Formulation and Evaluation of Mouth dissolving film of Diltiazem Hydrochloride by using factorial design

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Abstract- Objective: The present research work is focused to formulate and evaluate mouth dissolving film of an antihypertensive drug to enhance the convenience and compliance. Diltiazem hydrochloride is a calcium channel blocker used in the management of hypertension and angina pectoris.

Method: Films of Diltiazem hydrochloride were prepared by solvent casting method by using polymer HPMC E15 and Polyethylene Glycol 400 (PEG 400) as plasticizer in different concentrations. Films were subjected to physicochemical characterization such as thickness, weight uniformity, folding endurance, drug content uniformity, surface pH study, in- vitro drug release and stability studies.

Result: Films were found to be satisfactory when evaluated for thickness, weight uniformity, in-vitro drug release, folding endurance, drug content and disintegration time. The surface pH of all the films was found to be neutral. The optimized formulation F5 also showed satisfactory pH, drug content (99.63%), effective in vitro drug release (96.65%), disintegration time of 32.45 seconds and satisfactory stability.

Conclusion: It is concluded that fast dissolving films of Diltiazem HCl for control of Hypertension are successfully formulated using HPMC E15 polymer by solvent casting method.

1. INTRODUCTION

Because they are more adaptable and comfortable, fast dissolving oral films (FDOFs) are the most sophisticated oral solid dose form. As opposed to fast-dissolving tablets, it improves API efficacy by dissolving in the oral cavity in a minute after coming into touch with saliva, requiring no chewing and no water for administration. For the treatment of a variety of ailments and diseases, about 90% of medications are given to the body orally since this is thought to be the most efficient, convenient and safest drug delivery technique with the highest patient compliance.

Diltiazem hydrochloride has a half-life of 3-5 hour in the body. If given orally, Diltiazem hydrochloride will experience the first-pass metabolism; therefore, its bioavailability is low (40%). In order to avoid the first-pass metabolism, Diltiazem hydrochloride has been formulated into a buccal film. The buccal film has the advantage of bypass first-pass metabolism; hence, the bioavailability of drugs through this route will be better when compared with a conventional oral formulation.

Buccal films are flexible, elastic and soft but are still able to stay in the mouth. So, the system can prolong the duration of the medicine residence time in the buccal absorption site, reduce the frequency of use and modulate the permeability to epithelial tissue by loosening the intercellular junction. The length of residence time depends on the bio-adhesive strength of the polymer used. HPMC E15 is also a bio-adhesive with excellent water absorption capacity and is not easily eroded by saliva.

2. MATERIALS AND METHOD

Diltiazem hydrochloride was obtained from Arti Pharma Mumbai. HPMC E15, Polyethylene glycol 400, Citric acid, Sodium Phosphate and Tween 20 was procured from Research-lab Fine chemicals industries Mumbai. Potassium Dihydrogen Orthophosphate was obtained from Molychem industries Pvt. LTD. All other chemicals utilized were of analytical grade.

Determination of dose of drug

Every film of size 2x2cm^2 area must contain 30mg of Diltiazem Hydrochloride. The amount of drug in the castingsolution was calculated as follows:

The dose of the drug to be incorporated in each 4cm^2 film = 30mgDiameter of petri dish = 9 cm, so that the radius = 4.5cm

Area of petriplate =$\pi r2$

=3.14X4.5X4.5 = 63.58 sq.cm.

4 cm^2 film contains 30 mg of diltiazem hydrochloride

63.58 sq.cm. contains = x mg of diltiazem hydrochloride

For $4cm^2$ film = 63.58/4=15.88(Number of films)

For 30mg dose=15.88X30=0.4764 mg

Therefore, 0.4764 mg of drug should be incorporated in petri dish.

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem (mg)	0.476	0.476	0.476	0.476	0.476	0.476	0.476	0.476	0.476
HPMC E15 (gm)	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5
Polyethylene glycol400 (ml)	0.794	0.952	1.1	0.794	0.952	1.1	0.794	0.952	1.1
Citric acid (gm)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Tween 20 (ml)	0.1	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.

Method

Different formulae of film were prepared by considering all parameters and by taking appropriate quantities of ingredients into formulation. The films were prepared by solvent casting method. The quantity of the excipients citric acid and Tween 20 is kept constant. The concentration of HPMC E15 and Polyethylene Glycol 400 is according to standard concentration range.

