Original Research Article

Conceptuation, formulation and evaluation of sustained release floating tablets of captopril compression coated with gastric dispersible hydrochlorothiazide using 2^3 factorial design

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Abstract

Ambulatory blood pressure monitoring is regarded as the gold standard for hypertensive therapy in non-dipping hypertension patients. A novel compression coated formulation of captopril and hydrochlorothiazide (HCTZ) was developed in order to improve the efficacy of antihypertensive therapy considering the half-life of both drugs. The synergistic action using combination therapy can be effectively achieved by sustained release captopril ($t_{1/2} = 2.5$ h) and fast releasing HCTZ (average $t_{1/2} = 9.5$ h). The sustained release floating tablets of captopril were prepared by using 2^3 factorial design by employing three polymers i.e., ethyl cellulose (EC), carbopol and xanthan gum at two levels. The formulations (CF_1-CF_8) were optimized using analysis of variance for two response variables, buoyancy and $T_{50\%}$. Among the three polymers employed, the coefficients and P values for the response variable buoyancy and $T_{50\%}$ using EC were found to be 3.824, 0.028 and 0.0196, 0.046 respectively. From the coefficients and P values for the two response variables, formulation CF_2 was optimized, which contains EC polymer alone at a high level. The CF_2 formulation was further compression coated with optimized gastric dispersible HCTZ layer (HF_9). The compression coated tablet was further evaluated using drug release kinetics. The Q value of HCTZ layer is achieved within 20 min following first order release whereas the Q value of captopril was obtained at 6.5 h following Higuchi model, from which it is proved that rapid release HCTZ and slow release of captopril is achieved. The mechanism of drug release was analyzed using Peppas equation, which showed an $n > 0.90$ confirming case II transportation mechanism for drug release.

Key words: Ambulatory blood pressure monitoring, analysis of variance, compression coating, ethyl cellulose, floating drug delivery, non-dipping

RESEARCH BACKGROUND

For effective treatment of hypertension combination therapy is mostly prescribed by doctors. Among the drugs that are given in combination hydrochlorothiazide (HCTZ) is used as front line combination drug and it is highly compatible with angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. Most of the ACE inhibitors such as captopril, ramipril and enalapril possess short biological half-life (2-4 h.) whereas HCTZ possesses a biological half-life of 9-14 h. Due to variability in half-lives of drugs the synergistic action of combinational therapy is not achieved.

Considering various types of hypertensive patients as per American Heart Association, ineffective combination therapy could lead to long-term renal and cardiac damages. Therefore, in case of non-dipping patients it is highly essential to maintain drug concentration throughout 24 h. cycle irrespective of circadian pattern.

INTRODUCTION

Appropriate assessment of clinical blood pressure (CBP) level is the premise for risk stratification and adequate therapeutic strategy with regard to hypertension. CBP is usually just performed in the daytime. CBP is rarely performed

at night-time in the hospital ward, unless there are acute or severe conditions thereby providing poor information about non-dippers. Many evidences have proved that non-dippers are more favorable in predicting the mortality and morbidity related to dippers.[1,2] Therefore, nocturnal BP should be taken seriously in the hospital setting for every patient, especially for those with abnormal BP. Ambulatory blood pressure monitoring is regarded as the gold standard for monitoring nocturnal BP. According to many suggestions from various clinical trials, 75% of patients will require combination therapy for effective control of blood pressure. As per the seventh report of Joint National Committee guidelines, combination therapy is suggested as first line treatment for patients with >20 mmHg systolic and >10 mmHg diastolic BP respectively.[3] Combination therapy increases the rate of BP control and requires less time to reach target BP with better tolerability than high dose therapy. It has fewer side-effects, better patient compliance and low in cost.[4,5]

Captopril ([2S]-1-([2S]-2-methyl-3-sulfanylpropanoyl) pyrrolidine-2-carboxylic acid) is an ACE inhibitor. It affects the rennin-angiotensin system, thereby inhibits the conversion of angiotensin I to angiotensin II. The drug is considered as a drug of choice for the treatment of hypertension[6] and congestive heart failure.[7] The bioavailability of captopril is approximately 60-75% and it has elimination half-life after an oral dose is 2-3 h. It is stable at acidic pH (1.2) and is specifically absorbed from the stomach. As the pH increases, the drug becomes unstable and undergoes a pseudo first order degradation reaction.[8,9] The drug is susceptible to produce stability problems.[10] In aqueous solutions due to degradation reaction. The drug being freely water soluble suffers from burst effect and also from dose dumping phenomenon when formulated as sustained or controlled formulation. There is a strong prerequisite to localize the developed captopril formulation at the target area of the gastrointestinal tract.[11] To overcome the above drawbacks the present study is aimed at developing a floating dosage form to be remained buoyant in the stomach, thereby, increasing the gastric residence time, stability, patient's compliance and enhancing the bioavailability of drug through sustained release.

