Original Article

Amalgamation of QbD and Alcohol Induced Dose Dumping Studies on Diltiazem Hydrochloride Modified Release Tablets

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ABSTRACT

Background: Alcohol induced dose dumping is a noteworthy question in designing of modified release dosage forms and it led the marketed products withdrawal by regulatory agencies. Diltiazem HCl is a highly water-soluble drug and may undergo faster dissolution in presence of alcohol. The purpose of the present study was to develop extended-release tablets of Diltiazem HCl tablets by direct compression method having robustness in hydro-alcoholic media. **Materials and Methods:** Using QbD approach, lubricants and polymer as CMAs and drug release as CQAs were identified and further optimization was done by employing 3^2 factorial design. The extended-release tablets were evaluated for hardness, friability, weight variation and dissolution study was performed in 40% Alcoholic Phosphate buffer pH 5.8. **Results:** The scientific finding reveals that the concentration of HPMC K-100M DC (12%) and xanthan gums (12%) are capable of providing extended release of drug till the end of 12 hr in pH 5.8 phosphate buffer as well as in 40% Alcoholic Phosphate buffer pH 5.8. **Conclusion:** These results showed a robust *in-vitro* drug release profile when exposed to hydro-alcoholic media till 12 hr. Formulation was subjected to accelerated condition for stability testing and was found satisfactory.

Keywords: Diltiazem Hydrochloride, Extended release, Hydroalcoholic dissolution media, Dose dumping, Factorial Design.

INTRODUCTION

In recent years, understanding of the effects of alcohol-induced dose dumping in controlled-release oral dosage forms has increased. The definition of dose dumping is "unintended, fast drug release in a short period of time of the whole or a portion of drug contained in a modified-release dosage form, can have severe adverse effects".[1,2] Dose dumping with modified drug release dosage forms led to the withdrawal of marketed products by the regulatory agencies[1] draw the attention to develop the formulation having robustness in alcoholic dissolution media.

Modified-release oral dosage forms containing highly water-soluble drugs have more solubility in alcoholic solutions compared to water. These types of products may undergo fast drug dissolution and release rate in the presence of alcohol.[3]

Diltiazem is a highly water soluble drug which is available in the market in the form of tablets and is used to treat high blood pressure, angina and certain heart rhythm disorders.[4] Disease related to cardio vascular system is common now a days. Its need lifelong medication treatment so, oral drug delivery is best for drug administration.[5] Avoiding alcohol-induced *in-vitro* dose dumping effects in Diltiazem extended release tablets is a prerequisite to ensure *in-vivo* success and patient safety.[6]

The present study focused on development of Diltiazem HCl extended-release tablet using Qbd approach. Selection of polymers was done by QTPP, CQA and risk assessment parameters. DSC and FTIR were performed for compatibility study. Formulation was optimized using 3^2 full factorial design and statistical analysis was done using ANOVA.

MATERIALS AND METHODS

Materials

Diltiazem HCl was received as gift sample from Cadila Pharmaceutical Ahmedabad Polymers and other excipients and solvents were purchased from ACS chemicals, Ahmedabad and were of analytical grade. Double distilled water was prepared at lab scale for whole study.

Preformulation studies

Drug excipient compatibility study was done using Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC).

FTIR Study

The purpose of the study was to ascertain compatibility of the medicament with various co-other excipients. Samples of the drug and excipients were taken in a 1:1 ratio and ground for optimal mixing with completely dried KBR. Sample was inserted into the stainless-steel disk's holes and sandwiched in a hydraulic press until 20,000 psi of pressure was reached. Pressure was released and the pellet was recovered after a period. The pellet was then placed inside the sample holder, and the spectrum was run. To confirm compatibility, FTIR spectra of the pure medication and excipients were performed separately. The spectra were scanned between 4000 and 400 cm^{-1} in terms of wave number.[7–9]

DSC Study

DSC is a thermal method used to determine whether a drug and its excipient are compatible. In which a function of temperature is used to assess the difference between the amount of heat needed to raise the temperature of a sample and a reference. From 50 to 350°C, all of the samples were run at a scanning rate of 10°C per minute.[7,10]

Defining QTPP and CQAs

QbD approach was presented by ICH Q8 guidelines for the optimization of formulation.[11–13] It includes quality target product profile (QTPP), critical quality attributes (CQAs), initial risk assessment, design space, etc.[14] The QTPP has been configured to include a potential quality characteristics summary of the product adapted as extended release of Diltiazem HCl without alcohol induced dose dumping.[15] The various elements of QTPP in development of Diltiazem HCL formulation was displayed in Table 1. Various Critical quality attributes (CQAs) were identified as per Table 2, such as drug product's physical characteristics (polymorphism), assay (drug purity) and drug release (for extended period) with justification for the formulation development.