The calculated amount of the polymer was dispersed in three forth volume of water with continuous stirring using mechanical stirrer. Calculated dose of diltiazem hydrochloride was incorporated in the polymeric solutions after levigation with Polyethylene Glycol 400 and the final volume was adjusted with distilled water. The gels were cast on a glass surface and allowed to dry in an oven maintained at 121°C, till a flexible film was formed. The dried films were cut into films of area 4 cm^2, packed in aluminum foil and stored in a desiccator until further use.

3. EVALUATION OF FILMS

a. Organoleptic properties

Diltiazem hydrochloride was studied for organoleptic characters such as Colour, Odour and Melting point.

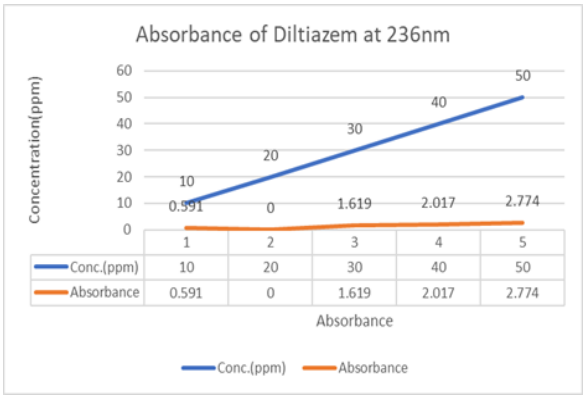
Identification test	Result of sample obtained	Reported standards
Colour	White	White
Odour	Characteristic	Characteristic
Melting point	185-186^{0}C	187-188^{0}C

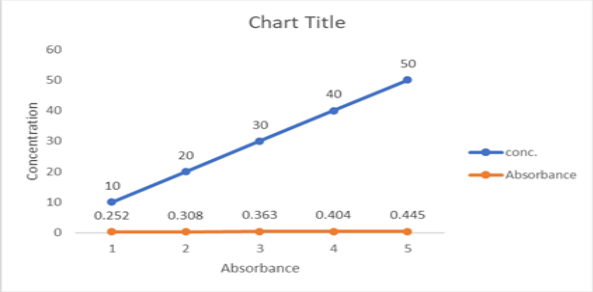
Determination of λmax of Diltiazem HCl in Distilled Water and Phosphate buffer 6.8

The UV spectrum of Diltiazem HCl was obtained using UV (Shimadzu 1800 series). Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of distilled water and phosphate buffer pH 6.8 respectively and volume made up to 100 ml. The resultant solution was scanned from 200 to 400 nm and the spectrum was recorded to obtain the value of maximum wavelength.

Preparation of Calibration curve in Distilled Water and Phosphate buffer pH 6.8

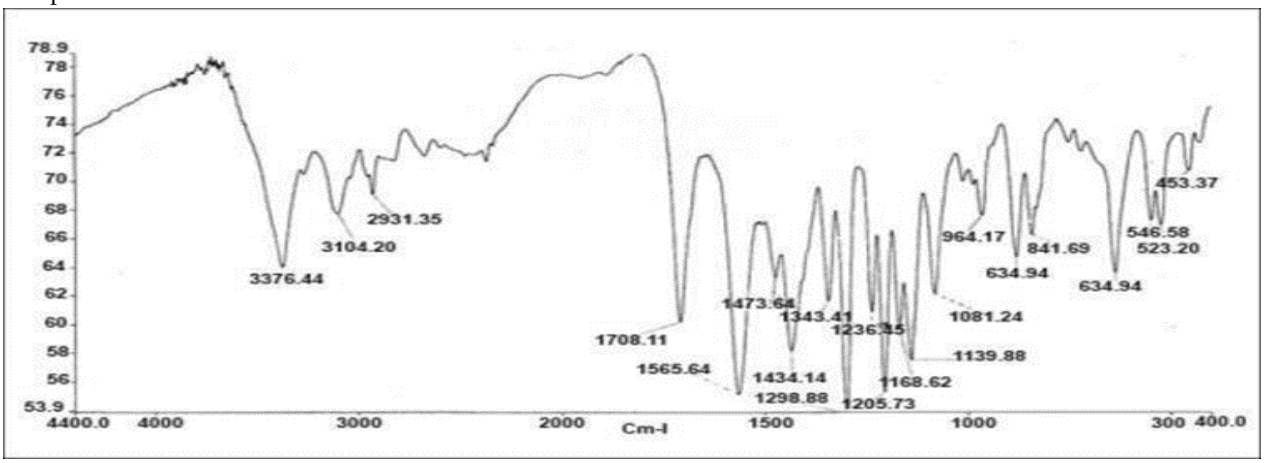
The stock solution of 100ug/ml was prepared in distilled water and phosphate buffer pH 6.8 respectively. The stock solution of 100ug/ml was used to prepare different dilutions in the range of 10-50 ppm in respective solvents. The absorbance of resulting solutions was measured at 236 nm using respective blank solvents by UV- Visible spectrophotometer shown



