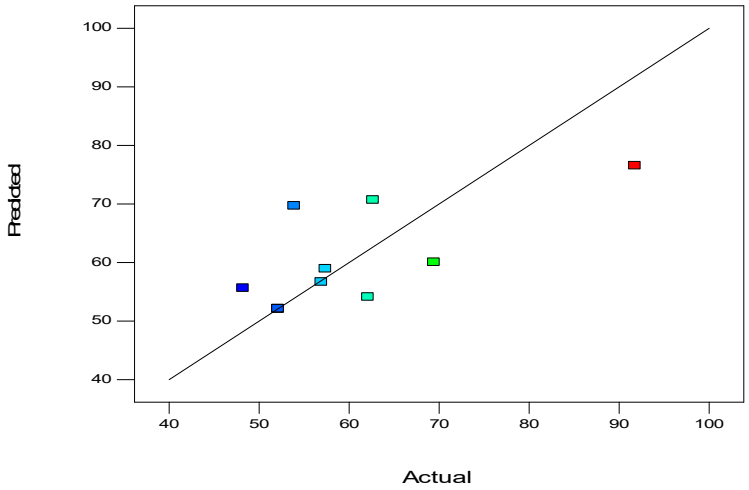

Figure 9: Plot for residual predicted vs actual for mucoadhesive polymeric gel of Terbinafine HCL

