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DEVELOPMENT AND OPTIMIZATION OF FAST DISSOLVING STRIP OF TIZANIDINE HYDROCHLORIDE USING 3^2 FULL FACTORIAL DESIGN

HITESH D. KAREN, HARDIK M. SHAH, PRIYANK M. SHAH, CHHAGANBHAI N. PATEL

Department of pharmaceutics and pharmaceutical technology, shri sarvajanik pharmacy college, shri sarvajanik vidhya sankul, near arvind baug, Mehsana, Gujarat, India.

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Abstract: Tizanidine hydrochloride is a α_2-adrenergic agonist, centrally acting skeletal muscle relaxant, indicated for the symptomatic relief of spasticity associated with multiple sclerosis or spinal cord injury or disease or painful muscle spasm. This work aimed to develop and optimize fast dissolving strip of Tizanidine hydrochloride by two factor, three level Full Factorial design as the two independent variables such as polymer (X_1) and plasticizer (X_2) were selected on the basis of the preliminary studies carried out before the experimental design is being implemented. Various grades of hydroxypropylmethylcellulose (HPMC) and plasticizer such as Polyethylene Glycol 200, Polyethylene Glycol 400, Polyethylene Glycol 600, Propylene Glycol, Glycerin, and Triethylcitrate used for preparation of strip by solvent casting method. FTIR and DSC studies showed no interaction between drug and polymer or with other additives. A second order polynomial equation used to construct contour plots for the prediction of responses of the dependent variables such as Disintegration time (Y1), *in vitro* drug release at 2 min (Y2), and Tensile strength (Y3) were studied. The 3D Response surface plots were drawn, statistical validity of the polynomials was established to find the compositions of optimized formulation which was evaluated using the Franz type diffusion cell. The designs establish the role of the derived polynomial equation and contour plots in predicting the values of dependent variables for the preparation and optimization.

Keywords: Tizanidine Hydrochloride, Fast Dissolving Strip, 3^2 Full Factorial Design, Solvent Casting Method, HPMC, Glycerin

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Corresponding Author: DR. HITESH D. KAREN

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INTRODUCTION

The ultimate goal of any drug delivery system is the successful delivery of the drug, in which almost 90% of the drugs are administered to the body for the treatment of various disorders and diseases as it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. [1–3] In this the drug is dissolved or swallowed and then enters into the systemic circulation to produce the desired effect. [4,5] Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. [6]

Anatomy of Oral Cavity:

Oral cavity offers a unique environment for delivering the drugs. The oral mucosa allows direct access of drug to the systemic circulation and avoids first pass metabolism. The epithelium of the oral cavity is quite similar to that of the skin, with slight differences with regard to keratinization, protective and lubricant mucous which is spread across its surface.[7] The permeability of oral mucosa is 4–1000 times greater than that of the skin. The oral cavity is divided into two regions: outer being the oral vestibule bounded by the lips and cheeks; the hard and soft palates, the floor of the mouth and tonsils.[8]

Tizanidine hydrochloride is a α_2-adrenergic agonist, centrally acting skeletal muscle relaxant, indicated for the symptomatic relief of spasticity associated with multiple sclerosis or spinal cord injury or disease or painful muscle spasm.

Tizanidine hydrochloride is available as conventional tablet, in which drug undergoes hepatic first pass metabolism which leads to lower bioavailability (30-40%) and physical problems with swallowing also can occur.[9] The other dosage forms have many disadvantages like in nasal administration, chances of high variability in the amount of drug absorbed and also risk of harmful long term effect on the nasal epithelium[10]; in parenteral administration, chances of infection at site and needle stick risk[10]; Sublingual and buccal dosage forms are inconvenient for patient. [11]

Thus a novel approach is required to design and develop an ideal dosage form for tizanidine HCL. Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. Now a day, many pharmaceutical industries are reformulating the existing drugs into new dosage forms by effective life cycle management. One such relatively new dosage form is the fast dissolving film. Basically the fast dissolving film is formulated using hydrophilic polymers and other excipients that rapidly dissolve on the tongue or buccal cavity. Fast dissolving films offer fast, accurate dosing in a safe, efficacious approach that is both convenient and portable, without the need for water or measuring devices.[12,13] These dosage

devices offer many advantages like accurate dosing, no risk of choking, rapid release profile, enhanced stability, taste masking and improved patient compliance and convenience.

In the present research work an attempt was made to formulate and evaluate fast dissolving oral films of tizanidine hydrochloride using different polymers.

MATERIAL AND METHOD:

Tizanidine hydrochloride was obtained from Themis Healthcare Pvt. Ltd., Vapi, Gujarat, India. Various grade of Hydroxypropylmethylcellulose (Yarrow Chem. Products, Mumbai, India), Polyethylene glycol 200, Polyethylene glycol 400, Polyethylene glycol 600 (S.D.Fine Chemical Limited, Mumbai, India), Propylrne Glycol, Glycerin (Chemdyes Corporation Ahmedabad, India), Triethylcitrate (Finar Chemicals Ltd, Ahmedabad, India) were used as a film base material. Aspartame, Sodium Saccharine and Mannitol (Yarrow Chem. Products, Mumbai, India) as a sweetener and Menthol (Yarrow Chem. Products, Mumbai, India) as a flavouring agent.

Preparation of Strip:

Accurately weighed quantity of drug was dissolved in 4 ml water. Specified amount of polymer and other excipients were dissolved in 6 ml water. The polymeric solution was added to the prepared drug solution. The mixture of solution was casted in petri plate and kept for drying at room temperature. Dried strip was removed safely from petriplate, cut in 2×2 cm^2 size and stored in aluminium foil.

Evaluation of Strip:

1) Transparency and Surface texture

Transparency and Surface texture were evaluated by visual appearance of oral strip and categorized in various levels such as best, good, medium, bad for transparency and smooth and rough for surface texture. [13,14]

2) Film thickness

A thickness of the film should be calculated by using micrometer screw gauge at 5 different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the dose in the strip. [13]

3) Tensile strength

The tensile strength of the patch was evaluated by using the tensilometer. It consists of two load cell grip, the lower one was fixed and upper one was movable. Film strips with dimensions

of 2×2 cm2 were fixed between these cell grips and force was gradually applied till the film break. The tensile strength was taken directly from the dial reading in kg. [13,15]

It is calculated by following equation:

Tensile strength =F /A

Where,

F= Break force,

A=Area of film in mm2

4) Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value. [13]

5) Disintegration time

Six strips of 2×2 cm2 were kept in the disintegration tester (USP ED-2L) at room temperature in tubes in the environment of water until it disintegrates and time was measured. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral film. Disintegration time will vary depending on the formulation but typically the disintegration range from 4 to 30 seconds. No official guidance is available for oral fast disintegrating films. [15]

6) *In vitro* drug release test

Dissolution profile of tizanidine hydrochloride was carried out in a beaker containing 30 ml of the simulated salivary pH 6.8 as a dissolution medium, maintained at 37±0.5°C. The medium was stirred at 100 rpm with magnetic stirrer. Aliquatos of the medium were withdrawn at regular interval of 1 min and the same amount was replaced with fresh medium. Samples were analysed for cumulative percentage drug release by UV spectrophotometrically at 320nm. Three trials were carried out for all the samples and average was taken. [16]

7) Drug content

A specified area of strip (2cm×2cm) was dissolved in 100 ml water in volumetric flask and shaken continuously for 10 min., filter the solution by 0.45μm membrane filter paper. After filtration, 1 ml of solution was withdrawn from the solution and diluted up to 10 ml with water.