Preparation of Diltiazem HCl Extended Release Tablets

Direct Compression Method was used for preparation of Diltiazem HCl Extended-Release Tablets. Diltiazem HCl, Polymer, Micro crystalline Cellulose were sifted through Sieve No. 30. All sifted materials mixed for 10 min using double cone blender for 10 min at 10 RPM and finally blend was subjected for compression using tablet punching machine using Talc and Magnesium Stearate as lubricants. Total weight of tablet must be constant in all batches i.e. 200 mg.[6,16] Detailed formula of tablets is not disclosed in this work.

Experimental Design

After identifying potential CQAs and performing an initial risk assessment, it's crucial to fully comprehend the main and interaction effects of many variables or factors on product CQAs. Although an initial risk assessment revealed the key elements that influenced a product's quality, it may not sufficiently illustrate the effects of these factors on product quality.[17–19] In the present work, a 3^2 full factorial design was adopted to find out the optimum combination of independent variables X1, X2 to obtain desired values of dependent variables Y1, Y2, Y3, Y4 (Table 3). %CDR was performed in 40% alcoholic phosphate buffer pH 6.8 for Y1, Y2 and Y3, whereas for Y4, %CDR was taken in 0.1N HCl + 40% Alcohol. 3^2 factorial design was represented by equation 1.[20]

$$Y= B_0+B_1X_1+B_2X_2+B_{12}X_1X_2+B_{11}X^2+B_{22}X_2^2 \qquad [1]$$

Evaluation of formulation
Pre-Compressional Parameters

Formulated mixed powder blend ready for compression was evaluated for angle of repose, bulk density, carr's index and hausners' ratio.[21–23]

Post-compressional Parameters

All factorial batches of the tablets were evaluated for official and unofficial test as per pharmacopoeia for weight variation, thickness, hardness and friability.[22,24,25]

Table 1: QTPP hypothesized for Diltiazem HCl tablet.

QTPP element		Target	Drug Product CQAs	Justification
Dosage Design		Extended-release Tablets	-	Extended-release design needed to meet label claims.
Strength		90 mg	-	Pharmaceutical equivalence requirement: Same strength
Route of Administration		Oral	-	Pharmaceutical equivalence requirement: Same route of administration
Drug product Quality Attributes	Physical Attributes	White to off - white, round, tablets and plain on both the side.	NO	Physical attributes of test product shall be compliant to size and shape guideline of US FDA as compared to reference product
	Identification	Positive for Diltiazem Hydrochloride	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity.
	Assay	NLT 90.0% and NMT 110.0 % of label claim	Yes	Limit based on development
	Uniformity of dosage units	As per USP <905>	Yes	As per USP <905>
	Dissolution	Media: 900 ml of Phosphate Buffer, pH 5.8, USP Apparatus II (Paddle), stirred at 100 rpm. Time in hr / Amount Dissolved 2 / 30-40% 6 / 60-70% 10 / NLT 90%	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.
	Microbial attributes	As per USP <61> and <62>	Yes*	As per USP <61> and <62>
Container closure system		HDPE bottle	-	Needed to achieve the target shelf-life. Reference product blister packing but we are using HDPE bottle. Packaging components meet the USP <661> and <671> requirements.

*CQA were not considered for present work.

Table 2: CQAs for Diltiazem Tablet and their justification.

Quality Attributes of Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Colour and shape similar to Reference product. No visual tablet defects observed.	No	Colour, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical.
	Odour	No unpleasant odour	No	In general, a noticeable odour is not directly linked to safety and efficacy, but odour can affect patient acceptability. For this product, neither drug substance nor the excipients have an unpleasant odour. Organic solvents are not used in the drug product manufacturing process. Thus it will not critical.
	Size	Similar to Reference product (Similarity as per the USFDA Guidance: Size, Shape and other Physical attributes of Generic Tablets and Capsules)[1]	No	Tablet size correlates to swallow ability; therefore, it is critical. For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for size and shape resemble to reference product.
	Friability	NMT 1.0% w/w	No	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for Diltiazem Hydrochloride	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity.
Assay		NLT 90.0% and NMT 110.0% of the labelled amount of Diltiazem	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout formulation and process development.
Dissolution In Phosphate Buffer pH 5.8 and dissolution medium 900 ml at 37°C, USP Apparatus 2 (paddle), stirred at 100 rpm		Time (hr) / Amount dissolved: 2 / 30%-40%; 6 / 60-70%; 10 / NLT 90%	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.