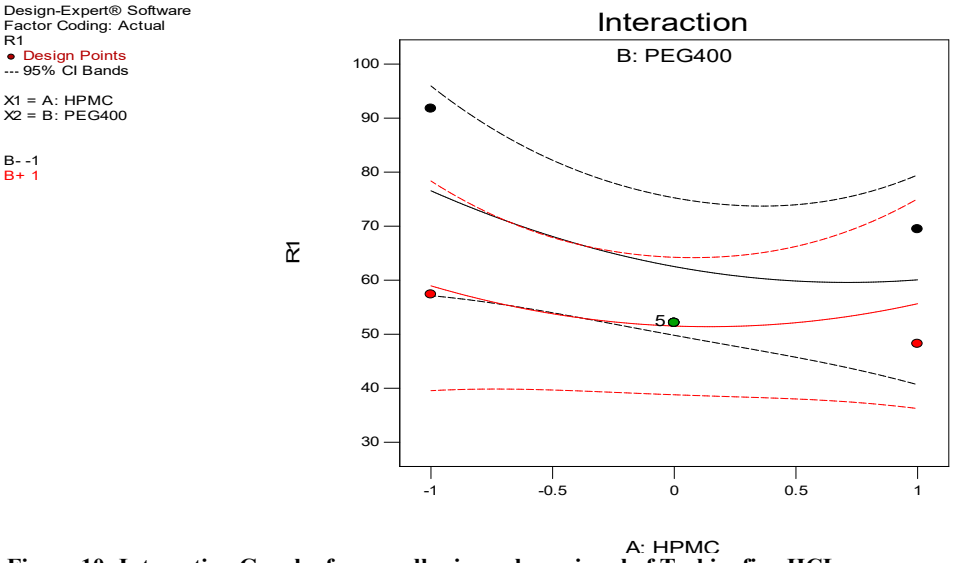

Figure 10: Interaction Graph of mucoadhesive polymeric gel of Terbinafine HCL

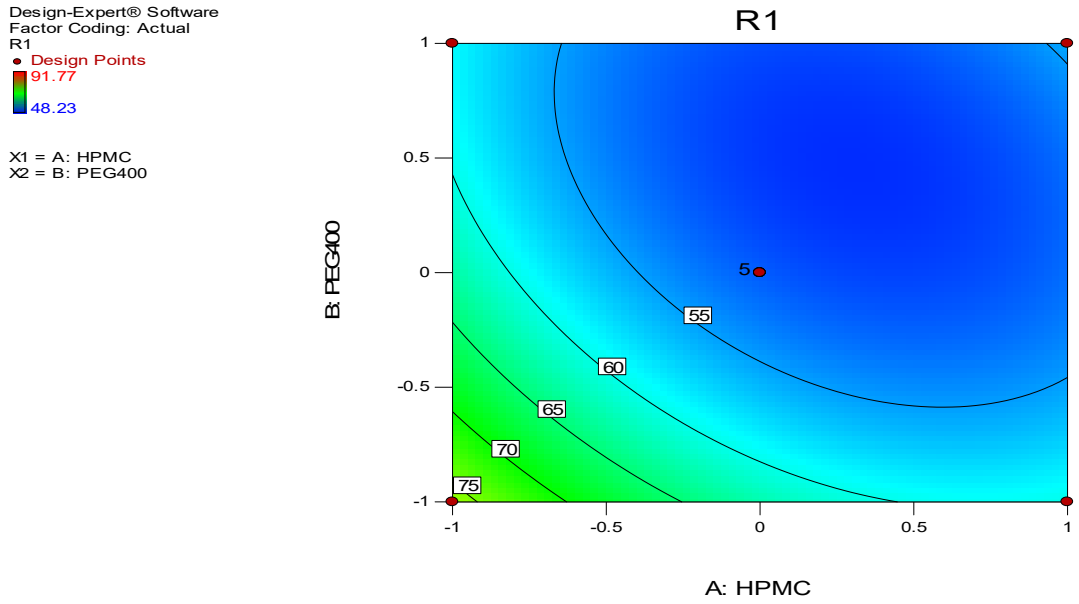

Figure 11: Contour Plot of mucoadhesive polymeric gel of Terbinafine HCL

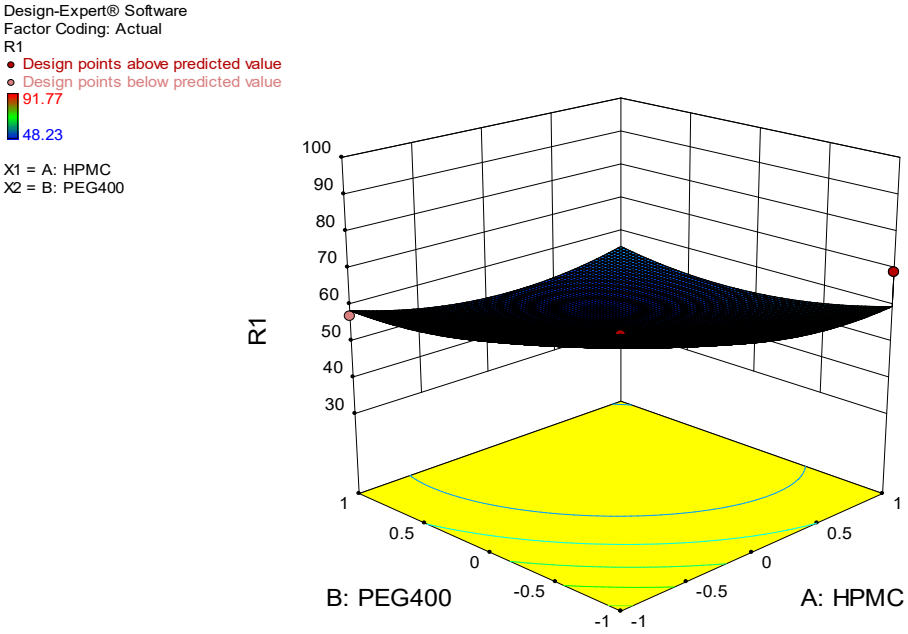

Figure 12: 3D Plot for mucoadhesive polymeric gel of Terbinafine HCL

ANOVA, Pure error and Lack of fit:

The results of ANOVA demonstrate that the model was non significant for all dependent variables (Figure 11, 12). In case the graph bar was in red color it shows model was significant. Both drug content and entrapment efficiency graph bar was without red color hence it is non significant. Regression analysis was carried out to determine the regression coefficient. All the independent variables were found to be non significant for all response variables. The linear, interaction and quadratic model was found to be significant for Y1. So above result indicate that both the factors play an important role in formulation of buccal gel containing Terbinafine hydrochloride. The data of pure error and lack of fit are which can provide a mean response and an estimate of pure

experimental uncertainty. The residual are the difference between observed and predicted values.