The absorbance of the solution was measured at 320 nm and concentration was calculated and determined the drug content. [17-19]

Drug Excipient Compatibility Study:

1) FTIR Study

Drug-excipients interactions play a vital role in the release of drug from formulation. Fourier transform infrared spectroscopy has been used to study the physical and chemical interaction between drug and excipient. Fourier transform infrared (FTIR) spectra of Tizanidine, HPMC E15 and mixture of drug and excipient were recorded using KBr mixing method on FTIR instrument.

2) Differential Scanning Calorimetry Study

The DSC study of Tizanidine oral strip was performed using DSC instrument (DSC-60, shimadzu). The DSC study carried out on pure drug (Tizanidine hydrochloride), HPMC E15, mixture of drug and excipient. The thermogram of Tizanidine oral strip was obtained by Differential scanning calorimeter (DSC). Two mg of amount was taken in aluminium cell and scanned at 30°C to 300°C, at 20-30 ml/min nitrogen flow rate against blank DSC aluminium cell as a reference.[15]

Optimization of Final Formulation using 3^2 Full Fctorial Design:

From the results of preliminary studies, optimization was carried out using design of expert (DOE) approach. In 3^2 full factorial design HPMC E15 (X_1) and Glycerin (X_2) were used as independent variables while disintegration time, *in- vitro* drug release at 2 min, tensile strength were selected as response variables. The detailed layout of factorial batches is shown in table 1. The equations relating independent variables and responses were obtained by subjecting the results to statistical evaluation. Design – Expert 9.0.0.7 was used to perform multiple linear regressions to determine the control factors that significantly affect the responses.

Polynomial equation for 3^2full factorial design: $Y = ß_0 + ß_1X_1 + ß_2X_2 + ß_{11}X_{11} + ß_{22}X_{22} + ß_{12}X_1X_2$ was used. In this equation Y is the dependent variable, $ß_0$ is the arithmetic mean response of the nine runs, $ß_1$ to $ß_{12}$ are the coefficients for factors.

The significant factors in the equations were selected using a stepwise forward and backward elimination for the calculation of regression analysis. The terms of full model having non-significant p value ($p > 0.05$) have negligible contribution and they were neglected.

RESULTS AND DISCUSSION:

In the preliminary trial it was found that HPMC E15 and Glycerin containing strips gave best transparency, smooth surface texture, moderate tensile strength, low brittleness, and least

disintegration time; while Aspartame (5%) containing strip gave best transparency, smooth surface texture and sweet in taste.

Drug Excipient Compatibility Study:

1) FTIR Study for Compatibility

The FTIR spectra of Tizanidine hydrochloride showed a characteristic peaks of tizanidine hydrochloride appeared at 3245 (N-H stretching), 711 (C-Cl stretching) shown in figure 1.

It was observed that no changes in main peaks in FTIR spectra of a mixture of drug and excipients shown in figure 2. The FTIR study demonstrate that no physical or chemical interactions of Tizanidine hydrochloride with other excipients.