*CQA were not considered for present work.

Table 3: 3² Full factorial design matrix.

CMAs	Coded and Actual values		
	Low (-1)	Medium (0)	High (+1)
Concentration of HPMC K100M DC (X1)	18%	24%	30%
Concentration of Xanthan Gum (X2)	18%	24%	30%
CQAs	Target		
%CDR at 2hr (Y1)	30-40%		
%CDR at 6hr (Y2)	60-70%		
%CDR at 10hr (Y3)	NLT 90%		
%CDR in 0.1N HCl + 40% Alcohol at 2hr (Y4)	30-40%		

In-vitro Dissolution Studies

The USP Dissolution type II dissolution equipment was used to assess the release rate of Diltiazem HCl tablets. Six dissolution flasks containing 900 ml of the designated dissolution medium and previously kept at 37±0.5°C and 100 RPM each received one tablet. 5 ml of the sample m were withdrawn for analysis and replaced with fresh dissolution medium after each prescribed time period. After filtering and diluting the samples, absorbance at 237 nm was measured using a UV-visible spectrophotometer, and the % drug release was determined.[4,9,26]

Comparison with Marketed formulation

For comparison with marketed preparation, i.e. Dilzem-SR 90 was selected. This tablet containing Diltiazem was taken and *in-vitro* drug release study was conducted. Compare its cumulative drug release profile with final optimized formulation drug release profile.

Stability Study

For stability study, the optimised formulation was subjected at temperature 40°C±2°C and relative humidity 75% RH ± 5%RH. It was tested for content homogeneity and dissolution rate after 1 month.[22,27,28]

RESULTS

Preformulation Studies

Drug-Excipients Compatibility Studies

FTIR spectra of pure drug and its mixture with other excipients used in formulation were recorded as shown in Figure 1. The DSC curve of Diltiazem showed a sharp endothermic peak at 212.97°C. DSC spectra of mixture of pure drug and excipients were observed at 211.61°C (Figure 2).

Pre-compressional parameters

For factorial batches, Bulk density and tap density were found in range of 0.37-0.39g/ml and 0.42-0.45 g/ml respectively. Angle of repose was found in range of 29.43°-32.30°. Carr's Index and Hausner's ratio were found in range of 11.18-13.97% and 1.13-1.16% respectively.
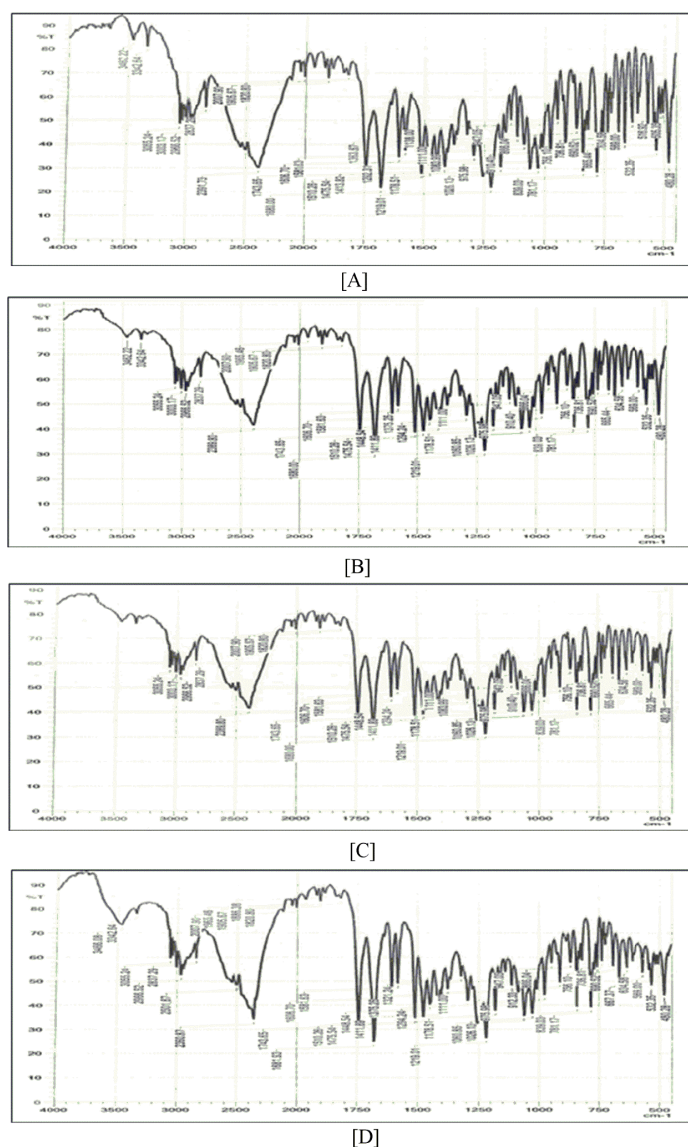
Figure 1: FTIR Spectra. (A) Diltiazem HCl (B) Diltiazem HCl + HPMC (C) Diltiazem HCl + Xanthan Gum (D) Diltiazem HCl + Composite excipients.

