ORIGINAL ARTICLE

Formulation and Optimization of Expandable Gastroretentive Tablet of Diltiazem Hydrochloride using Factorial Design

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Abstract

Aim: An attempt has been made to improve drug concentration in the stomach by preparing gastroretentive, swellable, matrix-based sustained release tablets of diltiazem hydrochloride that due to their size would be retained in the upper part of gastrointestinal tract. **Materials and Methods:** A 3^2 full factorial design was employed for the formulation of expandable tablets; two variables were evaluated. In the present investigation, the amounts of HPMC K100M and sodium carboxymethyl cellulose were selected as independent variables and effect of these variables, on swelling index (SI) and drug release was studied. Tablets were prepared and characterized by physical properties of compressed tablets such as hardness, friability, weight variation, content uniformity, SI, and drug release were determined. **Results and Discussion:** The SI of optimized batch varied between 114.21% and 220.41%. The percentage drug release of optimized batch was 15.60 at 1 h and 71.97% at 12 h. From the drug release kinetic study, Peppas model was found to be the best fit. Infrared spectrum and differential scanning calorimetric thermograms showed that there was no interaction between drug and polymers in the formulation. Expandable gastroretentive tablets were achieved a size more than the diameter of the pylorus and are not able to pass through the pylorus, thus causing prolongation of gastric residence time. **Conclusion:** The study indicates that development of diltiazem hydrochloride tablet can be beneficial in the treatment of hypertension. It releases drug in sustained manner for an extended period of time to reduce frequency of administration and improve patient compliance.

Key words: Diltiazem hydrochloride, expandable tablet, factorial design, gastro retentive, swelling study

INTRODUCTION

The gastroretentive drug delivery system can be retained for longer period in stomach region. Such systems are more advantages in improving gastrointestinal (GI) absorption of the drug with narrow absorption window as well as for controlling release of drug having site specific absorption limitation. The retention of drug delivery system in the stomach prolongs overall GI transit time, thereby resulting in improved bioavailability of some drugs. However, oral route has certain problems such as unpredictable gastric emptying rate, short GI transit time, and existence of an absorption window in the gastric and upper small intestine for several drugs.[1,2] A hydrophilic matrix system was simple, cost-effective, reduced risk of systemic toxicity, and minimal chances of dose dumping. It can be used to control the release of both water-soluble and water-insoluble drugs. The drug release pattern is a complex phenomenon at the molecular level, it involves water penetration, polymer swelling as well as drug dissolution, diffusion and polymer erosion process.[3-6] For drugs with a narrow absorption window in the GI tract, the challenging task was not only to prolong drug release but the retention of the dosage form in the upper GI tract. This results in increase bioavailability, reduced dose, and frequency for drug administration. The approaches for gastroretentive

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dosage forms have been proposed including mucoadhesive systems, swellable, and floating systems.[7,8] Diltiazem is a calcium channel blocker, which has been used in the treatment of cardiovascular disorders, particularly angina pectoris and systemic hypertension. It has short biological half-life of about 3.5 h and rapidly eliminated. It is favorably absorbed from stomach and oral bioavailability is 40%.[9-11] It is necessary to improve its concentration and its absorption in the upper part of GI tract (GIT). This concentration was improved by preparing expandable gastroretentive sustained release matrix tablets of diltiazem.

The oral route is the most preferred because of its better patient compliance. The majority of the drugs having site-specific absorption in the GIT and parameters such as pH dependent solubility, stability, and ionization of the drug in different portions of the GIT influence the absorption. Gastric retention time is one of the important factors, which adversely affect the performance of the drugs, when administered simply by an orally. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GIT is to increase the gastric residence time.[12,13] Gastroretentive drug delivery systems, allowing the drug to retained for a longer time in the gastric region for increasing the bioavailability. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset than conventional dosage forms.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape system, or by the simultaneous administration of pharmacological agent that delay gastric emptying.[14-16].The objective of this study was to maintain the levels of diltiazem within a desired range, reduction in its dosing frequency and to increase its bioavailability. It is necessary to improve its concentration and its absorption in the upper part of GIT. The expandable diltiazem hydrochloride tablet, which after oral administration could prolong the gastric residence time for sustained drug release.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was procured from Nicholas Piramal Ltd., Mumbai. Hydroxypropyl methylcellulose (HPMC K100M) was supplied by Colorcon Ltd., Goa. Sodium carboxymethyl cellulose was gifted by Cellulose Pharma Chem, Jalgaon; microcrystalline cellulose was procured from Molychem, Mumbai, and all the other chemicals used were of analytical grade.

Experimental

The sample of diltiazem hydrochloride was analyzed for its nature, color and taste. The melting point was taken by open capillary method. Diltiazem hydrochloride was estimated by ultraviolet (UV) spectrophotometry method.

Compatibility studies

The Fourier transform infrared (FTIR) spectra are used to identify the drug and detect the interaction of drug with polymers. FTIR spectrum of pure drug and physical mixture of drug with polymers were obtained on FTIR (Shimadzu 4100) instrument. The physical mixture of drug and polymers was prepared (1:1), and spectrum of physical mixture and potassium bromide (1:100) was taken.

Formulation design

Formulation design study is important for selection of the appropriate excipients for the preparation of expandable tablets. The four grades of HPMC namely HPMC K4M, HPMC E4M, HPMC K100M, and HPMC E15 were used for the trial batches of tablet. The trial batches of tablets were prepared by direct compression using commonly used excipients.

Preparation of expandable tablet

The expandable gastroretentive tablets were prepared by direct compression method. The proportionate composition of various ingredients was given in Table 1. The hydrophilic polymers such as HPMC K100M and sodium carboxymethyl cellulose (SCMC) were used as hydrophilic matrix forming agents in each formulation according to the results of trial batches. Microcrystalline cellulose was used as diluents. Magnesium stearate and talc were used as lubricant and as glident, respectively. All ingredients were mixed thoroughly, and the tablets were prepared using a rotary tablet machine of 13 mm punch.

Factorial design

A 3^2 randomized full factorial design was used for the study. In this design, 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The time required for 50% drug dissolution ($t_{50\%}$), percentage release at 6 h (Q_6), percentage drug release at 12 h (Q_{12}), and swelling index (SI) were selected as dependent variables. The values of variables in a 3^2 factorial design are indicated in Tables 2 and 3, respectively.