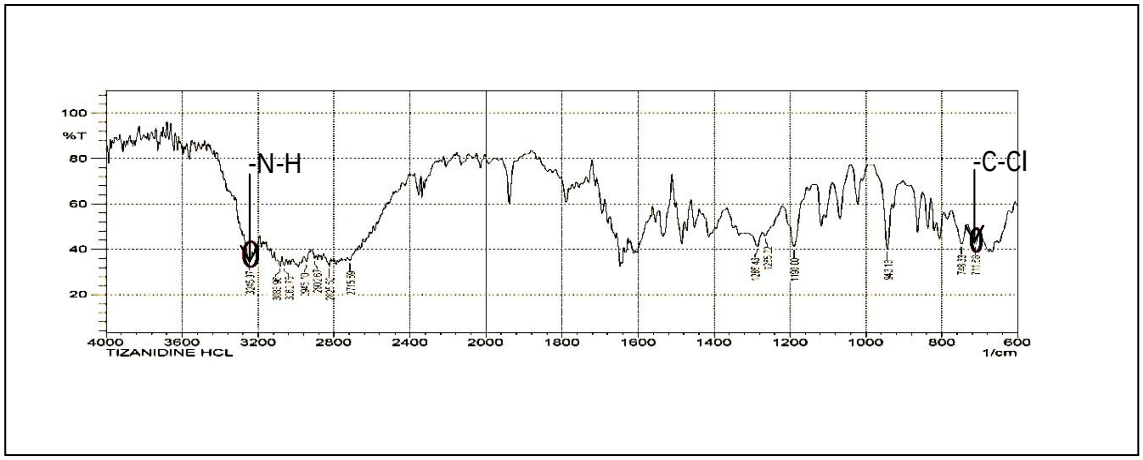

Figure 1: FT-IR Spectra of Tizanidine Hydrochloride

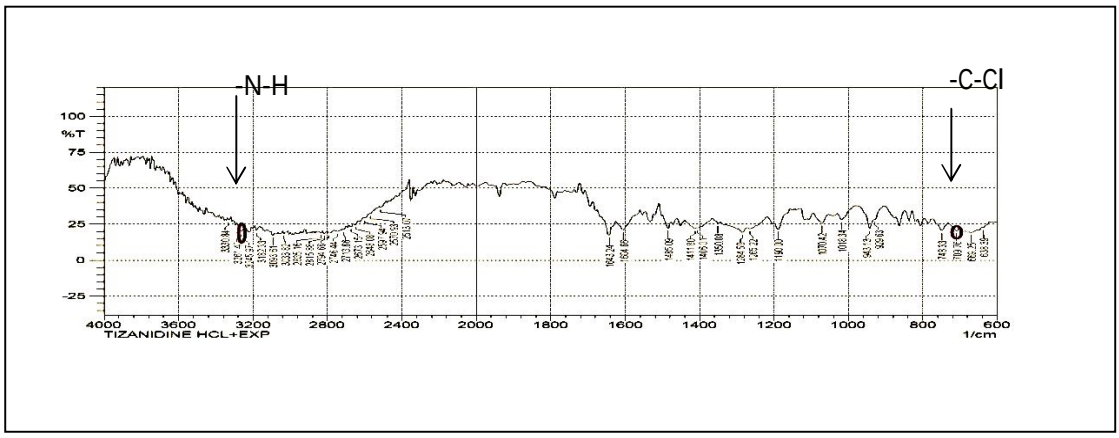

Figure 2: FT-IR Spectra of Tizanidine Hydrochloride with Excipients

2) Differential Scanning Calorimetry Study

The DSC thermogram of Tizanidine hydrochloride, HPMC E15 and mixture of Tizanidine hydrochloride and other excipients are shown in figure 3-5. Thermogram of Tizanidine hydrochloride, HPMC E15 and drug-composite mixture were showed melting endotherm at 297.96ºC, 75.67ºC and 293.29ºC respectively, which indicate no significant changes in melting endotherm of pure drug.

