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Formulation and Development of Sustained Release Floating Tablet of Diltiazem Hydrochloride

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ABSTRACT

This study was performed to design a sustained release floating tablet of diltiazem as the model drug for prolongation of gastric residence time. Diltiazem hydrochloride is a potent calcium channel blocker which is freely soluble in water and readily absorbed from the stomach. 3^2 factorial design was followed to formulate the diltiazem hydrochloride floating tablets. The experimental design included 2 factors and 3 levels. The two factors were a polymer (HPMC K100) and sodium bicarbonate (gas generating agent). The tablets after formulation were evaluated for weight variation, thickness, hardness, floating lag time. The polymer HPMC K100 is used here to sustain the drug release for over 12 h.

1. INTRODUCTION

Diltiazem is a calcium channel blocker belonging to benzothiazepine family. It is used in the treatment of hypertension, angina pectoris, and some types of arrhythmia.[1] The Bioavailability of diltiazem hydrochloride is 40 % owing to a first pass metabolism. It has an elimination half-life of 3.5h.[3] The gastroretentive drug delivery can help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. [4] Previous attempts for improving the bioavailability of Diltiazem included prolongation of gastric residence time by formulating floating matrix tablet of Diltiazem hydrochloride using the polymer HPMC K4M and Carbopol P934which increased the extent of absorption and bioavailability.[2] Other reports include sustained release tablet using different release-retarding polymers such as sodium alginate, HPMC K15 and Carbopol 934 [3], Stomach targeted controlled release floating tablet using polymers like methocel, sodium alginate and HPMC K4M.[4]

The present study describes formulation development of sustained release floating tablet of diltiazem using floating tablets. The formulation was optimized using 3^2 factorial design to attain desired drug release up to 12 h and minimum floating lag time.

2. MATERIAL AND METHODS:

2.1 MATERIAL:

Diltiazem hydrochloride was a gift sample from Evonik Pvt. Ltd, Mumbai. HPMC source Colorcon, Asia, India. Other chemicals were procured from local sources and were of EP grade.

2.2 Drug excipient compatibility study:

Compatibility of Diltiazem HCl with polymer HPMC K100 and PVP K30 in 1:1 ratio of the physical mixture were analyzed by FT-IR spectroscopic analysis after storage at 40C for two weeks in sealed containers.

2.3 Experimental Design: Factors and levels used in Formulation and development

Table 1: Factors and levels used in Formulation and development

Variable	Low	Intermediate	High
HPMC K100	120	150	180
Sodium bicarbonate	10	15	20

A 3^2 factorial design was followed. In this experimental design was built up using 2 factors that are polymer HPMCK100, and sodium bicarbonate each at 3 levels. The chosen response was floating lag time and drug release at 12 h.

2.4 Preparation of floating tablet

The floating tablet was prepared by release retarding polymer HPMC K100 and gas generating agent as sodium bicarbonate.[3] The tablets were prepared by direct compression method. The other concentrations of the above ingredients were determined by trial preparations of the tablets (table 1). The ingredients were mixed evaluated for precompression properties and then directly compressed on the RIMEK multi-station punching machine using 10mm concave punch at constant pressure.

Table 2: The composition of Diltiazem HCl floating tablet as per factorial design layout

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCl	60	60	60	60	60	60	60	60	60
HPMC K100	120	150	180	120	150	180	120	150	180
PVP K30	10	10	10	10	10	10	10	10	10
Sod.Bicarbonate	10	10	10	15	15	15	20.	20	20
Lactose	30	30	30	30	30	30	30	30	30
Citric Acid	10	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5	5
Talc	2	2	2	2	2	2	2	2	2

2.5 Pre compression analysis:

The pre-compression analysis included bulk density, tapped density, the angle of repose, compressibility index of the powder that is to be compressed in to tablet. It was performed as per the standard reported methods.[5,6]

2.6 Post Compression analysis:

Post-compression analysis includes Weight variation, hardness, thickness, friability, drug content,[7,8] Floating lag time of the tablets that are compressed. It was performed as per the procedure mentioned in the literature.

2.7 Floating lag time:

The time required for the tablet to rise to the surface and float is called floating lag time.[9] Individually, each tablet was added to the 100 ml of 0.1N HCl in beaker and time required for the tablet to float was recorded. The experiment was conducted in triplicates.

