FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF DILTIAZEM HYDROCHLORIDE BY FACTORIAL DESIGN

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Abstract

Diltiazem is a calcium channel blocker used in the management of hypertension and angina pectoris. The purpose of this research work was to formulate a fast dissolving film of Diltiazem for the treatment of hypertension, by using polymers such as HPMC E15 and Polyethylene Glycol 400 in different concentrations. Films of Diltiazem were prepared by solvent casting method using polymers in different ratios. Polyethylene Glycol 400 was used as a plasticizer. Films were subjected to physicochemical characterization such as thickness, weight uniformity, folding endurance, drug content, surface pH study, in vitro drug release, and stability studies. 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.

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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 under a minute after coming into touch with less saliva, requiring no chewing, and no water for administration [1,2].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 [4,5]

Diltiazemhas a half-life of 3-5hr in the body. If given orally, Diltiazemwill experience the first-pass metabolism; therefore, its bioavailability is low (40%). In order to avoid the first-pass metabolism, Diltiazem 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 is also a bio-adhesive with excellent water absorption capacity and is not easily eroded by saliva. [6,7]

2. MATERIALS AND METHOD

- **Materials**

Diltiazem hydrochloride is obtained from Arti Pharma, Mumbai. All the excipients used were of analytical grade.

Sr. No	**Material**	**Grade**	**Manufacturer**
1.	Diltiazem	Pharma	Panchsheel Organics Ltd
2.	HPMC E15	LV Premium	Research-Lab Fine Chem Industries, Mumbai
3.	HPMC E5	LV Premium	LOBA Chemie Laboratory Reagent and fine chemicals
4.	Polyethylene Glycol	-	Research-Lab Fine Chem Industries, Mumbai
5.	Citric Acid	LR	Research-Lab Fine Chem Industries, Mumbai
6.	Tween 20		Research-Lab Fine Chem Industries, Mumbai

	F1	F2	F3	F4	F5	F6	F7	F8	F9	Category of ingredient
Diltiazem (mg)	0.476	0.476	0.476	0.476	0.476	0.476	0.476	0.476	0.476	Antihypertensive
HPMC E15 (gm)	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5	Film forming polymer
Polyethylene glycol 400 (ml)	0.794	0.952	1.1	0.794	0.952	1.1	0.794	0.952	1.1	Plasticizer
Citric acid (gm)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	Saliva stimulating agent
Tween 20 (ml)	0.1	0.1	0.1.	0.1	0.1	0.1	0.1	0.1	0.1	Surfactant
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	Solvent

• **Method**[8,9]
The buccal film was prepared by the solvent casting method. All the ingredients are weighed accurately. The weighed HPMC polymer then dispersed in distilled water until a clear solution is formed. In another beaker, diltiazem is dissolved in sufficient amount of water. Diltiazem solution was then added to a mixture of polymer under homogenous stirring. In the mixture, the measured amount of Polyethylene Glycol 400 is added and the solution is stirred to get a thick viscous solution and then citric acid and Tween 20 is added.The film mixture was poured into the petri dish and dried using an oven at 45^{o}C for 24h. The dried film is cut into a size of 2x2 cm (4cm2).

3. Evaluation of films[10,14]
1. Organoleptic properties
Diltiazem 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

2. 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.

3. Percentage elongation of the films
The film of 3inch X 10 mm 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.

4. Thickness of the Film
Vernier callipers were used to measure the thickness of the drug-loaded films at various important points, including the four corners and the center of each film. The mean SD is computed. Film thickness should not be less than the standard range of 5%. The thickness of the film must be consistent, as the precision of the dose was directly correlated with this.

5. Weight variation of the film
Each filmstrip is weighed using an electronic analytical balance, and the weight fluctuation is calculated as mean SD. Weight fluctuation ranges from 24.30.421 to 30.10.461. Results indicate that all films passed the weight variation test because the fluctuation was within the +10% pharmacopeial limitations.