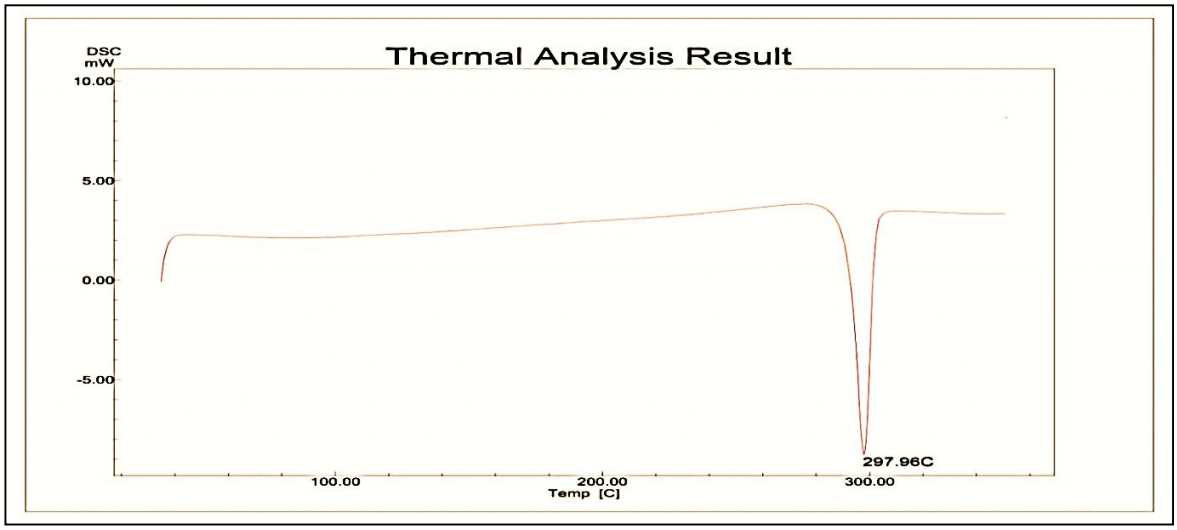

Figure 3: DSC Thermogram of Tizanidine Hydrochloride

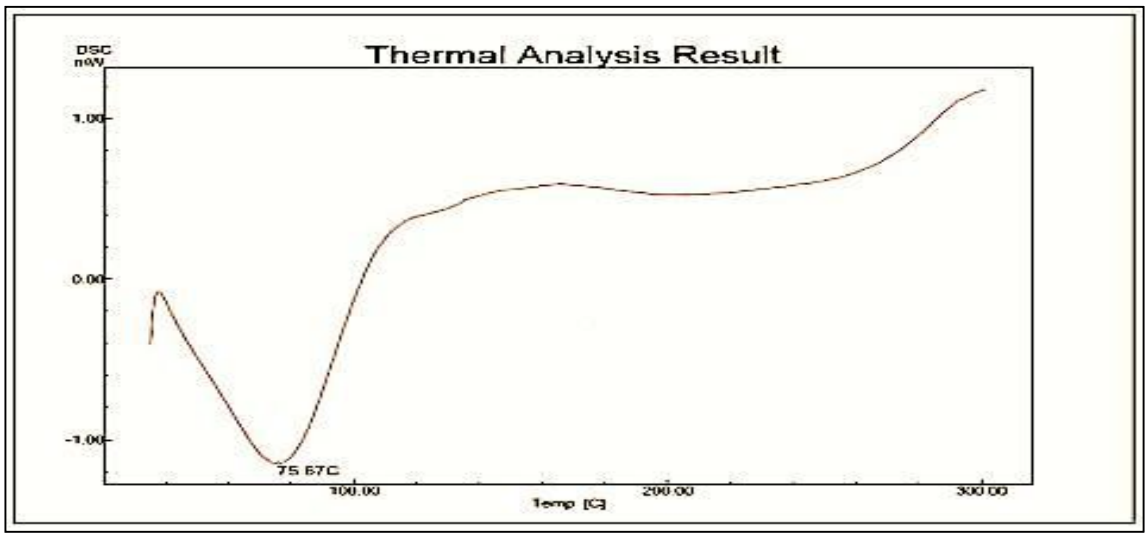

Figure 4: DSC Thermogram of HPMC E15

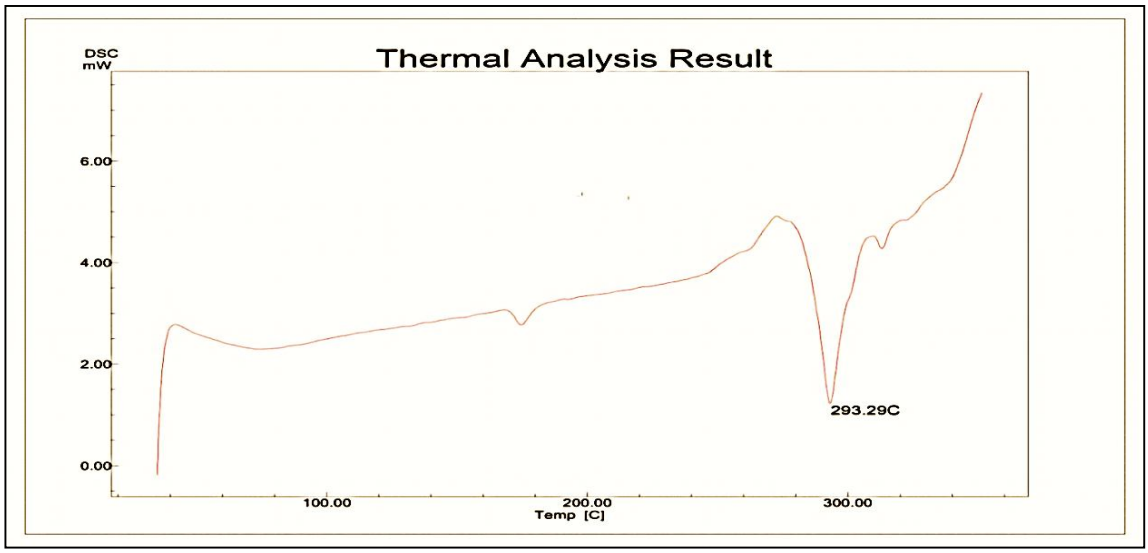

Figure 5: DSC Thermogram of Tizanidine Hydrochloride with Excipients

Optimization of Final Formulation using 3^2 Full Fctorial Design:

Table 1 Composition of 3^2 Full Factorial Design

Ingredients	Batches (Quantity in mg/50.24cm^2)								
	DE1	DE2	DE3	DE4	DE5	DE 6	DE7	DE8	DE 9
Tizanidine Hydrochloride	25.12	25.12	25.12	25.12	25.12	25.12	25.12	25.12	25.12
HPMC E15	180	180	180	240	240	240	300	300	300
Glycerin (µl)	14	22	29	19	29	38	24	36	48
Aspartame	12	12	12	12	12	12	12	12	12
Menthol	10	10	10	10	10	10	10	10	10
Water (ml)	10	10	10	10	10	10	10	10	10

Table 2 (a): Evaluation of Prepared Batches for Optimized Formulation

Batch	EVALUATION PARAMETERS			
	Thickness# (mm)	Tensile Strength* (kg/cm^2)	Transparency	Surface Texture
DE1	0.07 ± 0.001	0.27 ± 0.012	Best	Smooth
DE2	0.07 ± 0.002	0.29 ± 0.024	Best	Smooth
DE3	0.07 ± 0.001	0.32 ± 0.009	Best	Smooth
DE4	0.08 ± 0.002	0.32 ± 0.029	Good	Smooth
DE5	0.08 ± 0.001	0.35 ± 0.015	Good	Rough
DE6	0.08 ± 0.001	0.39 ± 0.019	Good	Smooth
DE7	0.09 ± 0.001	0.50 ± 0.021	Medium	Rough
DE8	0.09 ± 0.002	0.57 ± 0.015	Good	Rough
DE9	0.09 ± 0.002	0.58 ± 0.014	Good	Smooth

* Values are expressed as mean ± S.D, n=3,
# Values are expressed as mean ± S.D, n=5

Table 2 (b): Evaluation of Prepared Batches for Optimized Formulation

Batch	EVALUATION PARAMETERS			
	Folding Endurance	Disintegration Time(sec)*	Drug Content*	%CPR at 2min*
DE1	>160	14.25 ± 1.09	99.68 ± 0.48	74.81 ± 1.07
DE2	>160	15.36 ± 2.24	98.85 ± 1.01	79.48 ± 2.27
DE3	>175	16.21 ± 1.52	100.24 ± 0.27	86.07 ± 1.09
DE4	>190	24.27 ± 1.00	98.46 ± 0.94	60.77 ± 0.98
DE5	>190	25.39 ± 1.67	100.68 ± 0.51	64.31 ± 1.10
DE6	>200	26.45 ± 2.01	99.56 ± 0.21	72.19 ± 1.59
DE7	>250	44.81 ± 3.20	99.19 ± 0.64	51.63 ± 2.34
DE8	>250	46.30 ± 1.90	98.91 ± 0.87	57.81 ± 0.97
DE9	>250	49.12 ± 4.04	101.22 ± 1.18	61.14 ± 1.14

* Values are expressed as mean ± S.D, n=3

Table 3: Cumulative Percentage Release of Prepared Batches DE1 to DE5

Time (min)	(%) Cumulative Percentage Release*								
	DE1	DE2	DE3	DE4	DE5	DE6	DE7	DE8	DE9
0	0	0	0	0	0	0	0	0	0
2	74.81 ± 1.07	79.48 ± 2.27	86.07 ± 1.09	60.77 ± 0.98	64.31 ±1.10	72.19 ±1.59	51.63 ±2.34	57.81 ±0.97	61.14 ±1.14
4	88.16 ± 1.18	89.08 ± 0.86	95.76 ± 0.51	83.75 ± 1.29	87.23 ±1.24	87.83 ±1.15	61.18 ±1.43	69.27 ±1.12	76.49 ±0.51
6	93.84 ± 0.75	94.35 ± 1.11	98.56 ± 0.61	89.50 ± 0.41	95.87 ±0.90	95.23 ±0.86	66.48 ±0.59	71.25 ±0.94	81.84 ±0.34
8	98.43 ± 0.19	96.98 ± 0.58	100.70 ± 0.74	93.46 ± 0.63	97.73 ±0.23	98.33 ±0.16	69.86 ±0.29	75.91 ±0.21	87.14 ±0.49
10	100.14 ±0.35	99.89 ± 0.21	100.33 ± 0.13	94.95± 0.38	98.66 ±0.45	97.59 ±0.35	71.09 ±1.25	74.36 ±0.39	88.18 ±1.14