2.8 *In-vitro* dissolution studies:

Dissolution of all the formulations (f1 to f9) was carried out using USP apparatus type II using the paddle at 100 rpm. 900 ml of 0.1 N HCl at 37 + 0.5 ^{0}C was used as dissolution medium.[3] 5 ml of samples were withdrawn at 1h interval till 12 h. The aliquots were then analyzed by UV spectrophotometer at 236 nm. The dissolution profile of the optimized batch was fitted to various models such as zero order, first order, Peppas, Hixon- Crowell to ascertain the kinetic release modeling of drug release.

2.9 Optimization and validation model:

The response from the release data was fed to the design expert software 11.0 and the equations were generated to predict the responses release at 12 h and floating lag time. The numerical optimization was done using desirability function and predicted formula were prepared analysed to test whether the result matches to the optimized release data by DOE.

3. RESULTS AND DISCUSSION:

3.1 Calibration curve for Diltiazem HCl:

The standard graph of diltiazem HCl showed good linearity in 0.1N HCl (R^2 = 0.998) in the concentration range of 5-30ug/ml

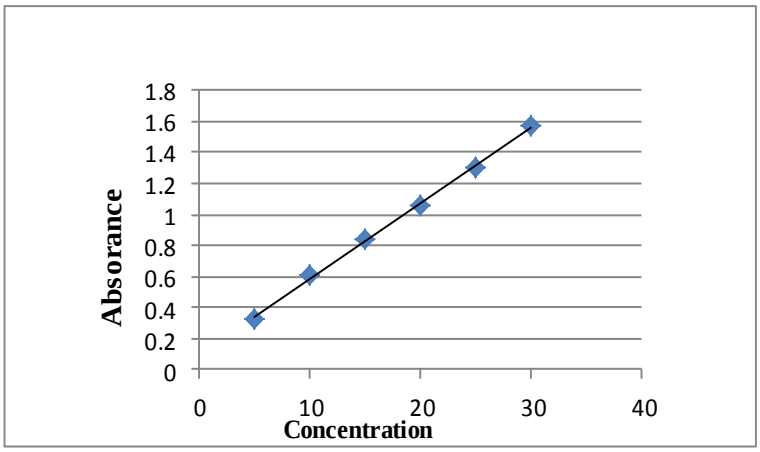


Fig.1: Calibration curve of diltiazem in 0.1N HCl

The equation for the line was found to be –

Y=0.048x-0.095

R^2= 0.998

3.2 Drug excipient compatibility

To study the compatibility of the drug with excipient the IR spectra with the combination of drug and excipient in 1:1 ratio was studied. The spectra obtained by FTIR spectroscopy was studied at wavelength 4500-400cm-1. The IR spectrum of drug and physical mixture showed no physicochemical interaction in between drug and used excipient.

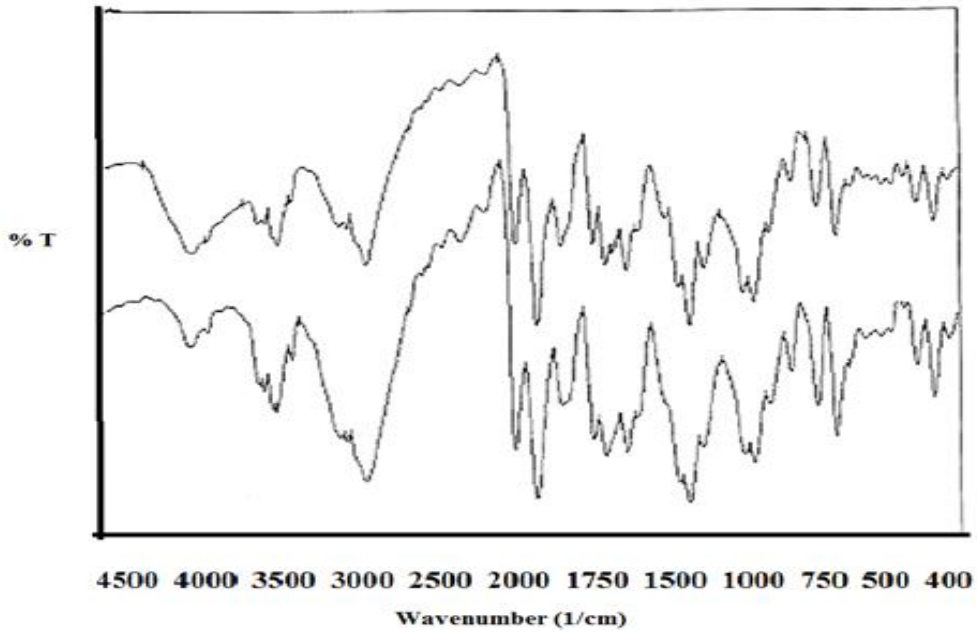


Fig. 2: FT-IR spectrum of Diltiazem hydrochloride and physical mixture

3.3 Precompression studies

Precompression studies such as bulk density, tapped density, the angle of repose, compressibility index, were determined and the results are summarized in Table 2