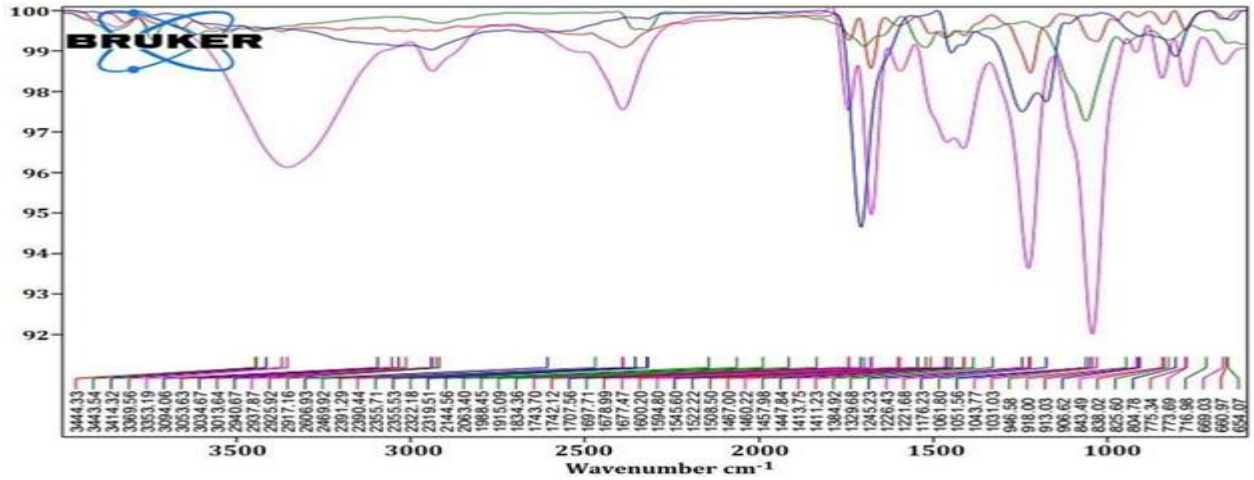


Sr. No.	1	2	3	4	5
Concentration (ppm)	10	20	30	40	50
Absorbance in Distilled water	0.591	1.072	1.619	2.017	2.774
Absorbance in Phosphate buffer pH 6.5	0.252	0.308	0.363	0.404	0.445

IR Spectra of Diltiazem HC



Sr. No.	Standard peaks(cm^{-1})	Observed peaks (cm^{-1})	Bond
1.	3100-3000	3035	Aromatic C-H stretch
2.	3100-3000	2966	Aromatic C-H stretch
3.	2830-2815	2837	O-CH_3 C-H stretch
4.	3000-2800	2393	Amine HCl N-H stretch
5.	1300-1000	1743	Acetate C=O
6.	1755-1735	1679	Lactum C=O
7.	840-790	839	O-Substituted C-H
8.	730-665	781	p-substituted C-H



b. Tensile strength

Films are held between two clamps positioned between 3 cm. During measurement the strips were pulled at the rate of 2mm/sec. From the results, it clears that when the concentration of the polymer increases, the tensile strength of the film also increases. The formulation F5 shows the maximum tensile strength. Presence of PEG 400 as a plasticizer imparts the flexibility to the Polymers. Tensile strength measures the ability of the film to with stand rupture. The Formulation F5 shows the maximum strength 1.9658±0.6747.