*Values are expressed as mean ± S.D, n=3

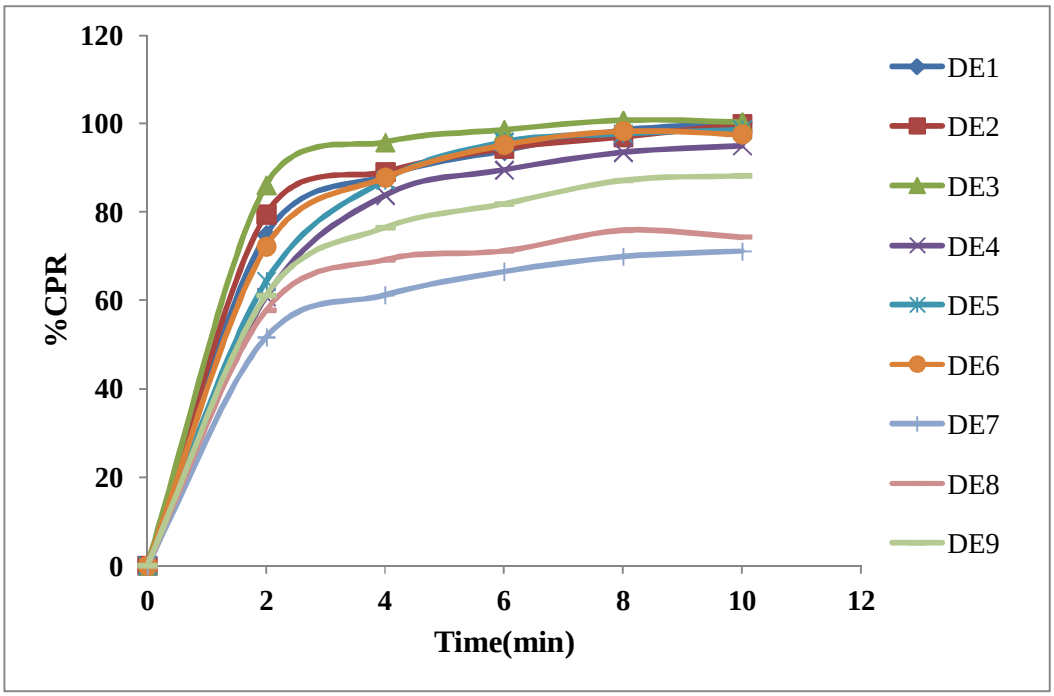

Figure 6: *In vitro* Drug Release of Batches DE1 to DE9

In vitro studies showed that batches DE1 to DE3 were gave more than 73 % release in 2 minute due to low concentration of polymer in strip. Batches DE4 to DE6 were showed more than 60% drug release in 2 minute, but batch DE7 to DE9 were not gave good release.

Statistical Analysis of Factorial Design Batches:

Full and reduced model for disintegration time

The summary of regression analysis and ANOVA for disintegration time is shown in table 4. The contour plot and 3D surface plot are shown in figure 7 and figure 8 respectively. Reduced model is obtained by rejecting insignificant factors in full model equation. From the reduced model, was found that variable X_1 i.e. concentration of HPMCE15, X_2 i.e. glycerin and X_1^2 shows positive effect on response Y_1. As its concentration increases, disintegration time of film increases. It can be qualitatively concluded that X_1, X_2 and X_1^2 had significant effect on the response.

Table 4: Summary Output of Regression Analysis and Anova for Disintegration Time

	DF	SS	MS	F	P-Value Prob > F
Regression	5	1562.46	312.49	1692.14	<0.0001
Residual	3	0.53	0.18		
Total	8	1563.01			**Significant**
Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Coefficient value	25.26	15.74	1.41	5.64	0.17	0.59
P-value	<0.0001	<0.0001	0.0040	0.0003	0.6182	0.0717
Full Model						
$Y_1=25.26+15.74X_1+1.41X_2+5.64X_1^2+0.17X_2^2+0.59X_1X_2$						
Reduced Model						
$Y_1=25.26+15.74X_1+1.41X_2+5.64X_1^2$						

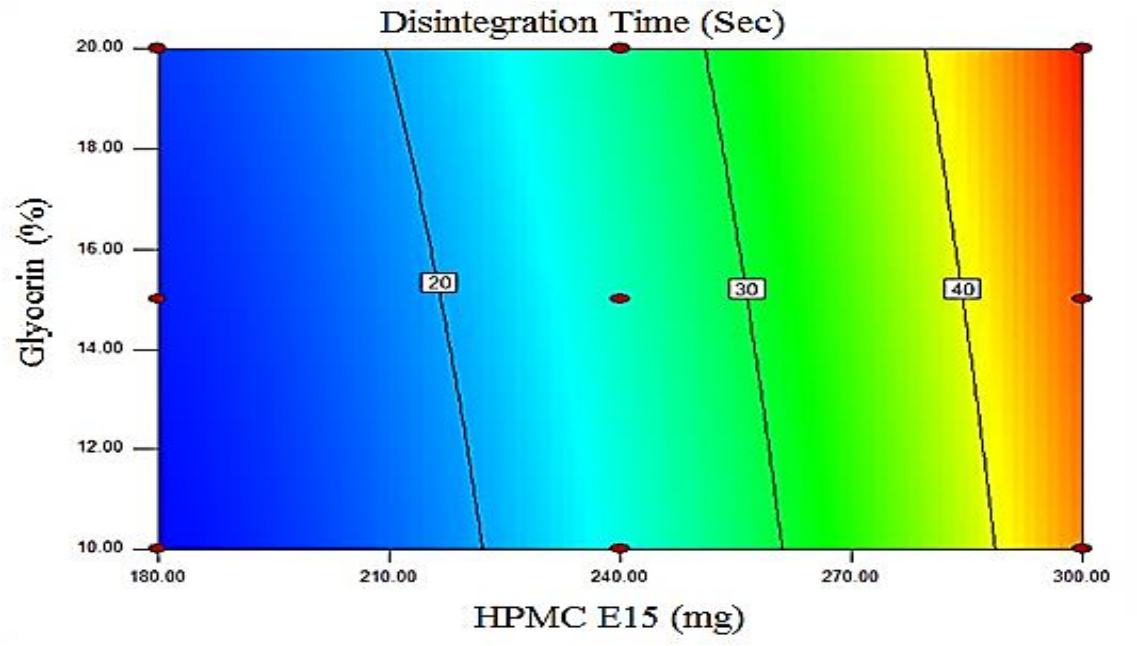

Figure 7: Contour Plot of Response 1 (Disintegration Time)