Table 3: Precompression parameters

Formulations	Bulk density g/ml	Tap density	Carr's index%	Hausner's ratio	Angle of repose
F1	0.47 ± 0.017	0.51 ± 0.011	6.71 ± 0.51	1.069 ± 0.015	28.51 ± 0.39
F2	0.46 ± 0.015	0.50 ± 0.005	9.28 ± 0.22	1.084 ± 0.01	25.81 ± 0.69
F3	0.47 ± 0.005	0.51 ± 0.01	6.91 ± 0.39	1.079 ±0.005	27.13 ± 0.99
F4	0.46 ±0.015	0.51 ±0.005	4.38 ± 0.80	1.045 ±0.009	27.36 ± 0.75
F5	0.47 ± 0.017	0.51 ± 0.01	4.90 ± 0.064	1.068 ± 0.017	28.56 ± 0.56
F6	0.45 ± 0.011	0.50 ± 0.011	9.28 ± 0.219	1.083 ±0.029	26.22 ± 0.57
F7	0.46 ± 0.005	0.51 ± 0.005	6.79 ± 0.29	1.087 ±0.012	28.32 ± 0.85
F8	0.47 ± 0.005	0.51 ± 0.005	9.42 ± 0.16	1.089 ±0.018	26.00 ± 0.48
F9	0.48 ± 0.023	0.53 ± 0.011	7.29 ± 0.76	1.090 ±0.016	25.91± 0.29

The bulk density and tap density values of the powder ranged from 0.45 ± 0.011 gm/ml to 0.48 ± 0.023 gm/ml and 0.50 ± 0.011 gm/ml to 0.53 ±0.011gm/ml. Angle of repose ranged from 25.81±0.69 to 28.56 ± 0.56 and Hausner's ratio below 1.10 which indicates that all the flow properties are excellent.

3.4 Post Compression analysis:

The post compression analysis, such as weight variation, hardness, friability, thickness, drug content, floating lag time was carried out as per the standard procedure reported in literature and results are shown in table no 3.

Table 4. Post-compression parameters

Formulations	Weight Mean ± SD	Hardness (kg/sq cm)	Thickness (mm)	% Friability	% Drug content	Floating lag time (min)
F1	247.5 ± 0.86	5.6 +0.41	4.10 ± 0.21	0.6 ± 0.07	97.86+0.57	15.33 ± 0.57
F2	277.45 ± 0.68	5.06 +0.11	4.38 ± 0.07	0.26 ± 0.13	98.49+0.32	15.66 ± 0.57
F3	307.10 ± 0.11	5.13 + 0.11	4.46 ± 0.12	0.31 ± 0.21	97.48+0.20	15.66 ± 0.57
F4	250.07 ± 0.06	5.06 + 0.11	4.12 ± 0.30	0.63 ± 0.22	98.43+0.30	17.66 ± 0.57
F5	282.05 ± 0.05	5.53+0.41	4.09 ± 0.05	0.53 ± 0.36	98.62+0.12	17.33 ± 0.57
F6	312.40 ± 0.24	5.03+0.05	4.40 ±0.25	0.69 ± 0.12	97.14+1.28	16.33 ± 0.57
F7	257.26 ± 0.27	5.26+0.11	4.15 ± 0.06	0.3 ±0.05	98.29+0.16	18.66 ± 0.57
F8	287.26 ± 0.13	5.63+0.15	4.22 ± 0.14	0.45 ± 0.17	98.02+0.39	18.66 ± 0.57
F9	317.18 ± 0.21	5.83+0.65	4.10 ± 0.12	0.34 ±0.20	97.75+0.45	17.66 ± 0.57

3.5 Optimization Equation:

Equation for drug release at 12 h.