The ANOVA for the dependent variables demonstrate that the model was significant for all response variables. The effects are like the concentration of HPMCK4M and PEG400 were found to be significant along with its quadratic and interaction terms for all the dependent variables. Hence the above results lead us to believe that the all independent variables are play important role and optimal concentration in buccal gel gives rise to optimum entrapment efficiency and drug content. The data for pure error and lack of fit provides a mean response and estimate of pure experimental uncertainty. The residual value show represents the difference between the observed and predicted value given that computated F- value were respectively lower than critical F- values, which denotes non significance with regard to lack of fit.

The three replicated centre point in central composite experimental design made it possible to assess the pure error of the experiments and enabled the models lack of fit to be checked. In this study, the model was checked for lack of fit for the all the responses. For lack of fit P- values we obtained are not showed for response Y_1, and hence the current model provided a satisfactory fit to the data and had no lack of fit.

Rheological Study

The viscosity of gels was measured using R/S Plus- Cone and Plate Rheometer; Brookfield, USA. Viscosity parameters were measured at different rpm with 1-minute equilibration time at each rpm. Samples were applied to the spindle using a spatula to ensure that formulation shearing did not occur and the viscometer was set at room temperature (Table 2). The average viscosity of gels was in between 0.3569-1.8815 Pa. S.

Viscosity: Viscosity of formulation was measured by increasing and decreasing shear rate from 100-1-100 sec^{-1} linearly for 150 seconds, because it not possible to predict the viscosity at single value, so the average of the viscosity was taken by increasing (1-100 sec^{1}) and subsequently decreasing (100-1 sec^{-1}) shear rate. From preliminary study and experimental design it was found that only prepared batch no 11 shows the higher average viscosity. It was observed that the polymer concentration was important parameter for increases and decreasing viscosity of the gel formulation. Depending on polymer concentration ratio viscosity of all prepared batch gel was varied from 0.2818-1.8815.Pa.S. The viscosity optimized of gel formulation was found to be 1.8815Pa.S (Figure 13)

Table 2: Viscosity of mucoadhesive polymeric gel of Terbinafine HCL (F1-F13)

Batch No	Viscosity (P.as)	Torque (mNm)	Shear Stress (Pa)	Shear Rate (1/S)	Kinematic Viscosity (m^2/S)
F1	0.7068	3.1296	28.33	50.49	0.0007
F2	1.3703	5.7043	51.64	50.49	0.0014
F3	0.4268	2.1852	19.78	50.49	0.0004
F4	1.2848	5.1304	46.45	50.48	0.0013
F5	0.7068	3.1296	28.33	50.49	0.0007
F6	0.7068	3.1296	28.33	50.49	0.0007
F7	0.7068	3.1296	28.33	50.49	0.0007
F8	0.9410	4.1383	37.46	50.49	0.0009
F9	0.7068	3.1296	28.33	50.49	0.0007
F10	0.3569	1.8210	16.48	50.48	0.0004
F11	1.8815	7.7883	70.51	50.49	0.0019
F12	1.1544	5.0061	45.32	50.48	0.0012
F13	1.3113	5.3817	48.72	50.48	0.0013