Figure 2: DSC Spectra. (A) Diltiazem HCl (B) Diltiazem HCl + Composite excipients.

Table 4: Initial Risk Assessment of Formulation Variables.

Drug Product CQA	Formulation variables				
	PSD of Diltiazem HCl	Diluents: Micro Crystalline Cellulose pH 101	Release Controlling Polymer: EC/PEO/ Xanthan gum/ HPMC	Glidant: Talc	Lubricant: Mg. Stearate
Physical Attributes	Low	Low	Low	Low	Medium
Assay	Low	Low	Low	Low	Low
Drug release	Low	Low	High	Low	Low

Post-Compressional Parameters

Prepared tablets of T1 to T9 batches were passes weight uniformity test as per IP. Hardness of the all tablets was within range of 5.50-5.80 kg/cm^2, which indicated structural integrity of formulation and friability was found in range of 0.08-0.14%.

Risk assessment

Table 4 explains the risk estimation matrix hypothesized for identifying the risk associated with CMA and CPP. Table 5 presents the rational justification of various risks for each of the material attributes and process parameters that correspond to the related CQAs.

Optimization of formulation

9 factorial batches were designed as per Table 3. All batches were analyses for dependent variables and results are shown in Table 6. Dissolution study was performed in 40% alcoholic dissolution media. %CDR was obtained in range of 18.00±2.55 to 50.00±1.56 for Y1 after 2 hr, between 49.08±2.94 to 79.32±1.52 for Y2 after6 hr was and after 10 hrs for Y3 it was 78.00±2.61 to 99.86±0.96. for Y4 after 2 hrs, %CDR was in range
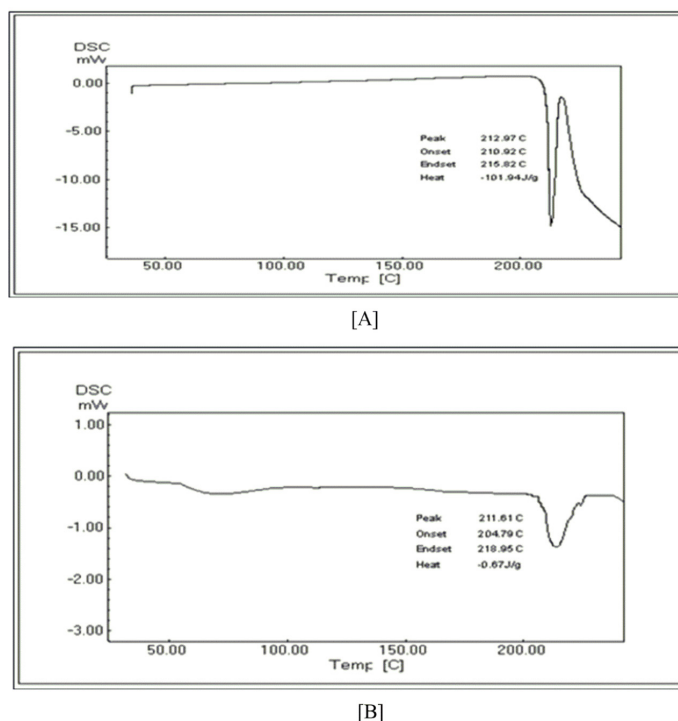
of 20.20±2.34 to 51.40±2.84. According to QTPP (Table 2), T5 was optimized batch. Further optimization was done on the basis of contour plots and response surface plots.