Drug release at 12 h =

$+10.433+1.5076A - 2.5663B + 0.0173AB – 0.0062A^2 +0.0018B^2$ …. (Equation 1)

The equation for floating lag time

Floating lag time =

$+3.166+0.0388A+ 1.333B-0.0033AB+2.152A^2-0.0200B^2$ ….. (Equation 2)

3^2 factorial design was followed, in which two factors were HPMC K100(A) and sodium bicarbonate(B). Two responses taken were drug release at 12 h and floating lag time. From equation 1 and 2, it can be seen that changing the polymer concentration from low to a high level a significant increase in the drug release (Fig. 3) and floating lag time was noticed. The

increase in HPMC K100 may have led to an increase in tablet compactness by the polymer thus hindering the upward movement of the tablet to an extent of increasing floating lag time.[4] The increase in sodium bicarbonate also increases the floating lag time (Fig.4). As the sodium carbonate increases the gas production and conserve the gas into the gel layer and hence increase the floating lag time.

3.6 Response Surface plot:

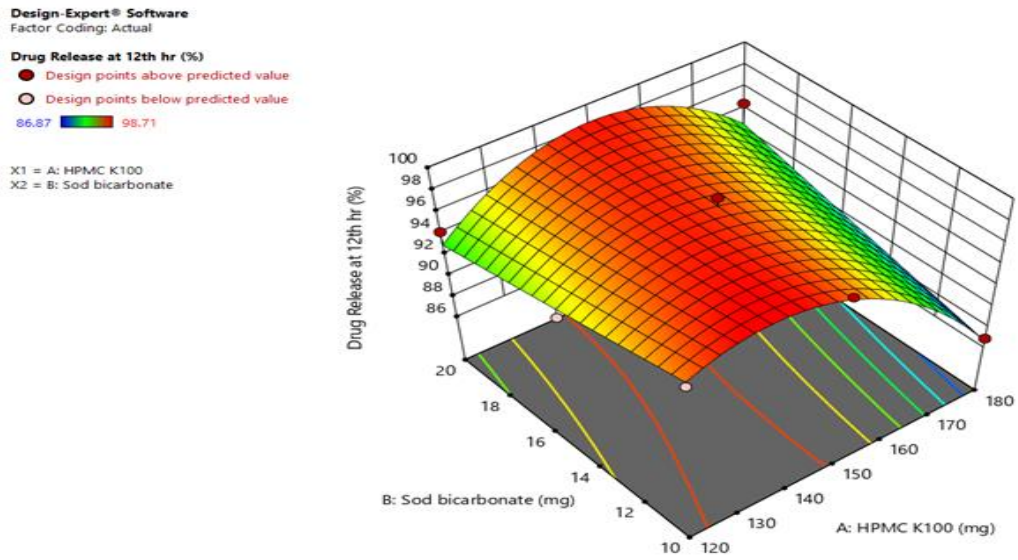


Fig. 3: 3D response surface plot for drug release at 12 h

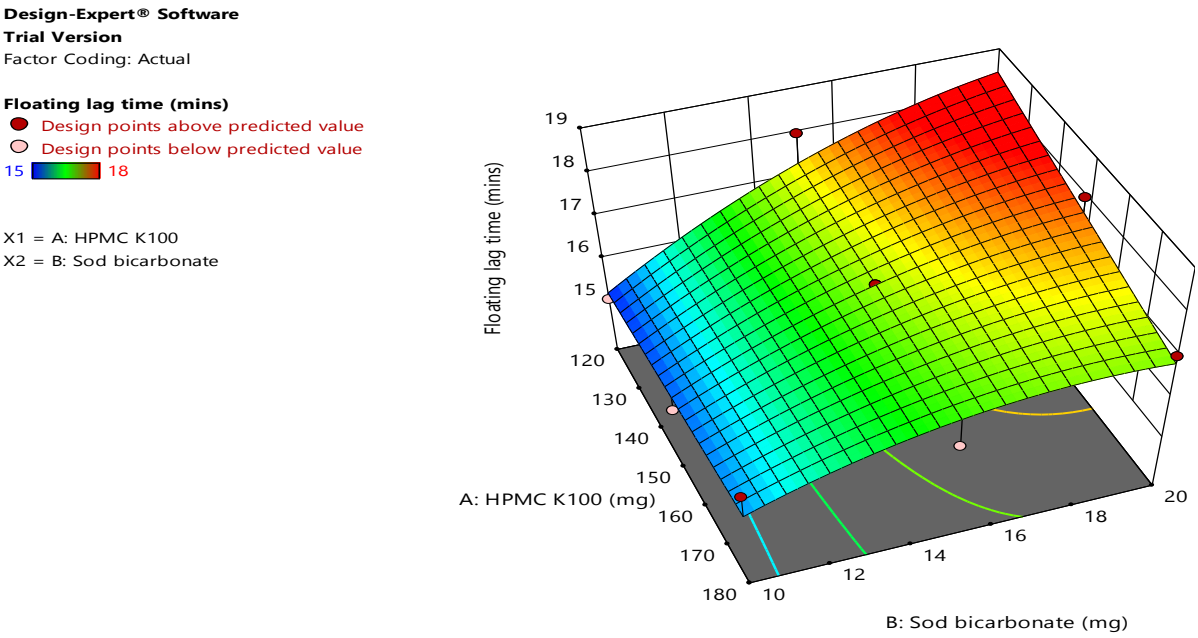


Fig. 4: 3D response surface plot for floating lag time

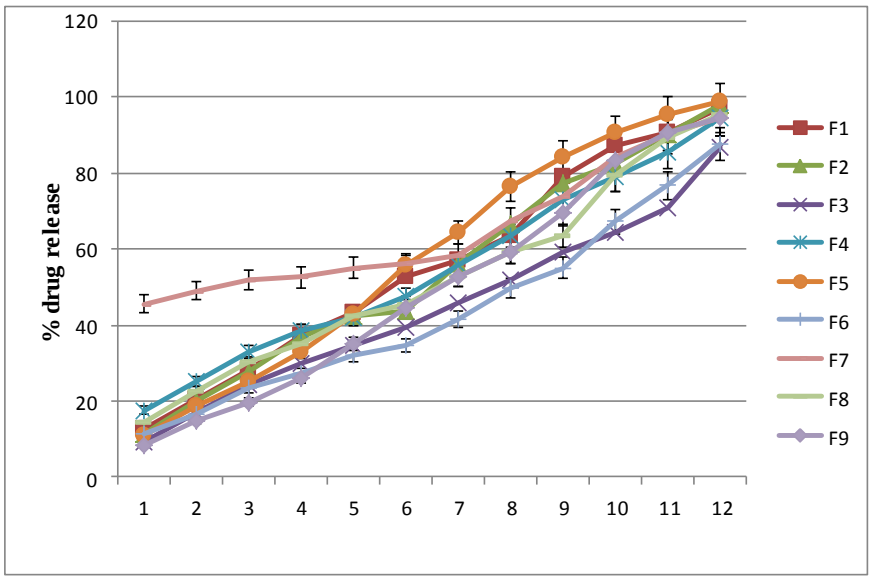
The tablets were prepared using the optimized formula and evaluated for drug release. The results showed appreciable agreement between the predicted and observed values as shown in table 5.