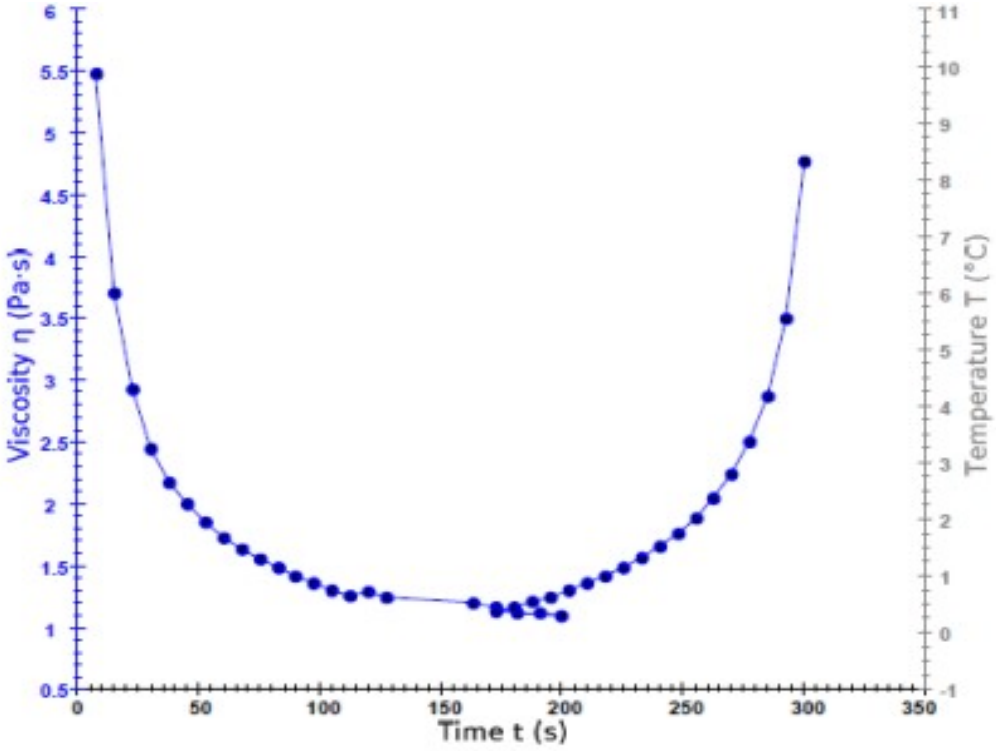

Figure 13: Viscosity of mucoadhesive polymeric gel of Terbinafine HCL of optimized batch