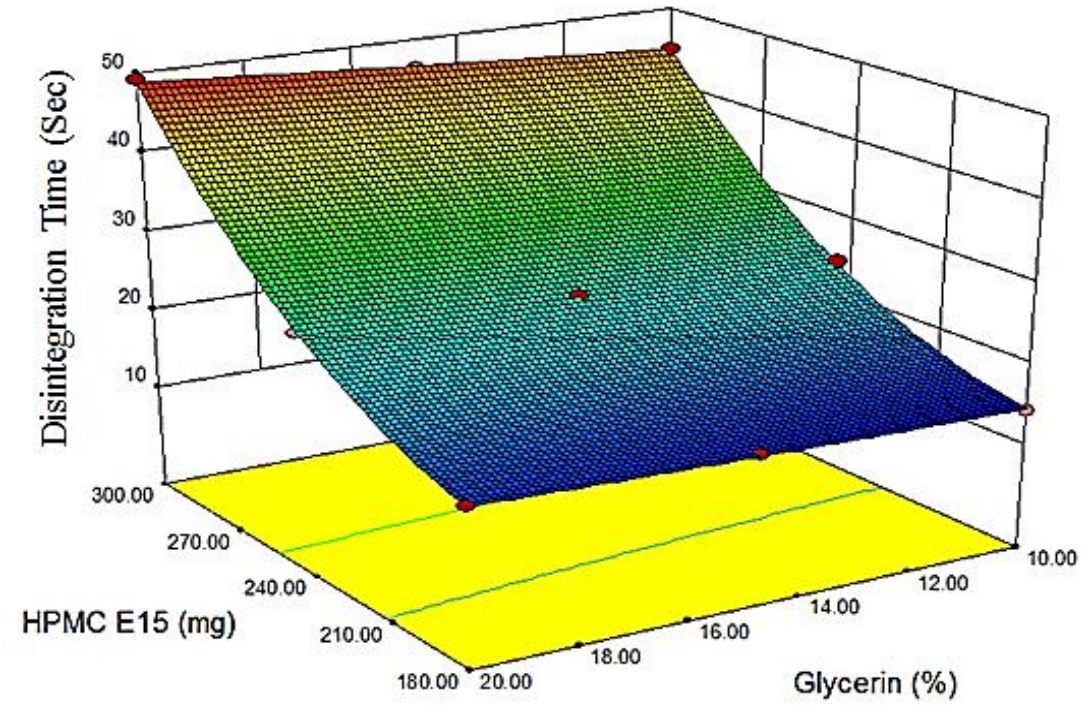

Figure 8: 3D Surface Plot of Response 1 (Disintegration Time)

Full and Reduced Model for *In Vitro* Drug Release at 2 Min.

The summary of regression analysis and ANOVA for *in vitro* drug release at 2 min. is shown in table 5. The contour plot and 3D surface plot are shown in figure 9 and figure 10 respectively. Reduced model is obtained by rejecting insignificant factors in full model equation. From the reduced model it was found that variable X_1 i.e. concentration of HPMC E15 shows negative effect on response Y_1 and X_2 i.e. glycerin shows positive effect on response Y_2. As concentration of HPMC E15 increases, *In-vitro* drug release of film decreases and as concentration of glycerin increases, *In-vitro* drug release of film increases. It can be qualitatively concluded that X_1 and X_2 had significant effect on the response.

Table 5: Summary Output of Regression Analysis and Anova for *In Vitro* Drug Release at 2 Min.

	DF	SS	MS	F	P-Value Prob > F
Regression	5	1000.59	200.12	124.59	0.0011
Residual	3	4.82	1.61		
Total	8	10005.41			**Significant**
Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Coefficient value	65.38	-11.63	5.36	2.73	0.57	-0.44
P-value	0.0011	0.0002	0.0019	0.0554	0.5710	0.5396
Full Model						
$Y_1=65.38-11.63X_1+5.36X_2+2.73X_1^2+0.57X_2^2-0.44X_1X_2$						
Reduced Model						
$Y_1=65.38-11.63X_1+5.36X_2$						

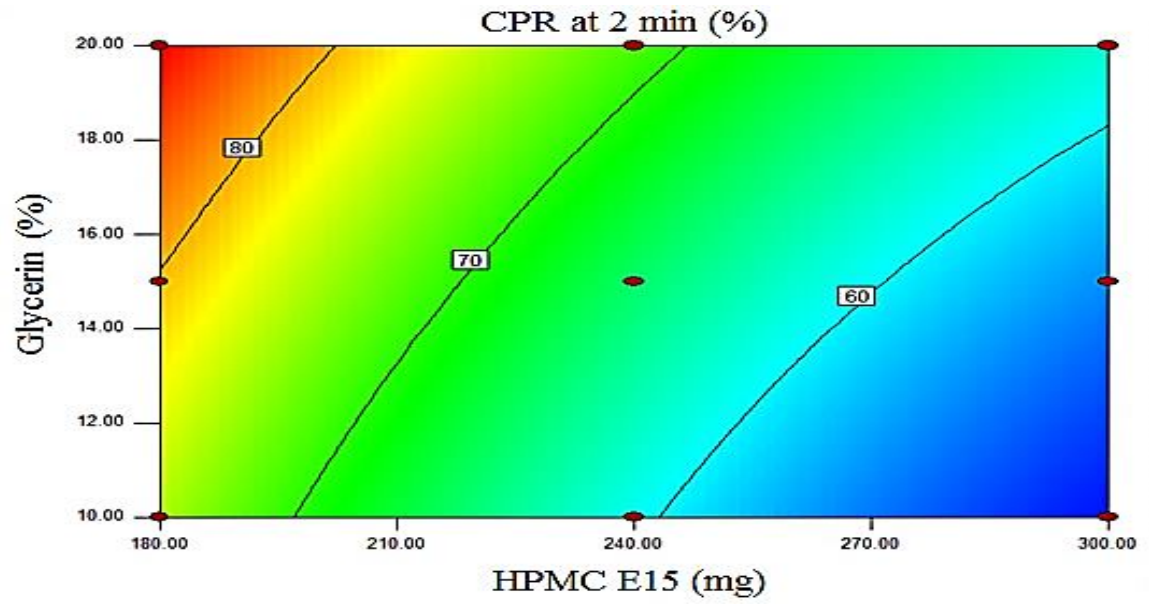

Figure 9: Contour Plot of Response 2 (*In-vitro* Drug Release)