Figure 3 and Figure 4 shows contour plots and response surface plots for responses Y1, Y2, Y3 and Y4 respectively using Design Expert® 11 software. ANOVA statistics is calculated in Table 7. The Predicted R^2 is in reasonable agreement with the Adjusted R^2; i.e. the difference is less than 0.2 in all responses as per Table 7. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Table 7 shows that adeq prescision is greater than 4 for all four responses which indicates an adequate signal. This model can be used to navigate the design space.

For polynomial equation, coefficient table is displayed in Table 7. A represents the effect of concentration of HPMC, B represents the effect of concentration of xanthan gum and AB represents combined effect on %CDR. As per QTPP (Table 3), overlay plot was designed by overlapping of contour plots.[29,30] T5 batch was highlighted in yellow portion of the plot (Figure 5) representing the optimized batch.

Table 5: Justification for Initial Risk Assessment of Formulation Variables.

| Formulation Component	Drug Product CQAs	Justification
Drug Substance PSD	Physical Attributes	As Diltiazem is high dose drug and to manufacture the drug product where several manufacturing steps like sifting, mixing, blending etc. ensures intimate mixing of drug substance with excipients (preferably granular grade). Therefore, risk is low.
	Assay	
	Drug Release	Drug substance is BCS I drug with high solubility and high permeability. Therefore, impact of drug substance particle size to drug release is low.
Diluents Microcrystalline cellulose PH 101	Physical Attributes	Direct Compression process is used to manufacture the drug product, the Microcrystalline cellulose quantity may have an impact on flow of blend but there was not any significant impact on physical attributes, assay and uniformity of dosage units. Hence, risk is low.
	Assay	
	Drug Release	
Release Controlling Polymer: EC/ PEO Xanthan gum / Methocel K100M DC (HPMC)	Physical Attributes	Since direct compression process is used to manufacture the drug product, the risk of Polymer Level to impact tablets physical attributes, assay is low.
	Assay	
	Drug Release	Polymer type and level affects drug release profile in an extended-release formulation. So, the risk is high. Trials have been taken in development stages to establish acceptable range of better polymer which also provide better desired release in hydro alcoholic media.
Lubricant Level: Magnesium Stearate	Physical Attributes	Lower levels of lubricant may cause the issues like sticking, picking etc. Therefore, the risk is rated as medium.
	Assay	Generally, lubricant enhances blend flow ability and they do not have any impact on assay and uniformity of dosage units. Therefore, the risk is low.
	Drug Release	Hydrophobic lubricants affect the wettability followed by drug release of the formulation but not effect on extended release formulation.So, the risk is ranked as low.

Table 6: Factorial design batches and response values.

Formulation code	Independent variables		Responses			
	X1	X2	Y1	Y2	Y3	Y4
T1	-1	-1	50.00±1.56	79.32±1.52	99.86±0.96	51.40±2.84
T2	-1	0	47.10±1.97	75.96±2.63	98.20±0.66	48.01±2.39
T3	-1	+1	44.44±1.25	73.04±2.84	96.40±1.85	47.00±2.14
T4	0	-1	41.00±1.27	72.00±1.27	93.00±2.52	41.25±2.61
T5	0	0	38.00±2.67	69.08±1.82	92.00±1.96	39.10±2.84
T6	0	+1	31.00±2.7	61.18±1.34	85.00±1.74	29.35±2.92
T7	+1	-1	35.00±1.68	65.00±1.47	91.20±3.64	35.80±2.57
T8	+1	0	23.20±3.76	55.20±2.53	82.00±2.88	24.10±2.56
T9	+1	+1	18.00±2.55	49.08±2.94	78.00±2.61	20.20±2.34
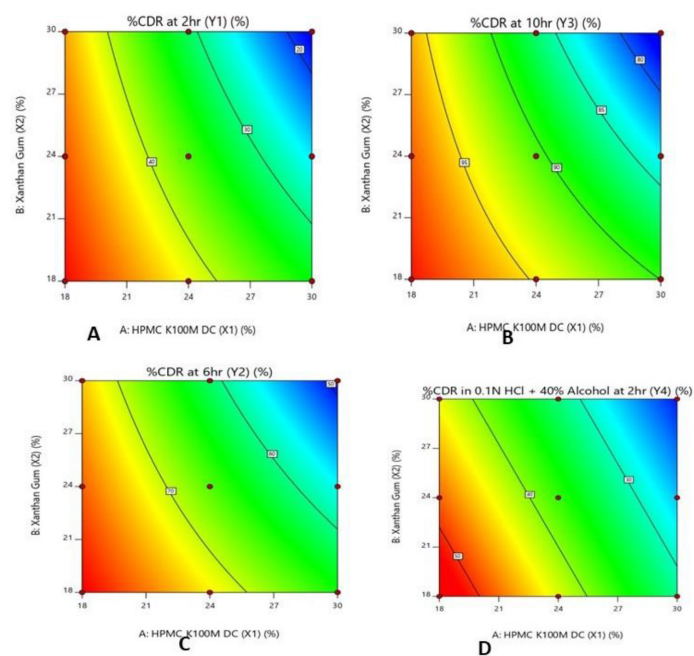
Figure 3: Contour Plots [A] Reponses Y1 [B] Reponses Y3 [C] Reponses Y2 [D] Reponses Y4.