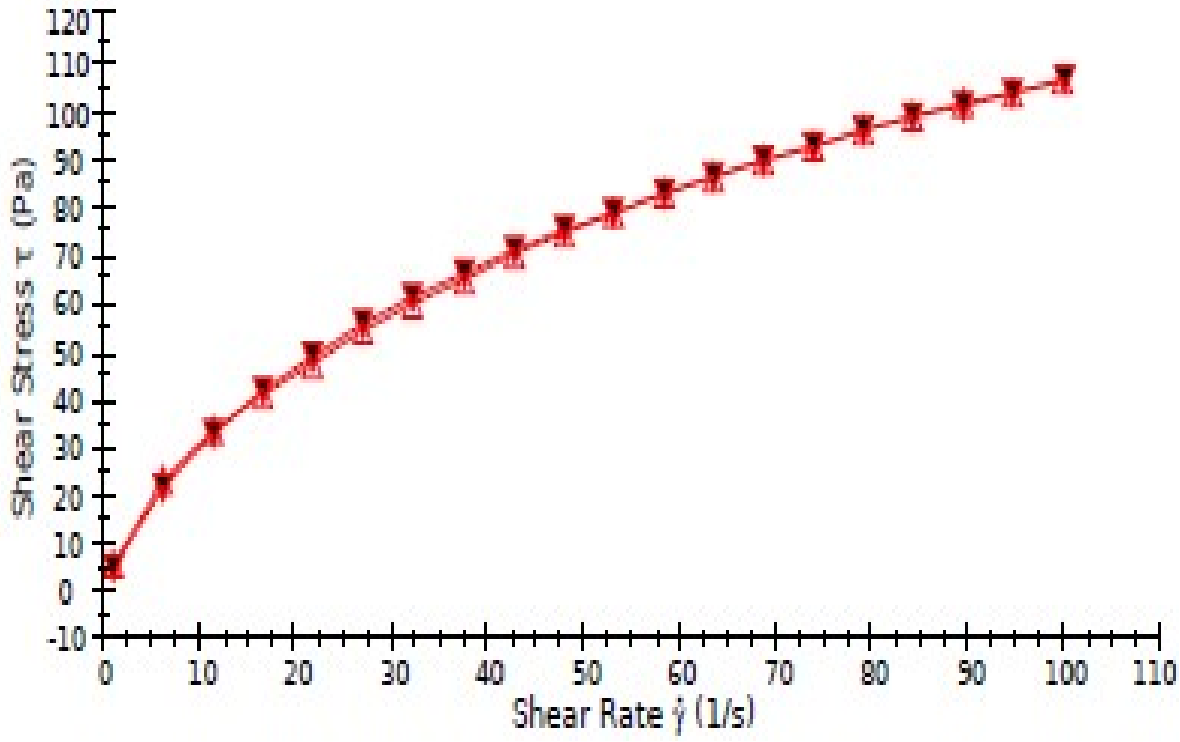

Figure 14: Thixotrophical analysis of mucoadhesive polymeric gel of Terbinafine HCL of optimized batch (Batch F11)

Thixotropy: Thixotropy is a property exhibited by non- Newtonian materials, they return to their original viscosity after lag time when applied shear stress is removed. This is the useful property for the topical formulations that ideally should have a high consistency in the container, yet pour or spread easily (Figure 14) shows that measured ascending and descending curves are combine showing that the formulation required less time for regaining its original viscosity. The gel undergoes gel-to-sol transformation. The area between two curve (hysteresis area) defines the extent of the time dependent flow behavior. The smaller hysteresis area shows less time is required for the regaining the original viscosity. After this lag time, droplets of the gel come into contact of each other by random Brownian movement and regain its original three-dimensional network through numerous points of contact.

In vitro dissolution/release

The in vitro drug release was performed using vertical Franz diffusion cell. The drug release rate was slow; within a period of 30 min 48.23% - 91.77% of cumulative drug is. It was concluded that Terbinafine Hcl loaded gel shows a sustained release effect (Figure 15).

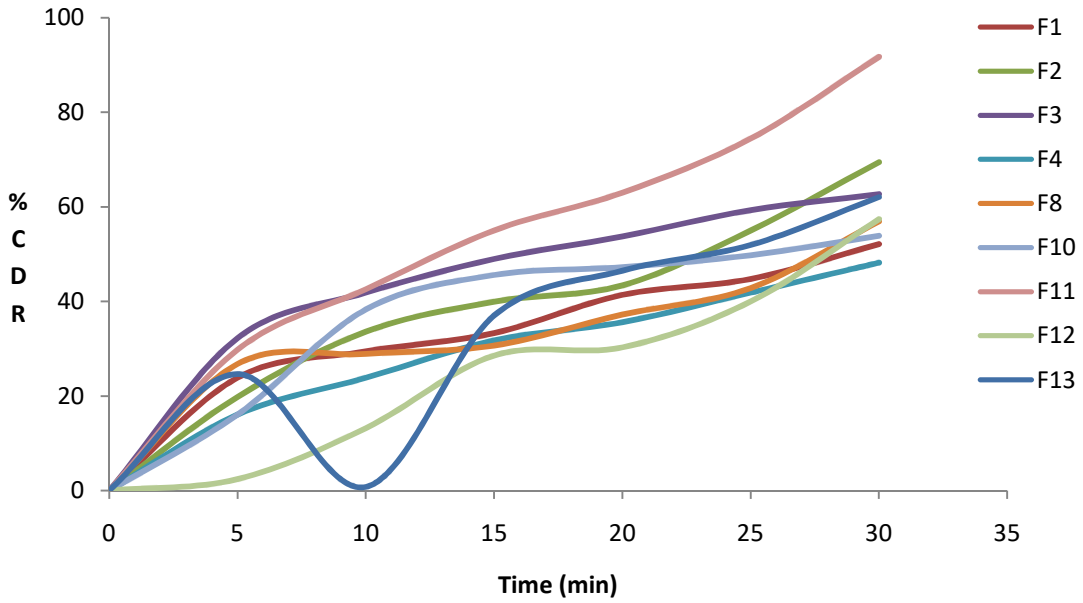

Figure 15: Drug Permeation of all prepared mucoadhesive polymeric gel of Terbinafine HCL