A statistical model incorporating interactive and polynomial term was used to evaluate the responses of formulations.

$$Y=b_0+b_1X_1+b_2X_2+b_{11}X_1^2+b_{22}X_2^2+b_{12}X_1X_2 \quad (1)$$

Where, Y is dependent variable, b_0 is the arithmetic mean response of the 9 runs and b_i (b_1, b_2, b_{12}, b_{11} and b_{22} is the

Table 1: Composition of expandable tablets of DTZ

Ingredient (mg)	Batches code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
DTZ	240	240	240	240	240	240	240	240	240
HPMC K100M	100	125	150	100	125	150	100	125	150
Sodium CMC	75	75	75	100	100	100	125	125	125
MCC	50	50	50	50	50	50	50	50	50
Magnesium stearate	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10

DTZ: Diltiazem hydrochloride, MCC: Microcrystalline cellulose, SCMC: Carboxymethyl cellulose

Table 2: 3^2 Factorial designs formulation

Batch code	Coded values	
	*X_1	*X_2
F1	−1	−1
F2	−1	0
F3	−1	+1
F4	0	−1
F5	0	0
F6	0	+1
F7	+1	−1
F8	+1	0
F9	+1	+1

*X_1: Amount of HPMC K100 M, *X_2: Amount of Sodium CMC, *−1, 0, +1: Low, medium and high amount of HPMC K100 M and sodium CMC

Table 3: Amount of variables in a 3^2 factorial design formulation

Coded values	Actual values	
	Amount of HPMC K100M X_1 (mg)	Amount of sodium CMC X_2 (mg)
−1	100	75
0	125	100
+1	150	125

CMC: Carboxymethyl cellulose

estimated coefficient for the factor X_1). The main effect (X_1 and X_2) represents the average results of changing one factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when 2 factors are changed simultaneously. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

Characterization of granules properties

Before compression, granules were evaluated for their characteristic parameters such as tapped density, Carr's index, and angle of repose. Carr's compressibility index was calculated from the bulk and tapped densities using a tap density apparatus.[17,18]

Compression of tablet

The granules were compressed lightly using a minipress rotary tablet machine, equipped with 13 mm round, flat and plain punches.

Physical tests for the tablets

Standard physical tests for the tablets were performed, and average values were calculated. Weight variation was determined by weighing 20 tablets individually; the average weight was calculated, and the percent variation of each tablet was calculated. Thickness and diameter were measured using Vernier caliper. Hardness was determined by taking 6 tablets from each batch using a Monsanto hardness tester (Electrolab Pvt. Ltd., India) and the average of pressure (kg/cm^{-2}) applied for crushing the tablet was determined. Friability test was determined, by weighing 10 tablets after dusting and placing them in a double drum friability tester apparatus (Veego Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablets was recorded, and the percent friability was calculated.

Drug content uniformity

About 10 tablets were finely powdered and an amount equivalent to 10 mg was accurately weighed and dissolved in 10 ml 0.1 N HCl using sonicator for 20 min. The resulting solution was further diluted with 0.1 N HCl to achieve concentration up to 10 µg/ml and the absorbance measured at the 237 nm using double beam UV spectrophotometer.

SI study

The SI of tablets was determined by placing the tablet in the dissolution test apparatus, in 900 ml of 0.1 N HCl at 37°C ± 0.5°C. The tablets were removed from dissolution medium at specified interval of 1 h up to 12 h. After draining

free from water by blotting paper, these were measured for weight gain. Swelling characteristics were expressed in terms of percentage water uptake (WU %) or SI according to the equation 2.[19]

$$SI=\frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}}\times 100 \quad (2)$$

In vitro drug release study

The *In vitro* dissolution study was carried out using USP tablets dissolution testing apparatus Type II (Paddle method). The tablet was placed to the dissolution medium (900 ml) of 0.1 N HCl, and temperature was maintained at 37°C and stirring at 100 rpm. An aliquot of the sample (5 mL) was periodically withdrawn at hourly for 12 h, and the volume was replaced with fresh dissolution medium. The samples were analyzed spectrophotometrically at 237 nm. The cumulative percentage drug release was calculated.[20-23]

Infrared spectra analysis study

FTIR spectrum of pure drug and physical mixture of drug with polymers were obtained on FTIR (Shimadzu 4100) instrument. The tablet of optimized batch was crushed and finely powdered and mixed with potassium bromide (1:100). Then, the spectrum of optimized batch was run. The spectrum was scanned over the wave number range of 4000-400/cm.[24,25]

Differential scanning calorimetric (DSC) study

The DSC analysis was performed for of diltiazem hydrochloride (DTZ), HPMC K100M, sodium CMC, physical mixture, optimized batch (F6) using SDT 2960 TA instrument, USA. Samples were heated in a hermetically sealed aluminum pan, heating rate of 10°C/min in the range 20°C-350°C, at a nitrogen flow of 20 mL/min.[25-30]

Stability study

The optimized batch of 6 tablets was individually wrapped using aluminum foil and packed in amber color screw cap bottle and kept at specified conditions of 40°C/75% RH for the period of 3 months. The remaining parameters were kept same as in dissolution study, and dissolution profile was analyzed after 3 months.[31,32]

RESULTS AND DISCUSSION

The sample of diltiazem hydrochloride was crystalline powder having off white to white color, odorless, and bitter in taste. The melting point was observed in the range of 210°C-212°C. The standard solution of diltiazem hydrochloride was scanned through 200-400 nm region on Jasco V-530 UV spectrophotometer. The diltiazem hydrochloride absorption maximum was found to be 237 nm.

The FTIR spectrum shows all prominent peaks of drug DTZ. IR spectrum of pure drug was found to be similar to that of the standard spectrum of DTZ. It showed characteristics peaks belonging to measure functional groups such as principle peaks at wave numbers 2389.37/cm, 1746.23/cm, 1213.97/cm, 1057.76/cm and 843.70/cm. The major IR peaks observed in DTZ were 2389.37 (2100-2600) (C=C), 1746.23 (1680-1760) (C=O), 1213.97 (1180-1360) (O-H), 1057.76 (1000-1300) (C-O), 843.70 (600-1500) (C-H).

The major IR peaks of HPMC K100 M were observed, 3431.71 (3300-3500) (N-H), 2886.92 (2850-3000) (C-H), 1451.17 (1430 - 1470) -CH3, 1075.12 (1000-1300) (C-O) cm^{-1}.