Comparison with Marketed formulation

Dissolution profile of Dilzem SR was displayed in Figure 6C. It shows dose dumping of drug after 10 hrs in alcholic media as compared to optimized formulation. It shows dissimilarity factor 3 (in range of 1-15) and similarity factor 83 (in range of 50-100).

Stability Study

Results of stability study of the optimised formulation were displayed in Table 8. There was no significant change in results of dissolution and no any dose dumping was observed in even ethanolic dissolution media.

DISCUSSION

Dose dumping in alcoholic patient is the biggest challenge for controlled release dosage forms.[31] This research work focuses on selection of best excipients to avoid the dose dumping problem and to develop the formulation in such a combination to release the drug over a period of 12 hrs.
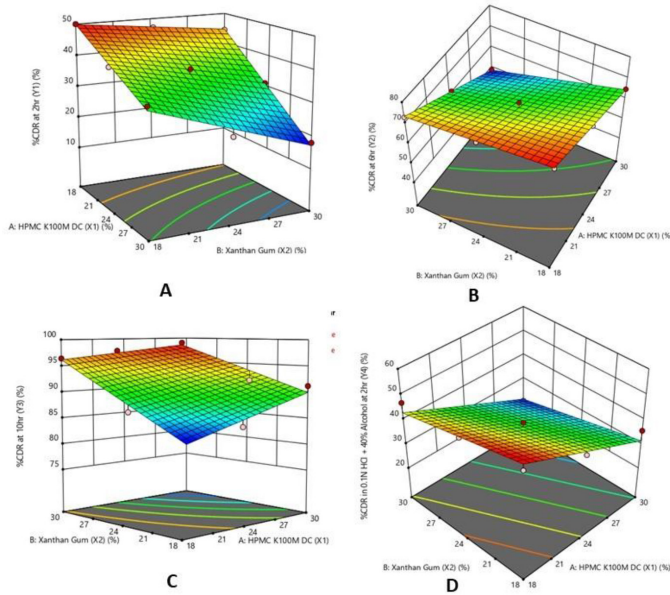
In-vitro Dissolution Studies

In vitro dissolution studies were performed in both media for comparison i.e. pH 5.8 Phosphate buffer (PB) and also in 40% alcoholic Phosphate buffer pH 5.8.

Dissolution data showed that upon increment of polymer concentration in formulation, rate of drug release was controlled. T1 was found to show continuous drug release upto 99.58±0.58% after 12 hrs in PB pH 5.8 dissolution medium (Figure 6A). According to Dissolution study, all batches showed dose dumping due to presence of alcohol due to more than 80% drug release after 8 hrs in alcoholic media. All T1-T9 batches showed continuous and controlled drug release up to 85-99% drug release after 12 hrs and does not undergo dumping in presence of 40% Alcohol (Figure 6B).

Figure 4: Response surface Plots [A] Reponses Y1 [B] Reponses Y3 [C] Reponses Y2 [D] Reponses Y4.

Figure 5: Overlay Plot.

Table 7: ANOVA Statistics and Co-efficients.