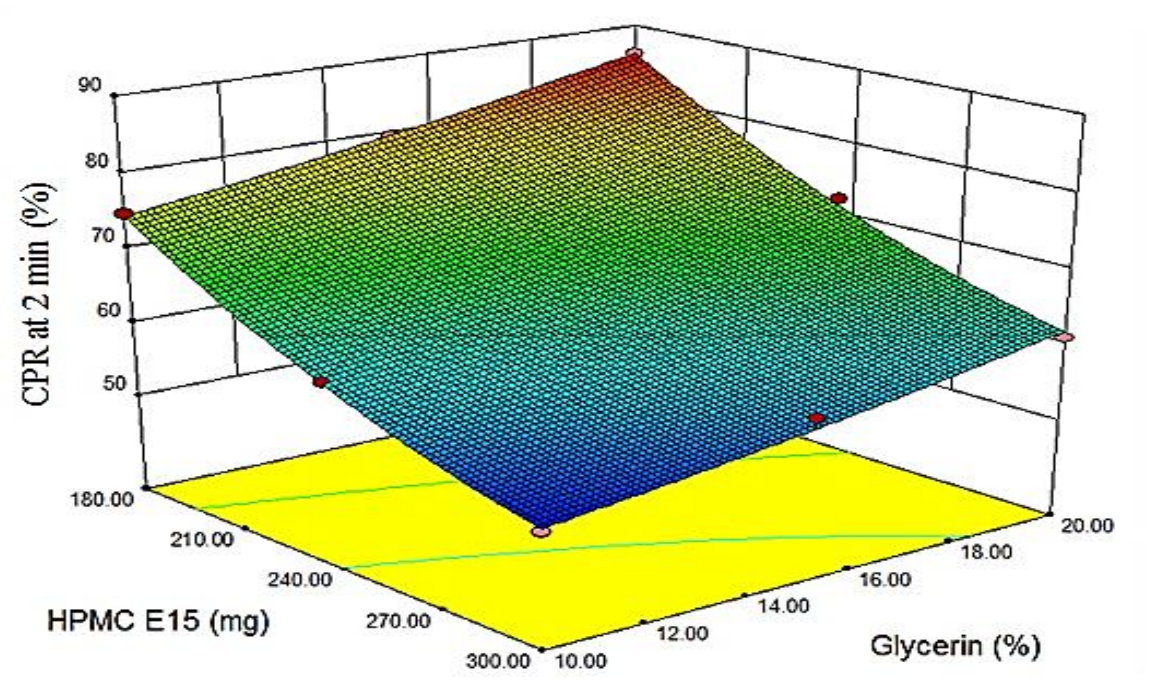

Figure 10: 3D Surface Plot of Response 2 (*In-vitro* Drug Release)

Full and reduced model for tensile strength

The summary of regression analysis and ANOVA for tensile strength is shown in table 6. The contour plot and 3D surface plot are shown in figure 11 and figure 12 respectively. Reduced

model is obtained by rejecting insignificant factors in full model equation. From the reduced model it was found that variable X_1 i.e. concentration of HPMCE15, X_2 i.e. glycerin and X_1^2 shows positive effect on response Y_3. As its concentration increases, tensile strength of film increases. It can be qualitatively concluded that X_1, X_2 and X_1^2 had significant effect on the response.

Table 6: Summary Output of Regression Analysis and Anova for Tensile Strength.

ANOVA TABLE

	DF	SS	MS	F	P-Value Prob > F
Regression	5	0.12	0.023	134.40	0.0010
Residual	3	5.167E-004	1.722E-004		
Total	8	0.12			**Significant**

Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Coefficient value	0.36	0.13	0.033	0.070	0.005	0.010
P-value	0.0010	0.0002	0.0084	0.0048	0.6274	0.2249

Full Model

$Y_1=0.36+0.13X_1+0.033X_2+0.070X_1^2-0.005X_2^2+0.010X_1X_2$

Reduced Model

$Y_1=0.36+0.13X_1+0.033X_2+0.070X_1^2$

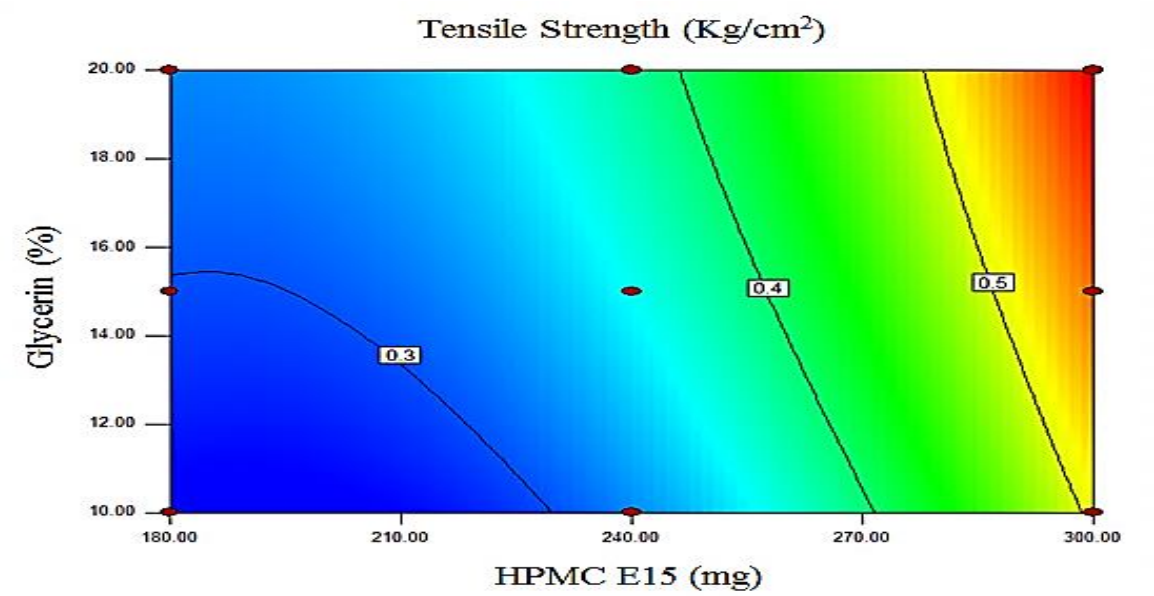

Figure 11: Contour Plot of Response 3 (Tensile Strength)