The major IR peaks of sodium CMC were observed, 3442.31 (3300-3500) (N-H), 2887.88 (2500-3000) (O-H) and 1641.13 (1620-1680) (C=C) cm^{-1}.

The FTIR spectra of physical mixture of polymers HPMC K100M and sodium CMC and DTZ (1:1:1) was studied. The major IR peaks observed in matrices were 3460.63 (3300-3500) (N-H), 2938.98 (2850-2960) (C-H), 1742.37 (1680-1760) (C=O), 1678.73 (1620-1680) (C=C), 1055.84 (1000-1300) (C-O) concluding no significant change of behavior in the physical mixture of DTZ and polymers (HPMC K100M and sodium CMC). The FTIR spectrum of DTZ, HPMC K100M, sodium CMC and physical mixture of DTZ and polymers shown in Figures 1-4, respectively.

Formulation design

The swelling properties of HPMC K4M, HPMC E4M, HPMC K100M, and HPMC E15 were studied. The polymers HPMC K4M, HPMC E4M, and HPMC E15 are of low viscosity grades and did not show optimum SI and dosage form integrity up to 12 h. Higher viscous variety of HPMC (Methocel K-100M) shows good swelling properties, and hence, it was selected for formulation. Sodium CMC is also hydrophilic polymer having good swelling behavior. The values of variables in a 3^2 factorial design are indicated in Table 4. The SI study of HPMC K4M, HPMC E4M HPMC K100M, and HPMC E15 is given in Tables 5-8, respectively.

Full factorial design

As per the 3^2 factorial design, the responses of formulation prepared are indicated in Table 4.

The data clearly indicate that the $t_{50\%}$, Q_{12}, Q_6 and SI are strongly dependent on the selected independent variables.

The fitted equation relating the response $t_{50\%}$, Q_{12}, Q_6, and SI to transformed factors are given in Equations 3, 4, 5 and 6, respectively.

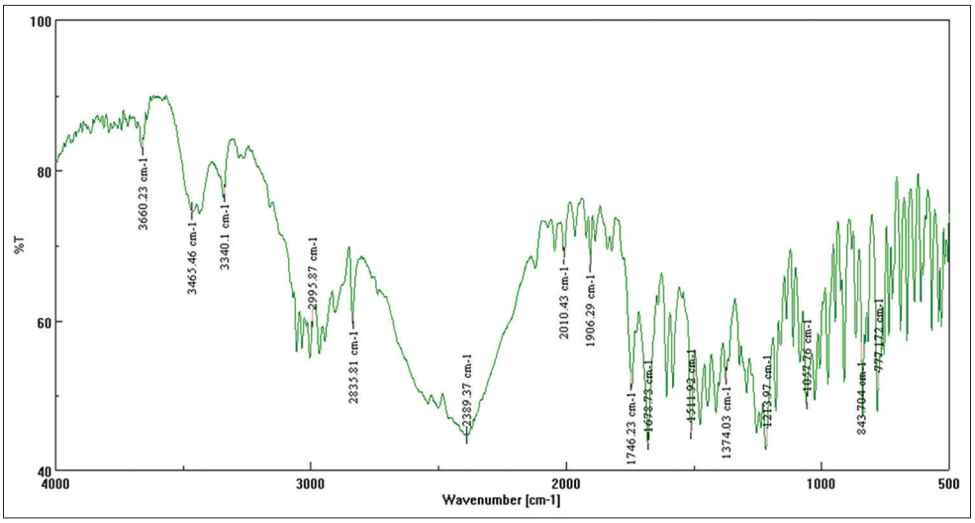


Figure 1: Fourier transform infrared spectral analysis of diltiazem hydrochloride