Dependent Variables	*p*-Value	Best Fitted Model	Adequate Precision	*F* Value	Predicted R²	Adjusted R²	R²
Y1	<0.0001	2FI	33.3586	142.571	0.95982	0.98151	0.98844
Y2	<0.0001	2FI	34.1024	143.793	0.97947	0.98167	0.98854
Y3	0.0003	2FI	21.6293	59.0857	0.89197	0.95611	0.97257
Y4	0.0002	Linear	18.5463	48.2737	0.8364	0.92199	0.94149

	Intercept	A	B	AB
%CDR at 2hr (Y1)	36.41556	-10.89	-5.42667	-2.86
p-values		< 0.0001	0.0003	0.0114
%CDR at 6hr (Y2)	66.65111	-9.84	-5.50333	-2.41
p-values		< 0.0001	0.0002	0.0160
%CDR at 10hr (Y3)	90.62889	-7.21	-4.11	-2.435
p-values		< 0.0001	0.0014	0.0268
%CDR in 0.1N HCl + 40% Alcohol at 2hr (Y4)	37.35667	-11.0517	-5.31667	
p-values		0.0001	0.0053	

Figure 6: Dissolution study in [A] Phosphate buffer pH 5.8 [B] 40% Alcoholic Phosphate buffer pH 5.8 [C] Marketed product and optimized formulation of Diltiazem HCl.

Preformulation study was foremost requirement for the dosage form design. Drug and excipients should be compatible and must not show chemical interactions. This results in better stability of the product throughout manufacturing and on storage also.[8] FTIR study and DSC spectra concludes no interaction between Diltiazem HCl and Excipients as no significant changes in peak shifting, No any extra appearance or disappearance of peaks with spectra of mixtures. This was endorsing the absenteeism of drugs, excipients and polymers chemical interaction.[10]
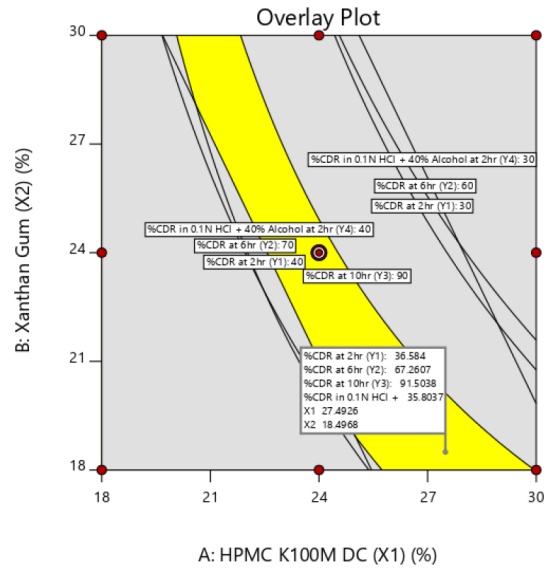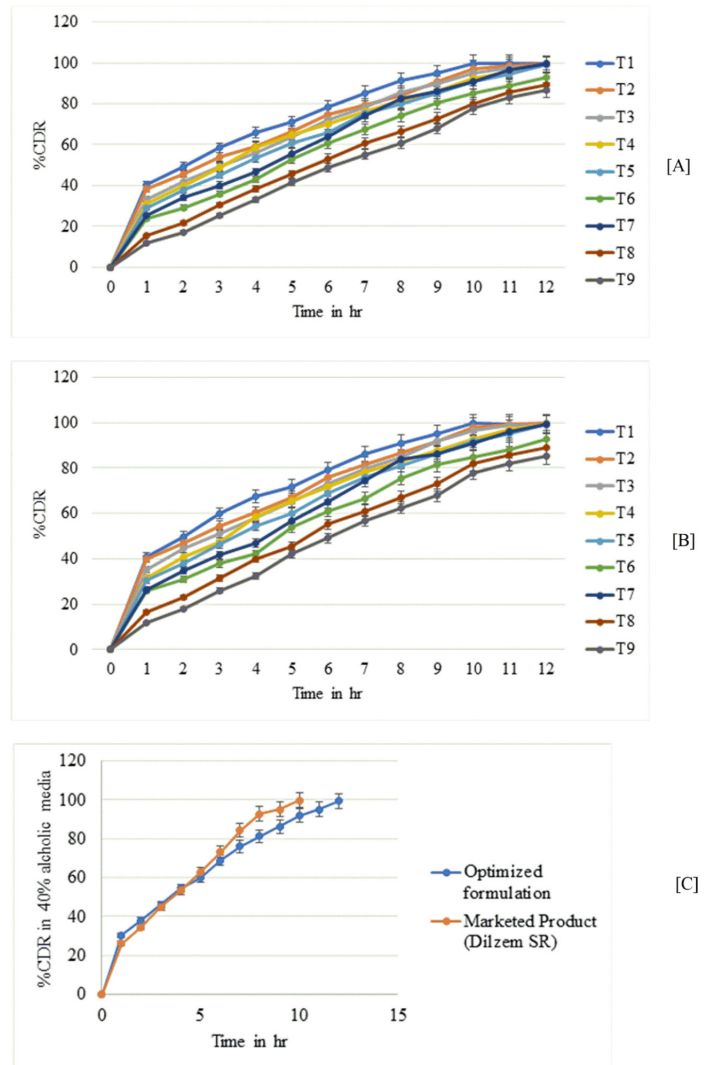
Table 8: Stability study results of batch T5