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

7. In-vitro disintegration test
In a glass dish filled with 25 ml of distilled water and swirled every 10 seconds, the in-vitro disintegration time is calculated visually. When a film breaks or disintegrates, that is the disintegration. All of the films undergo a disintegration test, with findings. The Indian Pharmacopoeia sets a limit of 1-3 minutes for

disintegration. Less disintegration time is shown by the F5.

8. In-vitro dissolution study

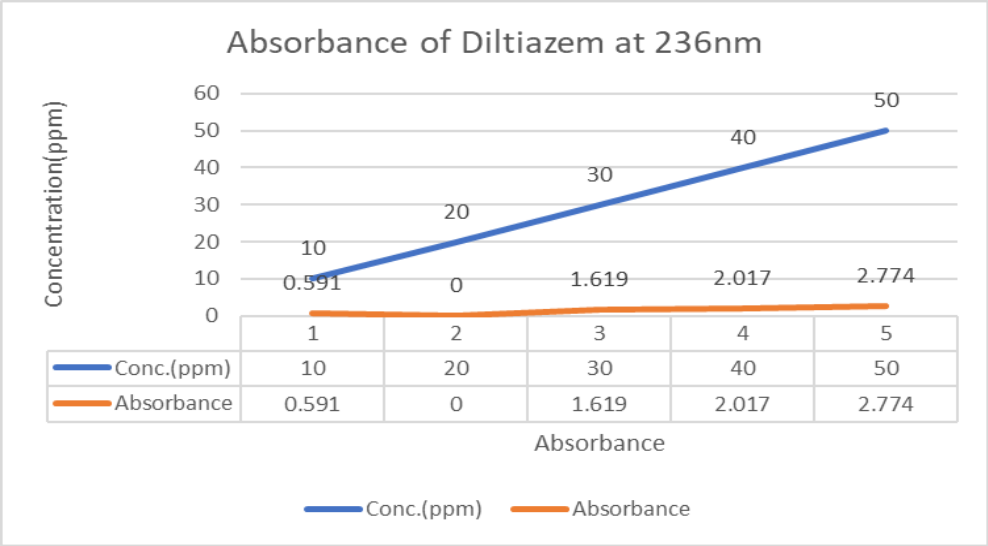
In-vitro dissolution study shows maximum release i.e. 100.85% for F5 formulation this could be attributed to higher concentration of HPMC and PEG 400 in the formulation.

9. % 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.

10. Uniformity of content

For content homogeneity, three films were examined. 4 cm2 films were placed in a 100 ml volumetric flask and dissolved in distilled water. The volume was then brought to 100 ml by adding distilled water (100 g/ml). Using distilled water, samples were appropriately diluted. In a UV spectrophotometer, the solution's absorbance was determined at 237 nm. The preparation's 85–115% acceptability value (AV).