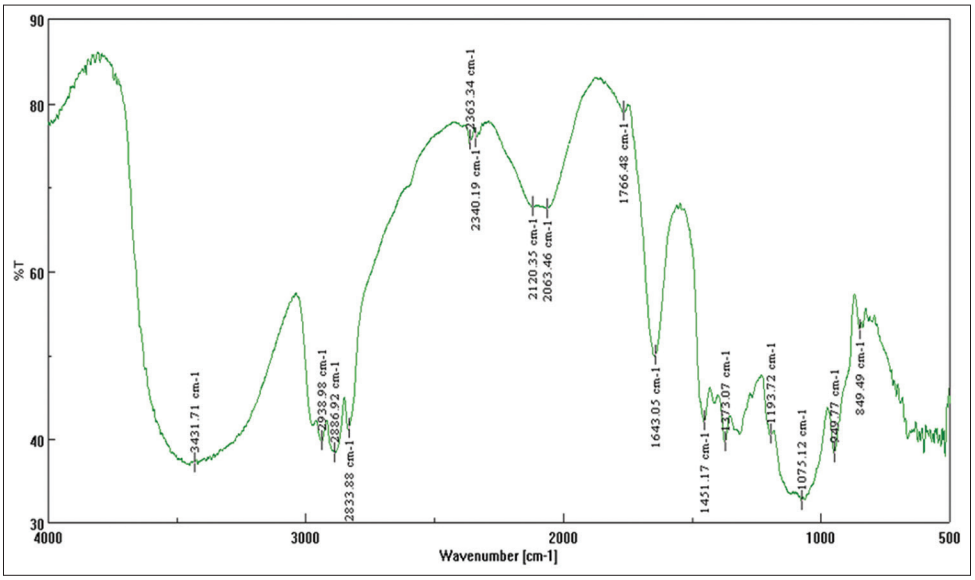


Figure 2: Fourier transform infrared spectral analysis of HPMC K100M

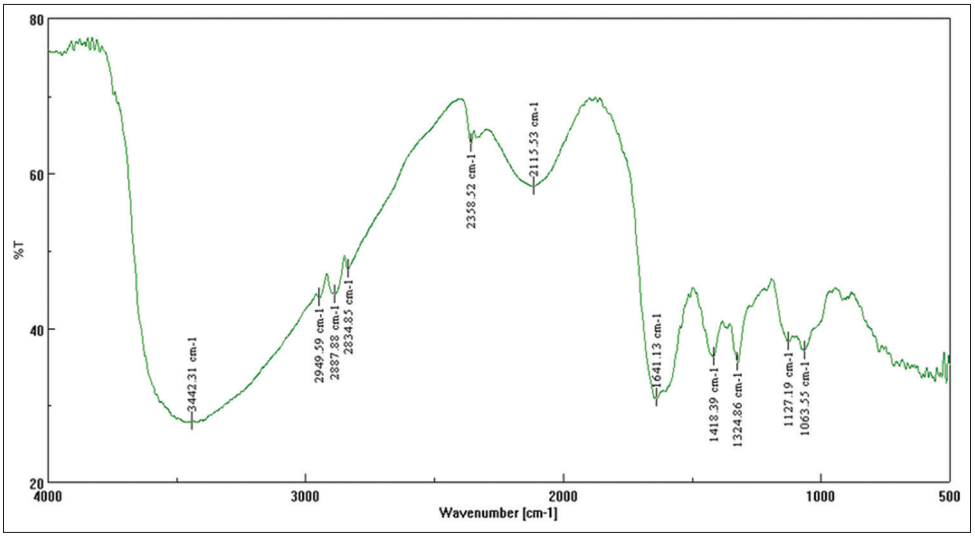


Figure 3: Fourier transform infrared spectral analysis of sodium carboxymethyl cellulose

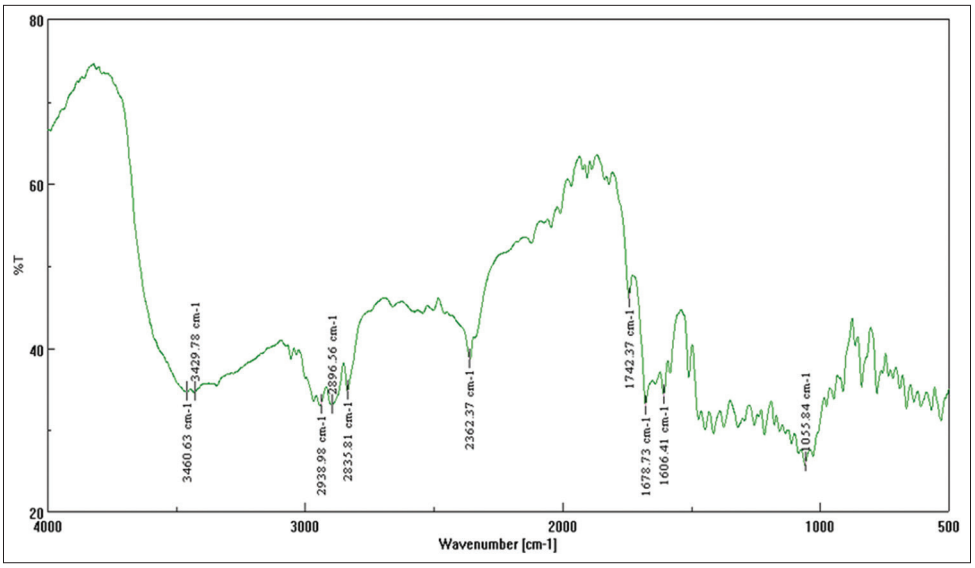


Figure 4: Fourier transform infrared spectral analysis of physical mixture

Table 4: 3^2 factorial designs formulation

Batch code	t_{50}% (min)	% release at 12 h (Q_{12})	% release at 6 h (Q_6)	SI at 6 h (%)
F1	276	83.09	59.98	150.48
F2	288	82.22	57.67	201.11
F3	300	80.95	57.16	189.56
F4	324	76.47	55.23	208.09
F5	336	76.42	53.90	189.67
F6	228	99.31	68.12	208.50
F7	372	71.97	49.79	220.41
F8	348	73.39	53.58	190.91
F9	282	83.59	59.53	181.48

SI: Swelling index

Table 5: Swelling properties of HPMC K4M

Time (h)	SI (%)*	Matrix integrity	Swelling duration (h)
1	45.34±0.19	✓	<5
2	44.30±0.13	✓	<5
3	43.12±0.14	✓	<5

*Indicates average three readings±SD (*n*=3). SI: Swelling index, SD: Standard deviation

Table 6: Swelling properties of HPMC E4M

Time (h)	SI (%)*	Matrix integrity	Swelling duration (h)
1	41.24±0.29	✓	<5
2	41.10±0.03	✓	<5
3	40.12±0.04	✓	<5
4	40.04±0.21	✓	<5
5	39.86±0.13	✓	<5
6	38.76±1.12	✓	<5

*Indicates average three readings±SD (*n*=3). SI: Swelling index, SD: Standard deviation

$$t_{50\%}=333.40+11.30X_1+27X_2-26.70X_1^2-15.60X_2^2+34.20X_1X_2 \quad (3)$$

($R^2=0.8940$)

$$Q_{12}=75.8245+0.4384X_1-5.3033X_2+5.4584X_1^2+3.1833X_2^2-6.8603X_1X_2 \quad (4)$$

($R^2=0.9044$)

$$Q_6=54.1040-0.2795X_1-3.2767X_2+3.3505X_1^2+1.9890X_2^2-4.0130X_1X_2 \quad (5)$$

($R^2=0.8259$)

$$SI\ 6\ h=198.789+18.106X_1+2.5850X_2-4.4305X_1^2-4.5240X_2^2-8.5270X_1X_2 \quad (6)$$

($R^2=0.5654$)

The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative).

The response surface plots of effects of HPMC K100M, sodium CMC on $t_{50\%,}$ Q_{12}, Q_6 and SI at 6 h shown in Figures 5-8, respectively. The plot was drawn using PCP-Disso v 3 software, India. The data demonstrate that both HPMC K100M (X_1) and sodium CMC (X_2) affect the drug release ($t_{50\%}$, $Q_{12,}$ Q_6 and SI). It may also be concluded that the level of X_1 (amount of HPMC K100M) and the level of X_2 (amount of sodium CMC) have the positive effect on $t_{50\%}$. The low levels of X_1 and X_2 favor the release and hence $t_{50\%}$ is less as compared to the high levels of X_1 and X_2. The levels of X_1 show the positive effect on Q_{12}, while the levels of X_2 have negative effect on Q_{12}. Thus, higher amounts of HPMC and lower amounts of sodium CMC favor the drug release. The amounts of X_1 and X_2 show negative effect on Q_6. Hence, it can be concluded that both factors show release retardant effect at 6 h. The amounts of X_1 and X_2 show positive effect on SI. Higher amounts of X_1 and X_2 increase the SI. It can be concluded that the drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels.