Permeation: The permeability of mucoadhesive polymeric gel of Terbinafine HCL were determined using franz diffusion cell. 0.1N HCL was used for permeability media which was having the acidic pH, similar to the buccal cavity. 5ml prepared gel sample were applied on the donar compartment which contains the 41.66 mg of drug among these optimized batch shows the 38.30 mg of drug release in 30 mints . The observed value of permeability coefficient and Steady state flux was 16.89 ±4.4 cm/h and 178.82 ±89.50 µg/cm^{2}h respectively.

Bioadhesion

The bioadhesive strength was influenced by the ratios of bioadhesive polymers. In all the formulations, as the HPMCK4M concentration increased, the mucoadhesive strength of polymeric gel of T-HCL increased. The higher bioadhesive strength may be due to the formation of secondary bonds with mucin and entanglement and interpretation of polymeric chain with mucin. The unexpectedly high bioadhesive values for polymeric gel of T-HCL were probably attributable to some kind of attraction between the smooth surface of gel and mucosa.

CONCLUSION

In the present study, the HPMC gel formulations of T-HCl were prepared. The properties of the formulations were investigated at different temperatures during 3 months, and no significant change was observed in tested properties. The mechanical properties of the gels were also determined using TPA, and the results were evaluated in relevance with viscosity measurements. Gel formulations prepared with HPMC were found more easily

applicable to the buccal mucosa when compared to marketed product.

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REFERENCES:

[1] Gurdale M. S., Lade M. S., Payghan S. A., D'Souza J. I.; Fast dissolving HPMC E5 based oral film for rapid absorption of Metoprolol Tartrate. *European Journal of Pharmaceutical and Medical Research* 2014, 1(1), 75-91, 2014.

[2] Patil A. A., Payghan S. A., Disouza J. I.; Bionanocomposites: Approach in Solubility and Bioavailability Enhancement of Poorly Water Soluble Drugs. *International Journal of Universal Pharmacy and Bio Sciences* 3(4), 258-268, 2014.

[3] Tsinontides, S.C., Rajniak, P., Hunke, W.A., and Placek, J., 2004. Freeze drying-principles and practice for successful scale-up to manufacturing. Int. J. Pharmaceut., 280 (1): 1-16.

[4] Shejwale Ankur, Kate Vaishali, Payghan Santosh. Lornoxicam Immediate Release Tablet Using Spray-Dried Cellulose Nanofibers (NFC) as Novel Tablet Excipient. Inventi Rapid: Novel Excipients, 2016(4):1-13, 2016.

[5] Madhav, N. V., Shakya, A. K., Shakya, P., Singh, K., 2009. Orotransmucosal drug delivery system review. Journal of controlled release. 140, 2–11.

[6] Payghan S. A., Kate V.; Interactive mixture of piroxicam and polymers for development of mucoadehsive fast disintegrating sublingual tablet: In vitro in vivo evaluation. Journal of Pharma SciTech 5(1), 32-44, 2015.

[7] Lade M. S., Payghan S. A., Tamboli Z. J., Disouza J.I.; Polymer Based Wafer Technology: A Review. *International Journal of Pharmaceutical & Biological Archives* 4(6), 1060 – 1074, 2013.

[8] Patil S. C., Payghan S. A., Disouza J. I.; Formulation and Evaluation of Oral Disintegrating Tablet of Lornoxicam. *International Journal of Pharmaceutical & Bio. Archieves* 2(5), 1518-1523, 2011.

[9] Shojaei, A. H., 1998. Buccal mucosa as a route for systemic drug delivery review. Journal of pharmaceutical sciences. 1(1), 15–30.