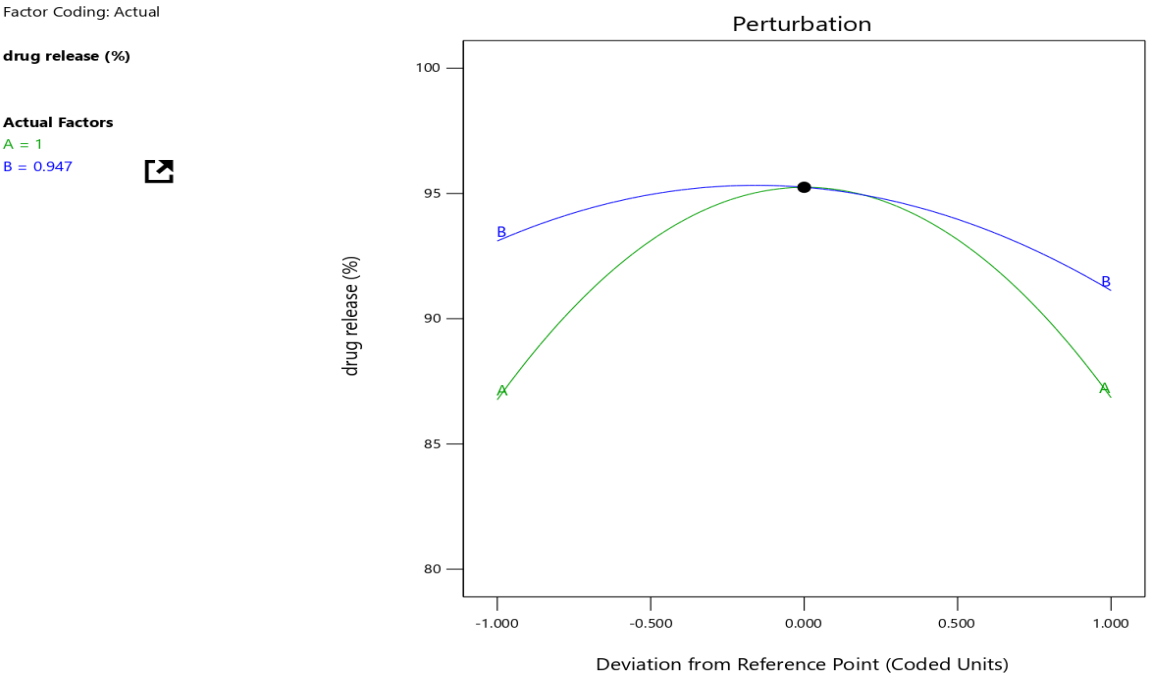


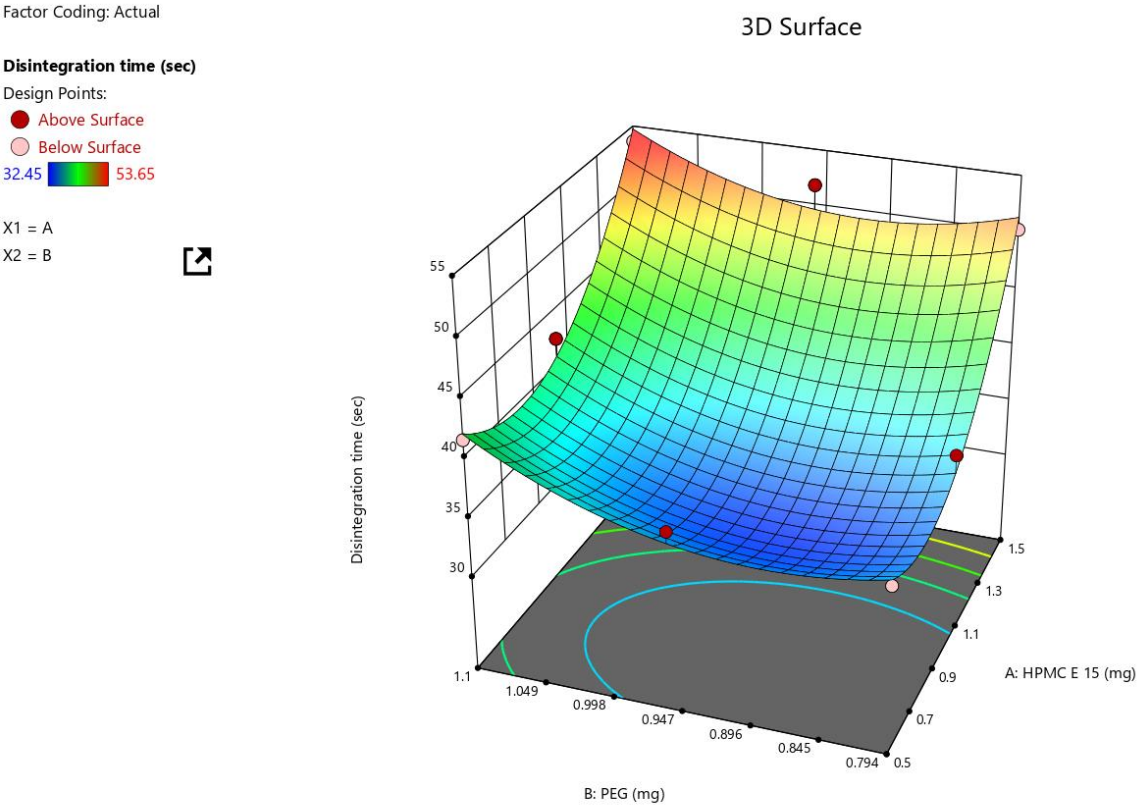
4. Results and Conclusion

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tensile strength	1.0058±0.2867	1.2865±0.1231	1.6569±0.5894	1.1424±0.9251	1.9658±0.6747	1.8291±0.06289	1.0956±0.5785	1.0065±0.2892	1.8537±0.1158
% elongation	21.56±0.5784	25.62±0.8904	46.28±0.6675	26.59±0.9053	28.32±0.2969	36.16±0.5529	27.23±0.9783	38.95±0.6389	47.12±0.2458
Thickness	0.64±0.01231	0.58±0.06758	0.66±0.07240	0.58±0.06785	0.75±0.09238	0.61±0.05342	0.53±0.02839	0.74±0.04351	0.81±0.05432
Weight variation	154± 0.275	206±0.512	249±0.421	157±0.322	182±0.461	213±0.235	178±0.386	188±0.324	222±0.695
Folding endurance	136±2.426	121±1.229	137±0.989	155±1.546	163±0.569	129±2.446	159±1.329	146±2.005	154±1.289
In-vitro disintegration test	36.12±0.005	38.21±0.247	50.36±0.056	37.11±0.721	32.45±0.228	38.21±0.098	41.75±0.536	42.68±0.998	53.65±0.087
In-vitro dissolution test	62.12±0.4378	82.12±0.3984	83.96±0.7623	70.50±0.2854	100.65±0.4623	88.24±0.2410	76.22±0.5313	80.45±0.4618	91.72±0.9432
% content	48.79± 0.256	61.69±0.538	85.95±0.0987	76.75±0.297	96.65±0.557	62.31±0.768	77.07±0.0982	75.37±0.885	91.27±0.569
Content Uniformity	97.32±0.05244	98.65±0.03921	97.54±0.07509	98.45±0.09263	99.63±0.248	98.64±0.05737	97.57±0.08974	99.28±0.07230	99.58±0.5524

Table 17. Factors of optimization

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





The drug loaded films of all batches were evaluated for weight variation and thickness uniformity, tensile strength and percent elongation showed satisfactory result. The films were exhibited optimal folding endurance without any batch variation. All formulations with surface pH measurements