Bulk density may influence compressibility, tablet porosity, and dissolution rate depends on the particle size, shape and tendency of particles to adhere together. The bulk density and Carr's index of granules were found to be between 0.3028 ± 0.07 and 0.3551 ± 0.09 g/cm^3 and 10.40 ± 0.04 to 25.46 ± 0.05, respectively. The angle of repose was indicative of the flowability of the material. It was between 25°C and 30°C showing good flowability. This indicates good packing capacity of powder. Adhesive/cohesive forces of particles as they relate to flow behavior by examining normal and shear stresses on powder beds. The values of bulk density, tapped density, Carr's index, and Hausner's ratio were given in Table 9.

Table 7: Swelling properties of HPMC K100M

Time (h)	SI (%)*	Matrix integrity	Swelling duration (h)
1	100.12±0.2	✓	>12
2	114.02±2.18	✓	>12
3	120.25±1.34	✓	>12
4	124.25±1.19	✓	>12
5	128.66±1.24	✓	>12
6	135.72±0.09	✓	>12
7	133.44±2.22	✓	>12
8	130.78±2.12	✓	>12
9	125.54±1.23	✓	>12

*Indicates average three readings±SD (*n*=3). SI: Swelling index, SD: Standard deviation

Table 8: Swelling properties of HPMC E15

Time (h)	SI (%)*	Matrix integrity	Swelling duration (h)
1	30.45±0.12		<4
2	30.30±0.23		<4
3	29.12±0.21		<4
4	28.13±0.45		<4
5	23.46±0.56		<4

*Indicates average three readings±SD (*n*=3). SI: Swelling index, SD: Standard deviation

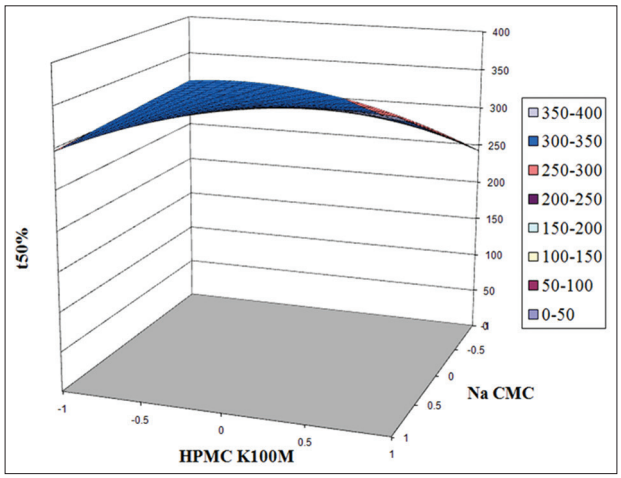


Figure 5: Response surface plot for $t_{50\%}$

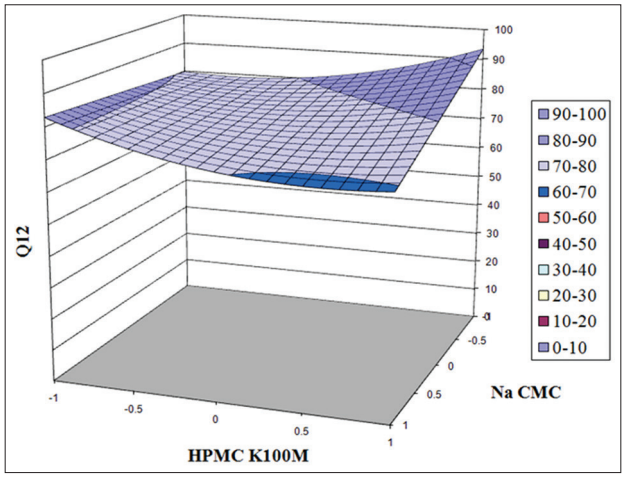


Figure 6: Response surface plot for Q_{12}

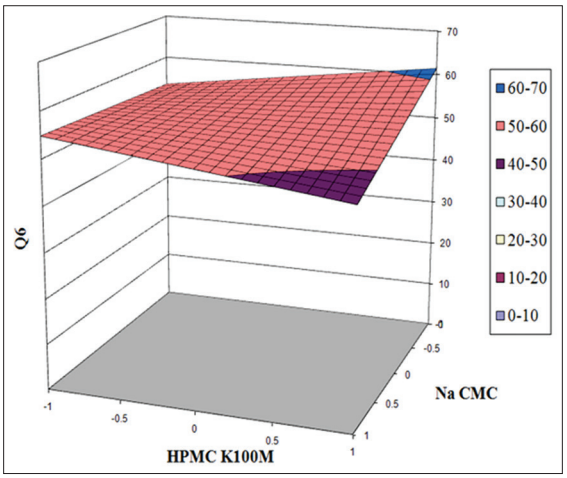


Figure 7: Response surface plot for Q_6

All the formulations of tablet batches F1-F9 were evaluated with average weight, thickness, diameter, hardness, friability and drug content. Thickness and diameter of tablets were found to be in the range of 4.03 ± 0.07 to 5.75 ± 0.07 mm and 13.01 ± 0.01 and 13.10 ± 0.05 mm, respectively. The hardness and friability were found to be in the range of 5 ± 0.14 to 5 ± 0.42 kg/cm^2 and 0.0011 ± 0.05 to 0.0024 ± 0.02%, respectively. The average weight of tablets was within limit, and drug content was in the range of 96.61 ± 0.14 to 99.44 ± 0.12%. The prepared formulation results were shown in Table 10.

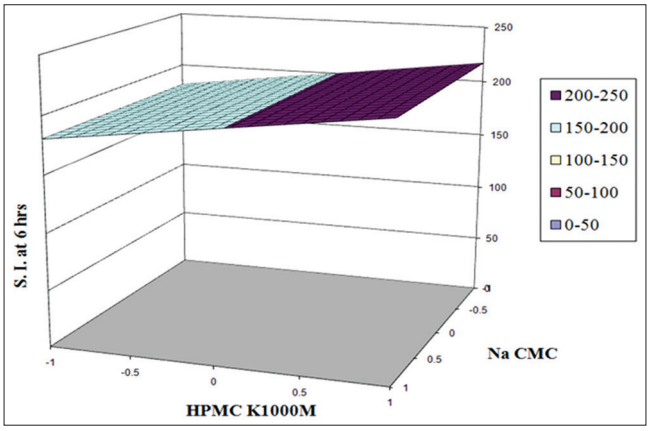


Figure 8: Response surface plot for swelling index at 6 h

Selection of optimized batch

The formulation was optimized on the basis of SI, matrix integrity and *in vitro* drug release. The phenomenon of swelling resulted in the retardation or slows the drug release. The batch F6 fulfilled all these requirements. For optimized batch F6, SI was 114.21% at 1 h and 220.41% at the end of 6 h, which indicated that the tablet showed good swelling behavior, which could be useful to retain tablet in the upper GI tract and it would not be able to pass through the pylorus (diameter 1.2-1.4 cm). *In vitro* drug release study of DTZ expandable tablets indicated sustained release for 12 h. The percentage release of optimized batch was found to be 15.60% at 1 h and 71.97 % at 12 h. Hence, batch F6 was selected as optimized batch considering slow release and high SI.