[10] Yang, S., Jeong, S. H., Kimura, S., Park, K., 2004. Orally fast disintegrating tablets developments technologies taste masking and clinical studies. Critical reviews in therapeutic drug carrier system. 21(6), 433–475.

[11] Shojaei, A. H., 1998. Buccal mucosa as a route for systemic drug delivery review. Journal of pharmaceutical sciences. 1(1), 15–30.

[12] Ryder NS. Terbinafine: mode of action and properties of the squalene epoxidase inhibition. Br J Dermatol 1992; 126 (suppl 39): 2-7.

[13] Miller, N. S., Chittchang M., Johnston T. P., 2005. The use of mucoadhesive polymers in buccal drug delivery. Advanced drug delivery reviews. 57(11), 1666–1691.

[14] JA, Faulds D. Terbinafine. A review of its Pharmacodynamics and pharmacokinetic properties, and therapeutic potential in superficial mycoses. Drugs 1992;43(2):259-84.

[15] Chokshi, R., and Hossein, Z., 2004. Hot Melt Extrusion Technique: A Review. Int. J. Pharmaceut. Res., 3: 3-16.

[16] Payghan, S. A., Shrivastava, D. N.; Potential of solubility in drug discovery and development. Pharmaceutical Reviews/ www.pharmainfo.net.

[17] Payghan, S. A., Khade, D., Sayyad, F. J.; Formulation and Evaluation of New Effervescent Tablet of Famotidine for Peptic Ulcer Therapy. Inventi Rapid: Pharm Tech 2015 (2), 1-19, 2015.

[18] Kate, V. K., Payghan, S. A., Physicochemical Evaluation of mannitol Based mucoadhesive fast disintegrating tablet for rapid absorption of piroxicam. Inventi Rapid: Pharm Tech 2013(3), 1-15, 2013.

[19] Breitenbach, J., 2002. Melt extrusion: from process to drug delivery technology. Europ. J. Pharmaceut. Biopharmaceut. 54: 107-117.

[20] Nasr, A. M., 2002. Characterization of polymer gels for optical applications. Polymer testing. 21, 303–306.

[21] Khairnar, G. A., Sayyad, F. J., 2010. Development of buccal drug delivery system based on mucoadhesive polymers. International journal of pharmtech research. 2(1), 719–735.

[22] Nalavade P.S., Landge K.S., Kate V.K., Payghan S.A. Effect of formulation variables on physicochemical properties of cholecalciferol nonaqueous nanoemulsion, Asian Journal of Pharmaceutics, (Suppl)10 (3), 42-53, Jul-Sep 2016.

[23] Kate V. K., Payghan S. A., Development of Directly Compressible Mucoadehsive Fast Disintegrating Sublingual Tablet System of Piroxicam Using 3 factor, 3 Level Box Behnken Design. *Asian Journal of Biomedical and Pharmaceutical Sciences* 03(27), 1-6, 2013.

[24] Payghan, S. A., Mane, Y. V., Kate, V. K., Tamboli, Z. J.; Anhydrous Emulsion: Vehicles for Topical Delivery of

Ketoconazole. Inventi Impact: NDDS 2015 (1), 43-53, 2015.

[25] Aute, S. M., Kate, V. K., Payghan, S. A.; Formulation of Floating Microspheres of Nizatidine: Investigation of Effect of Solvent Evaporation and Spray Drying Technique. Inventi Rapid: NDDS 2015,(3), 85-100, 2015.

[26] Patil Prashant, Kate V. K., Payghan S.A., Potential Investigation of Peceol for formulation of Ezetimibe self nano emulsifying Drug Delivery Systems. Asian Journal of Biomedical and Pharmaceutical Sciences, 06(54); 21-32, 2016.

[27] Perissutti, B., Newton, J.M., Podezeck, F., and Rubessa, F., 2002. Preparation of extruded Carbamazepine and PEG 4000 as a potential rapid release dosage form. Europ. J. Pharmaceut. Biopharmaceut, 53: 125-132.