Table 5: Validation of model

Optimized formulation	Response variable	Experimental value	Predicted value	% prediction error	Desirablity
F5	Y1	98.71	97.99	2.08	1
	Y2	17	17	0.57	1

Here, Y1 – drug release at 12 h Y2 – Floating lag time

3.7 *In-vitro* release profile:



The drug release was determined from the formulated F1 to F9 batches. The *in-vitro* percentage drug release from the formulation F1 to F9 using different concentration of polymer HPMC K100 and sodium bicarbonate showed 96.96%, 97.81%, 86.87%, 94.40%, 98.71%, 87.56%, 94.28%, 95.40%, 94.59% respectively. Among all F5 was found to be the best formulation which sustains the drug release rate of Diltiazem Hydrochloride. The best fit model for optimized batch F5 was found to be Peppas with R^2 value 0.9957.

4. CONCLUSION

Diltiazem HCl sustained release floating tablet was prepared successfully using HPMC K100 polymer and sodium bicarbonate as a gas generating agent. It was observed that as when there is the increase in concentration HPMC K100 polymer there is the increase in release retarding of the drug. The floating time was increased as there was an increase in the concentration of Sodium bicarbonate. Thus F5 batch was found to be the optimized batch which achieved 98.71 % drug release up to 12 h with floating lag time of 17 min. Thus we can conclude that 3^2 factorial design was found to be quite efficient in optimizing the drug delivery system.

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