Swelling properties

The *in vitro* swelling study was showed that all batches had good swelling properties. The SI of all batches given in

Table 9: Evaluation of granules properties

Batch code	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Carr's index (I_C)*	Hausners ratio (H_R)*	Angle of repose (θ)*
F1	0.331±0.01	0.424±0.02	21.97±0.03	1.28±0.02	19.20±0.12
F2	0.316±0.01	0.352±0.05	10.40±0.04	1.12±0.03	19.76±0.14
F3	0.323±0.01	0.365±0.07	11.48±0.04	1.13±0.03	18.36±0.18
F4	0.302±0.07	0.406±0.09	25.46±0.05	1.34±0.08	16.67±0.13
F5	0.330±0.07	0.423±0.01	22.00±0.03	1.28±0.05	17.08±0.17
F6	0.321±0.03	0.398±0.04	19.32±0.02	1.24±0.02	21.96±0.12
F7	0.355±0.09	0.412±0.08	13.87±0.07	1.16±0.07	16.09±0.08
F8	0.352±0.02	0.434±0.05	18.91±0.03	1.23±0.03	18.36±0.14
F9	0.341±0.01	0.442±0.04	22.72±0.03	1.29±0.04	20.26±0.15

*All readings are average±SD (*n*=3). SI: Swelling index, SD: Standard deviation

Table 10: Evaluation of tablet properties

Batch code	Average wt. (mg)*	Thickness (mm)*	Diameter (mm)*	Hardness (kg/cm^2)*	Friability (%)*	Drug content (%)*
F1	489.45	4.83±0.02	13.02±0.04	5±0.14	0.0017±0.02	97.65±0.03
F2	516.15	4.18±0.02	13.01±0.01	5±0.38	0.0013±0.05	96.61±0.14
F3	542.58	4.03±0.07	13.05±0.03	5±0.21	0.0020±0.04	98.71±0.02
F4	512.80	4.18±0.01	13.10±0.05	5±0.32	0.0024±0.02	97.01±0.11
F5	543.45	4.90±0.04	13.04±0.01	5±0.25	0.0022±0.06	97.47±0.10
F6	568.82	5.06±0.02	13.03±0.08	5±0.33	0.0012±0.01	99.44±0.12
F7	543.34	5.75±0.07	13.10±0.03	5±0.28	0.0011±0.05	98.36±0.14
F8	567.20	4.88±0.04	13.02±0.03	5±0.42	0.0018±0.07	97.73±0.13
F9	592.10	5.30±0.05	13.01±0.07	5±0.23	0.0013±0.03	98.28±0.10

*All readings are average±SD (*n*=3). SI: Swelling index, SD: Standard deviation

Figure 9, and all batches were sufficient to retain the tablet in the stomach. For optimized batch (F6), SI was 114.21% at 1 h and 220.41% at the end of 6 h.

The integrity and swelling duration properties are given in Table 11. The water molecules enter the matrix and cause hydration of polymer to form gel. The water was trapped within the gel thus increasing the size of the tablet. The density of the tablet increases and tablet remains in stomach and does not pass through the pylorus. The results revealed that HPMC K100M and sodium CMC produced tablets with good gel strength showing stable and persistent swelling. The Photograph 1 shows *in vitro* swelling study of optimized batch (F6).

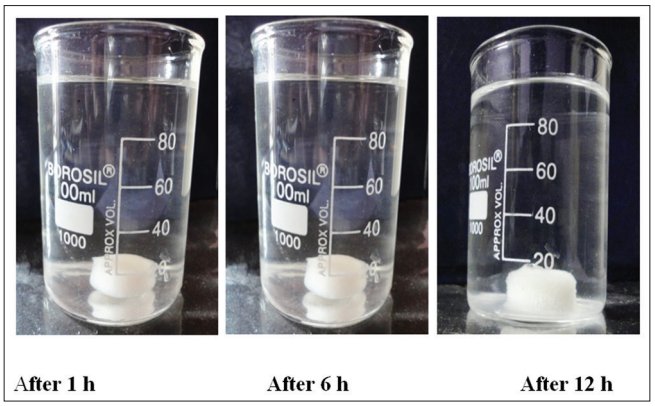
All the factorial design batches were showed good *in vitro* expansion. The tablets showed good integrity for 12 h. *In vitro* expansion study of the optimized batch (F6) showed that tablet had achieved good SI at 6 h and 12 h.

In vitro drug release study

In vitro drug release study of DTZ expandable tablets was indicated sustained release for 12 h. It was observed that all the tablets achieved good expansion within 1st h and remained swelled, until the complete of release studies. The release was affected by the swelling behavior of the tablet. The drug release study was carried out up to 12 h and results are shown in Figure 10.

The cumulative percentage drug release of batches F1-F9 was in the range of 71.97-99.31% for 12 h. The percentage release of optimized batch was found to be 15.60% at 1 h and 71.97% at 12 h. Large concentrations of hydrophilic polymers swell in the presence of water. These polymers form porous structures on the surface of tablet matrix and form strong viscous gel layer, which slow down the water diffusion. The phenomenon of swelling resulted in the slow the drug release. The optimized batch (F6) showed 71.97 ± 0.07 % for 12 h, which shows sustained release pattern and SI found to 183.90% in 12 h.

The value of exponent n can be used to characterize the release mechanism of controlled release matrix tablet. The mean diffusional exponent values (n) ranged from 0.5653 to 0.6573 indicating that formulations were presented of dissolution behavior, controlled by anomolous transport. The kinetic constant (k) ranged from 16.01 to 20.7 indicating that DTZ release from hydrophilic binder matrices followed super case II transport. The release kinetics for Korsmeyer-Peppas Model batch F1-F9 shown in Table 12 and various kinetic data of expandable tablet of DTZ shown in Table 13.