Final Batch T5	Initial	15 Days	1 Month
Appearance	White to off - white, round, tablets and plain on both the sides.	White to off - white, round, tablets and plain on both the sides.	White to off - white, round, tablets and plain on both the sides.
Average tablet wt. (mg)	199±1.59	200±0.02	199±1.25
Hardness (kg/cm2)	5.55±0.50	5.50±0.03	5.50±0.03
Friability (%)	0.09±0.002	0.05±0.007	0.07±0.006
Thickness (mm)	4.00±0.03	4.00±0.01	4.00±0.03
Diameter (mm)	8.01±0.02	8.00±0.01	8.01±0.01
%CDR in Phosphate buffer + 40% Alcohol	99.47±0.58	99.52±0.62	99.22±0.38

Pre-Compression parameters were mandatory requirement to check whether suitability of raw and intermediate product for final compression stage. Poor flow leads to problems with batch to batch variation in content uniformity and dose of drug.[32] When results compared with standards,[22,23,33,34] indicated good flow property and suitable compressibility index of powder blends for further processing and evaluation.

Controlled release dosage forms should have enough strength to remain in shape till its dissolution. Hardness of the tablet plays an important role in extended release formulation, was proved by researchers in 2002.[35] Here, Hardness and friability results indicated excellent strength of tablets to handle mechanical shocks during transportation.[21,22]

This research work focused on optimization of QbD parameters. Studies from Initial risk assessment using said tools have recommended that rate controlling polymer was found as critical material attribute (CMA) for drug release and lubricants were found as physical attributes for CMA. Assay, uniformity of dosage units and dissolution were found as CQA for further optimization of formulation.[13] From the analysis of QbD, Contour lines indicated the gradual control in release of Diltiazem HCl from the formulation on increment in concentration of both polymers HPMC and Xanthan gum.

ANOVA statistics explained *p*-value less than 0.05 the significance of the model. The Model *F*-value implies the model is significant in Y1 to Y4 all responses. There is only a 0.01% chance that an *F*-value this large could occur due to noise and A, B, AB are significant model terms. That means combined treatment of HPMC and Xanthan gum affects the %CDR from the formulation. In the case of Y4, there is a 0.02% possibility that noise contributed to the high *F*-value, and A and B are significant model terms. Negative signs in polynomial equations indicate the decrease in %CDR on increment of Polymer concentration in dosage form.

Dissolution study explained the designed formulation doesn't undergo dose dumping in alcoholic media due to optimized content of polymer and best excipients combination. Results of comparative study represent no significant changes between optimized formulation and marketed product. Stability results proved that the optimized batch was stable at specified temperature and humidity and no specific storage conditions are required for the formulation preservation.

CONCLUSION

Direct compression method was employed in preparation of Diltiazem HCl extended-release tablets using Ethyl cellulose, PEO, HPMC

K100M and xanthan Gum. The results of pre-compression and post-compression parameters of the tablets were found satisfactory. No chemical interactions between drug and excipients were proved using FTIR and DSC studies. The formulation was optimized using quality by design approach on using 3^2 full factorial design. According to QTPP targets, T5 batch was showed targeted drug release profile after 2, 6 and 10 hrs in 40% ethanolic phosphate buffer 5.8 dissolution media. It was also proved by contour plots, response surface plots and overlay plot. The optimized formulation T5 is found to be stable at accelerated condition (40°C ± 2°C and 75% ± 5% RH) in stability study evaluations. Hence the T5 formulation was selected as the final formulation having drug release profile up to 12 hr and robust to hydro-alcoholic media (40%) till 12 hr.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CMA: Critical material attributes; **CQA:** Critical quality attributes; **QbD:** Quality by design; **QTPP:** Quality target product profile; **ANOVA:** Analysis of variance.

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