[28] Patil Prashant, Kate Vaishali, Payghan Santosh. Development and Stability Assessment of Solid Self-micro Emulsifying System for Oral Bioavailability of Ezetimibe using Spray-drying Technique. *Inventi Impact: Pharmaceutical Process Development*, 2016(3):135-142, 2016.

[29] Shirke, S., Kate, V., Tamboli, Z., Payghan, S. A.; Nonaqueous Emulsion Based AntiWrinkle Preparation Restrain Vitamin C. Literati J. Pharmaceutical Drug Delivery Tech. 01 (02), 37-50, 2015.

[30] Jadhav, C. M., Kate, V., Payghan, S. A.; Investigation of effect of non-ionic surfactant on preparation of griseofulvin non-aqueous nanoemulsion. J. Nanostructure in Chem. (Springerlink.com) 5(1), 107-113, 2015.

[31] Jadhav C. M., Kate V. K., Payghan S. A., Disouza J. I.; Investigating Application of Non Aqueous Microemulsion for Drug Delivery. *Asian Journal of Biomedical and Pharmaceutical Sciences* 04 (29), 1-9, 2014.

[32] Patil Prashant, Kate V. K., Payghan S.A. Development and stability assessment of Solid self-micro emulsifying system for oral bioavailability of Ezetimibe using spray-drying technique. *Inventi Rapid: Pharmaceutical Process Development*, 2016(3):1-8, 2016.

[33] Payghan S. A., Raut M., Kate V. K.; Development of Sustained Release Desvenlafaxine Succinate Hydrophobic Matrix System using Melt Granulation Technique. *Literati Journal of Pharmaceutical Drug Delivery Technologies* 01 (01), 14-26, 2015.

[34] Jadhav C.M., Kate V. K., Payghan S. A.; Stability Study of Griseofulvin in Non Aqueous Microemulsion System. *Asian*

Journal of Biomedical and Pharmaceutical Sciences 4 (35), 79-83, 2014.

[35] Jadhav, C. M., Kate, V., Payghan, S. A.; Formulation and Evaluation of Antifungal Non-Aqueous Microemulsion for Topical Drug Delivery of Griseofulvin. Inventi Impact: Pharm Tech 2015(1), 38-50, 2015.

[36] Kate, V. K., Payghan, S. A., Shinde, A. J.; Effect of Aging Conditions on the Dissolution Stability of Piroxicam Mucoadhesive Fast Disintegrating Tablet. Inventi Rapid: NDDS 2013(2), 1-6, 2013.

[37] Kate, V. K., Payghan, S. A.; Effect of Bioadhesion and Permeability on Dissolution Behavior of Piroxicam Mucoadhesive Fast Disintegrating Tablet. Inventi Rapid: Pharm Tech 2013(2), 1-7, 2013

[38] Payghan, S. A., Kate, V. K., Purohi,t S., Bhandari, A.; Effect of Aging Conditions on the Dissolution and Diffusion Stability of Non Aqueous Emulsion. Inventi Impact: Pharm Tech 2012(3), 191-196, 2012.

[39] Payghan, S. A., Kate, V. K., Purohit, S., Bhandari, A.; Goodness of Fit Model Dependent Approach for Release Kinetics and In vitro Release of Piroxicam from PEGS Based Non Aqueous Emulsion. Inventi Impact: Pharm Tech 2012(3), 183-190, 2012.

[40] Khayyam S., Patwekar S., Payghan S. A., Disouza J. I.; Dissolution and Stability Enhancement of Poorly Water Soluble Drug – Lovastatin by Preparing SIolid Dispersions. *Asian Journal of Biomedical and Pharmaceutical Sciences* 1(4), 24-31, 2011.

[41] Payghan S. A., Toppo E., Bhargava S.; Evaluation of antibacterial activity of aqueous extracts of swarita chirata Buch. Ham. Root. *International Journal of Green Pharmacy* 1(02), 51-53, 2007.