fall within the permitted pH range of 6.28 to 7.33. This study also indicates how PEG 400 concentration affects formulation pH. The disintegration time study demonstrates that as PEG 400 concentration increases, the film's disintegration time reduces. The formulations exhibit minimal batch to batch variation and a fairly homogeneous drug concentration ranging from 99.63 to 97.32%. The highest medication release was found to be 96.65% up to 5 minutes with formulation F5, according to a study on drug release. This may be due to the concentration of polymers and plasticizers. This shows suitability of drug to be administered as anoral film form. The stability studies carried out for 60 days.At the predetermined intervals of 30 days, 45 days, and 60 days, the optimized sample was primarily assessed for its physical characteristics, such as appearance (colour changes), pH, drug content, and disintegration time. Results verify the formulation's stability in stability experiments.

5. Conclusion

Finally, it has been claimed that the use of a higher concentration of PEG 400 and HPMC improved the drug release from the oral film, contributing in a quicker disintegration in the buccal cavity. Due to the drug's high solubility, rapid disintegration may increase drug availability or dissolution, which would speed up absorption into the bloodstream. A requirement for antihypertensive patients is a speedy onset of action, which may result from increased systemic availability of the medicine. The improved formulation F5 satisfies all the criteria for an oral film and has the potential to replace the current marketed tablet.5. Acknowledgment

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