Photograph 1: *In vitro* swelling study of F6 batch

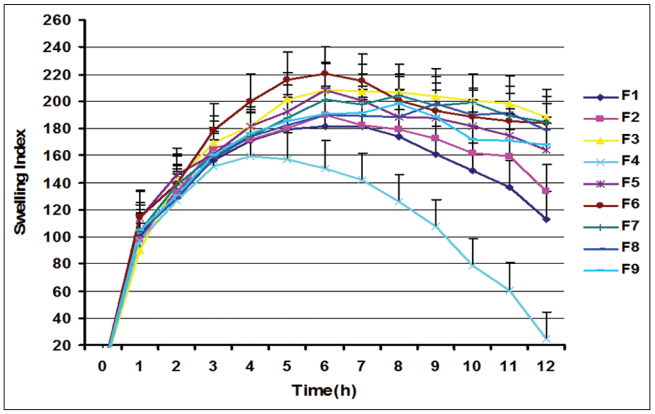


Figure 9: Swelling Index of batch F1-F9

Table 11: Expansion/swelling properties of DTZ tablets

Batch code	Matrix integrity	Swelling duration (h)	Average diameter at 1 h (cm)*	Average diameter at 6 h (cm)*
F1	✓	>12	15.30±0.09	15.30±0.12
F2	✓	>12	15.20±0.13	15.10±0.14
F3	✓	>12	14.10±0.14	15.60±0.03
F4	✓	>12	15.20±0.21	15.10±0.05
F5	✓	>12	15.60±0.03	15.70±0.12
F6	✓	>12	15.80±0.12	15.90±0.02
F7	✓	>12	15.50±0.13	15.40±0.13
F8	✓	>12	15.30±0.01	15.30±0.09
F9	✓	>12	15.40±0.14	15.40±0.15

*All readings are average±SD (*n*=3). DTZ: Diltiazem hydrochloride, SD: Standard deviation

FTIR spectra analysis

FTIR spectra analysis of optimized batch, the spectrum shows all prominent peaks. FTIR spectra analysis of optimized batch was shown in Figure 11. The major IR peaks observed in optimized formulation were 2390.33 (3300-2500) (O-H), 1744.3 (C=O), 1677.77 (1680-1760) (C=C), 1214.93 (C-N), 1058.73 (1000-1300) (C-O) cm^{-1}. All principle peaks of drug were observed, and thus it confirmed the stability of drug in the formulation.

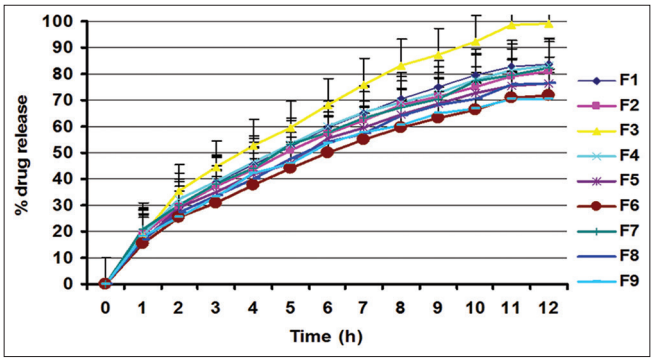


Figure 10: *In vitro* drug release of batch F1-F9

DSC study

DSC thermogram of DTZ shows endothermic peak at 214.78°C. Whereas HPMC K100M and sodium CMC shows melting endodermic peak at 52.10°C and 51.21°C. While optimized batch shows the endothermic peak at 201.89°C. Thermogram of physical mixture showed almost the same peaks at 52.10°C and 208.08°C with some reduced peak for DTZ, indicating reduction in crystallinity of DTZ. In the optimized batch thermogram, it was found that transition had shifted to slightly lower temperature at 201.89°C. DSC study showed that there was a significant reduction in the thermal transitions of drug in the optimized batch, indicating reduction of crystallinity in the formulation. It may be due to dilution effect of the polymers. The overlain DSC thermogram of DTZ, physical mixture, sodium CMC, HPMC is shown in Figure 12.

Stability studies

The stability study results reveal that after 3 months showed the percentage drug release of optimized batch (F6) was 15.58% and 71.47% at 1 h and 12 h, respectively. There was no change in physical appearance in the optimized batch of

Table 12: Release kinetics for Korsmeyer-Peppas model batch F1-F9

Batch code	N	k	R
F1	0.6166	19.1965	0.9985
F2	0.5912	19.4026	0.9991
F3	0.6573	20.7117	0.9954
F4	0.5836	20.4498	0.9975
F5	0.6121	17.7294	0.9963
F6	0.6221	16.0140	0.9988
F7	0.5653	20.6569	0.9990
F8	0.6189	17.2360	0.9987
F9	0.5829	17.8917	0.9969

Table 13: Kinetic data of expandable tablet of DTZ

Batch code	Zero order (R)	First order (R)	Matrix model (R)	Peppas model	Hix-Crowel model (R)
F1	0.9237	0.9981	0.9937	0.9985	0.9911
F2	0.9163	0.9978	0.9957	0.9991	0.9868
F3	0.9356	0.9007	0.9910	0.9954	0.9830
F4	0.9033	0.9975	0.9968	0.9975	0.9849
F5	0.9202	0.9955	0.9935	0.9963	0.9831
F6	0.9323	0.9958	0.9927	0.9988	0.9844
F7	0.9085	0.9963	0.9968	0.9990	0.9853
F8	0.9303	0.9966	0.9927	0.9987	0.9870
F9	0.9056	0.9903	0.9955	0.9969	0.9731

DTZ: Diltiazem hydrochloride

tablet. There was no significant change in the drug release after 3 months indicating the stability of the formulation. The results of stability study after 3 months were given in Table 14.