c. Percentage elongation of the films

The film was taken for the studies. Percentage elongation was found to be increased as increase in concentration of polymer in the film. Percentage elongation of the film varies from 21.56±0.5784 to 47.12±0.2458.

d. Thickness of the film

The thickness of the drug loaded films F1 to F9 formulations was measured with the help of Vernier calliper at different strategic locations like four corners and centre of each film. Mean SD is calculated. Film thickness should be controlled within a ±5% variation of standard value. This is essential to assure uniformity in the thickness of the film as this is directly related to the accuracy of dose and other mechanical properties of the film. Thickness of a single film varies from 0.53±0.02839 to 0.81±0.05432mm.

e. Weight variation of the film

The weight of each filmstrip is taken on Electronic analytical balance and the weight variation is calculated as mean SD. Weight variation varies from 24.3±0.421 to 30.1±0.461. Results shows that all the films passed weight variation test as the variation is within the pharmacopoeial limits of ±10%.

f. Folding endurance of the films

The number of times the film folded until it breaks is reported. The studies reflex the influence of concentration of Polyethylene glycol 400 in the formulation. As the concentration of Polyethylene glycol 400 is increased, folding endurance is also increased. Formulation F5 shows the largest folding endurance.

g. In-vitro disintegration test

In-vitro disintegration time is determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The disintegration is the time when film breaks or disintegrates.

All the films were subjected to disintegration test and results obtained. In Indian pharmacopoeia, limits for disintegration are 1-3 min. The F5 shows less disintegration time.

h. In-vitro dissolution study

In-vitro dissolution study shows maximum release i.e. 100.85% for F5 formulation this could be attributed to higher concentration of HPMC E15 and PEG 400 in the formulation.

i. % drug release

The films are tested for the % drug release. The nine formulations of size 4 cm^2 are placed in 100 ml volumetric flask and dissolved in distilled water, volume is made upto 100ml (300 µg). Then, 1ml stock solution is removed and diluted with distilled water and volume is made upto 10ml. The absorbance of the solution was measured at 237nm in UV spectrophotometer % drug release from the film is calculated.

j. Uniformity of content

Three films were tested for content uniformity. Films of size 4 cm^2 was placed in 100 ml volumetric flask and dissolved in distilled water, volume is made upto100ml with distilled water(100µg/ml). Samples were suitably diluted by using distilled water. The absorbance of the solution was measured at 237nm in UV spectrophotometer. The acceptance value (AV) of preparation 85-115%.

4. RESULT AND CONCLUSION

Formulation	Tensile Strength(Kg/mm^2)	Percentageelongation(%)	Thickness ofthe film(mm)	Weight variation(mg)	Folding endurance
F1	1.0058±0.2867	21.56±0.5784	0.64±0.01231	154± 0.275	136±2.426
F2	1.2865±0.1231	25.62±0.8904	0.58±0.06758	206±0.512	121±1.229
F3	1.6569±0.5894	46.28±0.6675	0.66±0.07240	249±0.421	137±0.989
F4	1.1424±0.9251	26.59±0.9053	0.58±0.06785	157±0.322	155±1.546
F5	1.9658±0.6747	28.32±0.2969	0.75±0.09238	182±0.461	163±0.569
F6	1.8291±0.06289	36.16±0.5529	0.61±0.05342	213±0.235	129±2.446
F7	1.0956±0.5785	27.23±0.9783	0.53±0.02839	178±0.386	159±1.329
F8	1.0065±0.2892	38.95±0.6389	0.74±0.04351	188±0.324	146±2.005

F9	1.8537±0.1158	47.12±0.2458	0.81±0.05432	222±0.695	154±1.289

Formulation	Surface pH	Disintegration Time (sec)	In-Vitro dissolution(%)	% drug release	Drug content (%)
F1	6.68±0.668	36.12±0.005	62.12±0.4378	48.79± 0.256	97.32±0.05244
F2	7.05±0.342	38.21±0.247	82.12±0.3984	61.69±0.538	98.65±0.03921
F3	7.23±0.589	50.36±0.056	83.96±0.7623	85.95±0.0987	97.54±0.07509
F4	6.89±0.742	37.11±0.721	70.50±0.2854	76.75±0.297	98.45±0.09263
F5	6.95±0.648	32.45±0.228	100.65±0.4623	96.65±0.557	99.63±0.248
F6	7.04±0.458	38.21±0.098	88.24±0.2410	62.31±0.768	98.64±0.05737
F7	6.28±0.773	41.75±0.536	76.22±0.5313	77.07±0.0982	97.57±0.08974
F8	7.02±0.289	42.68±0.998	80.45±0.4618	75.37±0.885	99.28±0.07230
F9	7.12±0.556	53.65±0.087	91.72±0.9432	91.27±0.569	99.58±0.5524