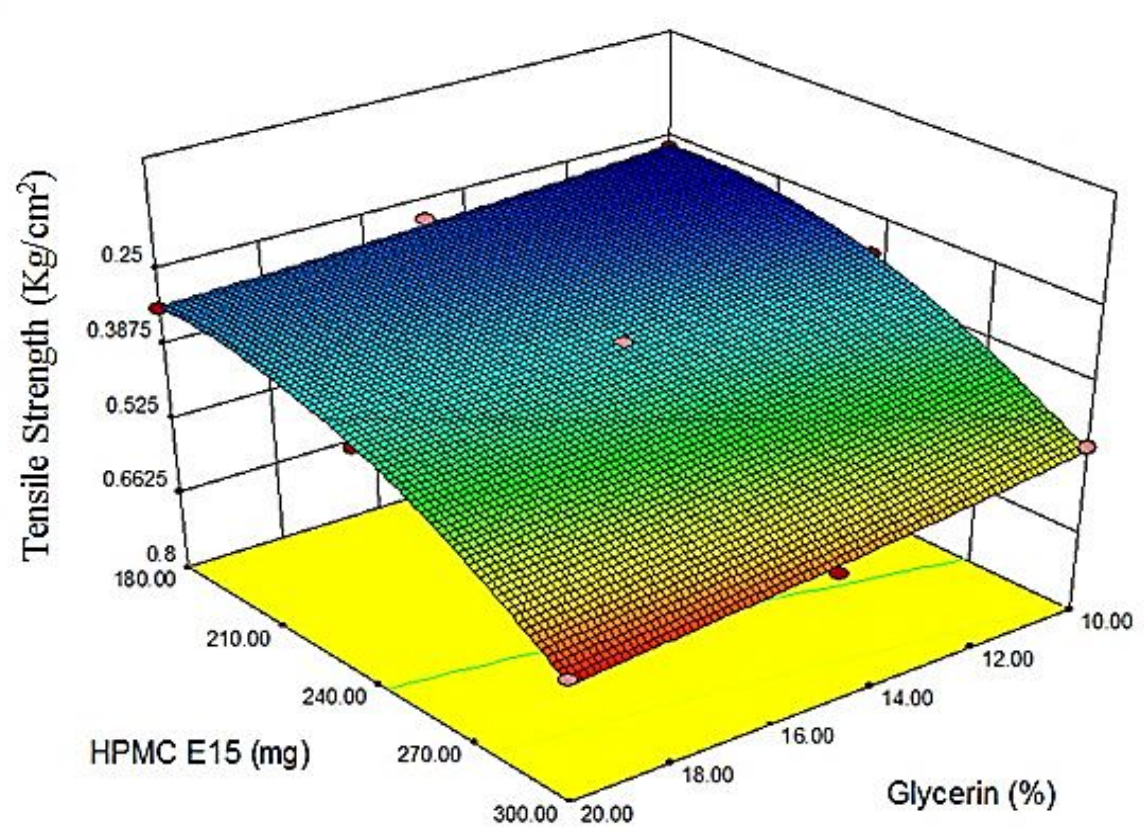

Figure 12: 3D Surface Plot of Response 3 (Tensile Strength)

Verification of Model by Check Point Batch:

Check point batch C1 and C2 were selected from the overlay plot of responses. The amount of HPMC E 15 and Glycerin were selected from overlay plot and predicted responses were given in the table 7. Actual response of C1 and C2 batch was measured and compare with the predicted response of check point batch. All the values of responses were within the upper and lower predicted interval. Hence, this model is valid and optimized batch can be selected from the overlay plot of this model.

Table 7: Predicted Response and Actual Response of Check Point Batch

Batch	Predicted Response			Actual Response		
	D.T. (Sec)	**%CPR at 2 min**	**Tensile Strength (kg/cm^2)**	**D.T. (Sec)**	**%CPR at 2 min**	**Tensile Strength (kg/cm^2)**
C1	15.99	84.63	0.31	15.33	85.56	0.29
C2	16.56	84.83	0.32	16.98	82.08	0.32

Optimization of Batch from Overlay Plot:

From the overlay plot it was seen that batch DE3 fall under the optimized region. So, the DE3 batch was selected as the optimized batch.

Ex vivo Permeability Study of Optimized Formulation:

The formulation DE3 showed suitable physicomechanical properties for mouth dissolving film and better *in vitro* drug release. So it was taken for *ex-vivo* permeability study.

Table 8: Cumulative Percentage Permeability (CPP) of Optimized Formulation

Time(min)	CPP
0	0
5	23.23
10	47.94
15	59.81
20	73.36
25	82.49
30	94.09
35	94.50

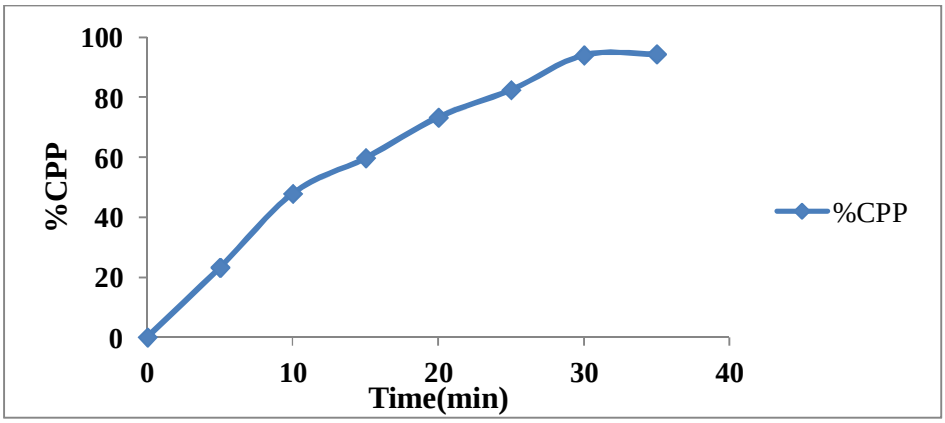

Figure 13: *Ex vivo* Permeability Study of Optimized Formulation

Drug permeation studies through porcine buccal mucosa conducted on oral strip of tizanidine hydrochloride showed nearly 90% permeation of drug in less than 30 minute. Fast permeation from strip indicated that suitability of tizanidine hydrochloride in fast dissolving strip for oral drug delivery. Cumulative percentage permeation showed rapid permeation in first 20 min than decrease gradually, it may be beneficial for rapid onset of action.

Short Term Stability Study of Optimized Formulation:

In order to determine the change in performance of dosage form on storage, stability study of optimized batch (DE3) was carried out at 40 ± 2 °C and 75 ± 5 % RH in a stability chamber for one month.

Table 9: Comparison of Physical Parameters after Stability

Parameters	Before Stability Study	After Stability Study
Thickness (mm)	0.07 ± 0.001	0.007 ± 0.001
Tensile strength (kg/cm^2)	0.32 ± 0.029	0.29 ± 0.018
Transparency	Best	Best
Surface texture	Smooth	Smooth
Folding endurance	>175	153
Disintegration time (sec.)	16.21 ± 1.52	18.12 ±0.91
Drug content	100.24	99.84
%CPR at 2 min	86.07	84.28

Samples were withdrawn after 1 month and evaluated for physical properties and *in vitro* drug release pattern. The similarity factor was applied to study the effect of storage on batch. The optimized formulation stored at 40 ± 2°C / 75 ± 5 % RH and it was found stable. Various morphological and mechanical properties were evaluated before and after stability, found in

range and not any large different between any two parameters. After stability tensile strength, folding endurance and drug release at 2 min were slightly decreased, and disintegration time was slightly increased, but all values were in accepted range. There was not any change observed in morphological properties like transparency and surface texture. Comparison of drug release after and before stability study was carried out by similarity factor (f2) and it was found to be 78.17.

CONCLUSION

It was concluded that the amounts of polymers, plasticizers and sweetener have significant effect on prepared oral strip. The development of oral strip of tizanidine hydrochloride is one of the alternatives routes of administration to avoid first pass metabolism and provide immediate action. In addition, these formulations enhance patient compliance. A combination of HPMC E15, Glycerin, aspartame and menthol showed improved in dissolution, permeability of drug and better morphological and mechanical properties to tizanidine hydrochloride strip. Prepared strips were stable at sort term stability condition for one month that prove prepared dosage form has no effect of storage condition.

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