CONCLUSION

This study was to formulation of expandable tablets using a 3^2 full factorial design. From the dissolution study, the results reveal that increase in the concentration of hydrophilic polymers causes slow the drug release. For the sustained release of the drug, optimum levels of concentrations of polymers are required. DTZ release from hydrophilic matrices indicated Super case II transport. For optimized batch (F6), SI was 114.21% at 1 h and 220.41% at the end of 6 h, which indicated that the tablet showed good swelling behavior. The percentage release of optimized batch was found to be 15.60% at 1 h and it was 71.97% at 12 h. Hence, batch F6 was selected as optimized batch considering slow release and

Table 14: Cumulative % drug release and SI of optimized batch

Time (h)	Cumulative % drug release (initial)*	Cumulative % drug release (After 3 months)*	SI (initial)*	SI (after 3 months)*
0	0.00	0.00	0.00	0.00
1	15.60±0.06	15.58±0.02	114.21±0.02	114.01±0.12
2	25.43±0.04	25.13±0.03	139.20±0.06	138.25±0.16
3	31.12±0.01	30.12±0.06	178.30±0.23	178.10±0.13
4	37.58±0.03	37.48±0.13	200.10±0.34	198.11±0.24
5	44.28±0.04	44.28±0.04	216.12±0.12	215.10±0.32
6	49.79±0.05	48.79±0.21	220.41±0.11	219.31±0.01
7	54.81±0.09	54.11±0.33	215.21±0.31	214.20±0.21
8	59.76±0.02	58.76±0.62	200.58±0.15	199.78±0.45
9	63.03±0.04	62.60±0.01	193.21±0.42	192.11±0.22
10	66.46±0.03	66.15±0.07	188.20±0.12	187.20±0.12
11	70.73±0.04	70.33±0.04	185.62±0.23	185.10±0.33
12	71.97±0.07	71.47±0.07	183.90±0.01	183.11±0.05

*All readings are average±SD (n=3). SI: Swelling index, SD: Standard deviation

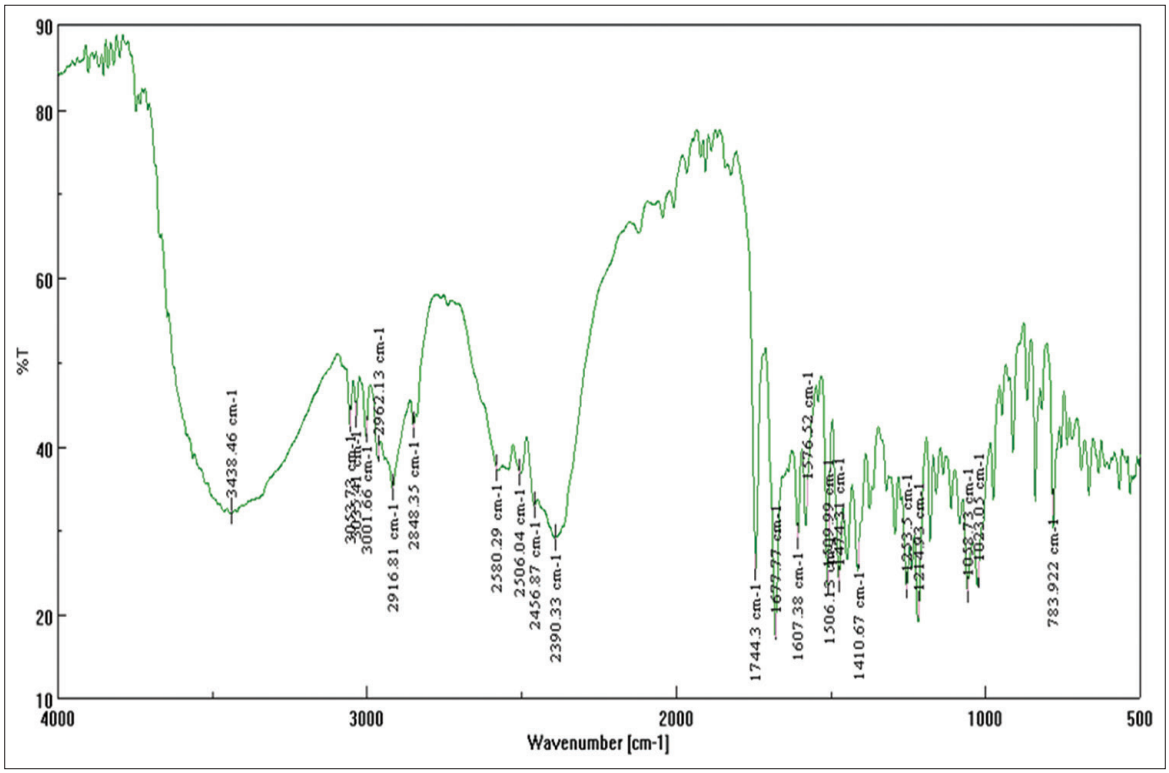


Figure 11: Fourier transform infrared spectral analysis of optimized batch

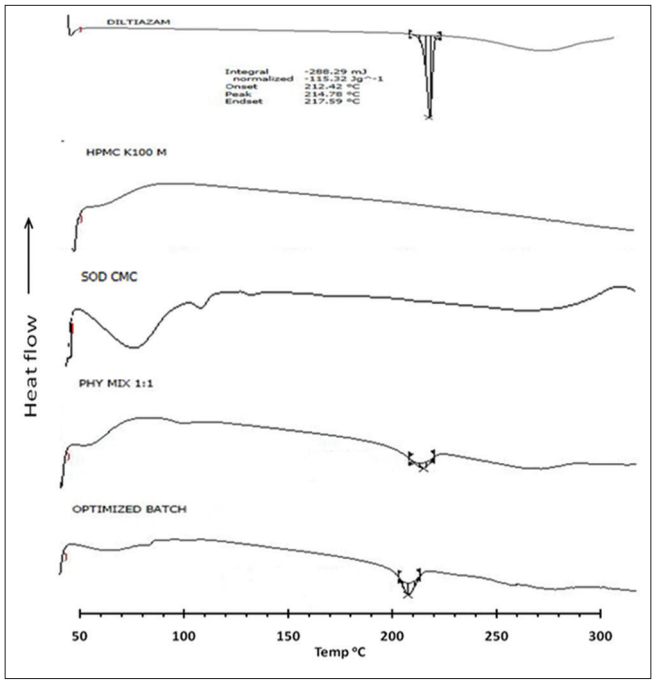


Figure 12: Differential scanning calorimetric overlain of diltiazem hydrochloride, HPMC K100M, sodium carboxymethyl cellulose, physical mixture, optimized batch (F6)

high SI. It was concluded that the development of expandable gastroretentive, once a day sustained release tablet of DTZ can be beneficial in the treatment of hypertension. It releases drug in sustained manner for an extended period of time.

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