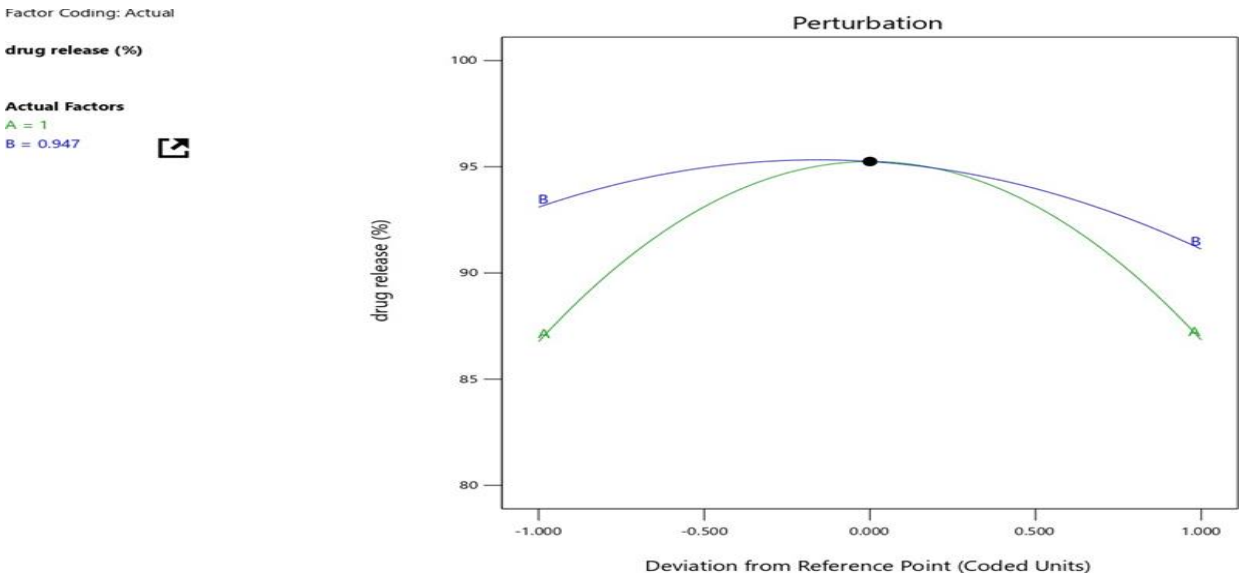
5. OPTIMIZATION OF FILMS

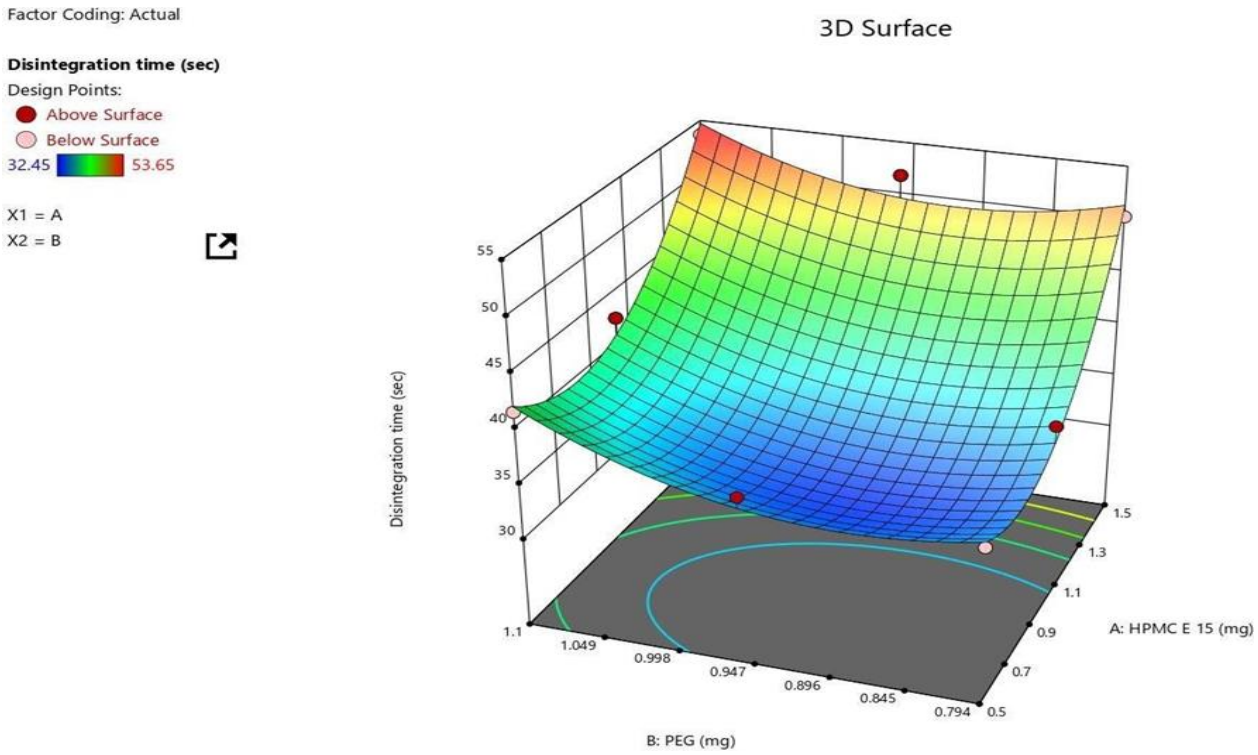
Study is carried using design expert software 13.0 version. Statistics apply to the results obtained from general factorial design in which two independent variables varied namely HPMC E15 and polyethylene glycol 400(X2) and their effect is recorded on dependent variable namely % drug release (Y1) and Disintegration Time. Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings.

Table 17. Factors of optimization

Variables	Factor
Independent	
X1	Polyethylene Glycol 400
X2	HPMC E15
Dependent	
Y1	% Drug Release
Y2	Disintegration Time

Formulation code	X1	mg	X2	mg
F1	+1	0.5	-1	0.794
F2	+1	0.5	0	0.952
F3	+1	0.5	+1	1.1
F4	0	1	-1	0.794
F5	0	1	0	0.952
F6	0	1	+1	1.1
F7	-1	1.5	-1	0.794
F8	-1	1.5	0	0.952
F9	-1	1.5	+1	1.1





6. ACCELERATED STABILITY STUDIES

Test Conditions	Maintained Values
Duration of Study	90 days
Temperature conditions	40±2 ^{0}C
Relative humidity conditions	75±5%
Frequency of testing the samples	30 days, 60 days and 90 days

7. SUMMARY AND CONCLUSION

The drug loaded films of all batches were evaluated for weight variation, thickness uniformity, tensile strength and percent elongation showed satisfactory result. The films were exhibited optimal folding endurance without any batch variation. Surface pH was determined for all formulations show acceptable pH range 6.28-7.33. This study also reflects the influence of concentration of PEG 400 on the pH of formulation. Disintegration time study shows that there is increase in concentration of PEG 400, disintegration time of the film decreases. The formulations show fairly uniform drug content ranging from 99.63 to 97.32% with minimum batch to batch variation. Drug release study was conducted to determine the % drug release with formulation F5 it shows the highest drug release to 96.65% up to 5min. This may be due to the concentration of polymers and plasticizers. This shows suitability of drug to be administered as an oral film form. The stability studies carried out for 90 days. Optimized sample was evaluated mainly for its physical characteristics at the predetermined intervals of 30day, 60day and after 90 like appearance (colour changes), pH, and drug content and disintegration time. The results favours the stability of the formulation within stability studies.

Finally, it is concluded that the drug release from the oral film was increased by using the increased concentration of PEG 400 and HPMC, thus assisting in faster disintegration in the buccal cavity. As the drug is having high solubility, fast disintegration may lead to more drug availability or dissolution, resulting in faster absorption in systemic circulation. Increased systemic availability of drug may lead to quick onset of action, which is a prerequisite for antihypertensive patient. Optimized formulation F5 fulfils all necessary attributes required for oral film and can become a promising alternative to present marketed tablet.

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