HCTZ is a thiazide diuretic. It is used in the management of edema and in patients with lower the blood pressure. It inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. HCTZ is poorly water soluble drug having plasma half-life of 6-14 h.[12] HCTZ is only absorbed from the upper part of the duodenum and once it passes this absorption site, little or no absorption takes place.[13] Since the half-life of captopril is very short, the combination of HCTZ which is having a long half-life will render synergistic effect on anti-hypertensive action.

The present study is aimed at formulation of floating captopril tablets compression coated with gastric dispersible HCTZ layer. The pictorial representation of mechanism of floating of optimized compression coated tablets was shown in Figure 1. In this study, the effort has been made to formulate captopril floating core tablets by using a single polymer, which has a dual action with better release profile of drug and enhancement in buoyancy rate. Screening of polymers has been done to obtain the optimized formulation.

MATERIALS AND METHODS

Captopril and HCTZ were obtained as a gift sample from Dr. Reddy's Laboratories. Ethyl cellulose (EC) was received from Indian research products. Xanthan gum and carbopol were gifted from Loba Chemie Pvt. Ltd. Lactose was obtained from Chem India. All the other solvents used were of pharmaceutical or analytical grade. Sodium starch glycolate (SSG), croscarmellose sodium and crospovidone were obtained from the Signet Chemicals, Mumbai. All the other solvents used were of pharmaceutical or analytical grade.

EXPERIMENTAL

Preparation of floating captopril core tablets using 2^3 factorial design

The screening of polymers for optimization of captopril core tablets was carried out by 2^3 factorial designs. The three factors each at two levels, i.e., actual values and coded values were considered as shown in [Table 1]. EC is considered as Factor A', Xanthan gum and carbopol were considered as Factor B and C respectively. "Factor C" was taken as polymer carbopol. A total

Table 1: 2^3 factorial design considered for screening of polymers

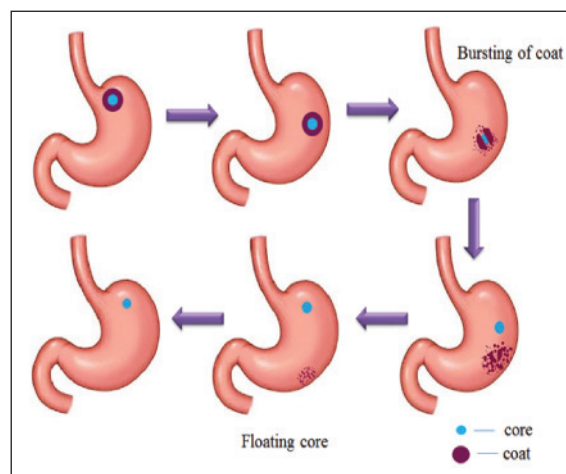| Factors	Low level (mg)	High level (mg)
Ethyl cellulose (A)	60	130
Xanthan gum (B)	0	5
Carbopol (C)	0	10

Figure 1: Pictorial representation of mechanism of floating of compression coated tablet

of eight formulations were obtained according to the model ($2^3 = 2 \times 2 \times 2 = 8$).

Floating tablets containing captopril were prepared by direct compression technique using various polymers. In all formulations, lactose is used as a diluent and talc as a glidant. The composition of various formulations of captopril floating tablets is given in the [Table 2]. All the ingredients along with the drug were weighed accurately, mixed thoroughly and passed through sieve #60 before processing. Sifting was carried out after addition of each ingredient to ensure uniform mixing. The resultant blend was subjected to direct compression using Elite 10 station rotary tablet compression machine containing round biconcave punches. The prepared tablets of captopril were subjected to various evaluation tests.

Evaluation of floating captopril core tablet formulations

Powder blend of captopril formulations was evaluated for various pre-compression parameters such as Bulk Density, Tapped Density, Compressibility index, Hausner's ratio and Angle of repose. The results for all the captopril formulations were shown in [Table 3].

The prepared captopril tablets were subjected to various evaluation tests such as weight variation, hardness and friability tests. The results of all these post-compression characteristics of captopril were shown in [Table 4]. Test for buoyancy was carried out and the results were shown in [Table 5 and Figure 2].

In vitro drug release study

The *in vitro* drug release study was performed for the formulation and pure drugs using USP type II dissolution apparatus (paddle type). The samples were withdrawn at regular intervals and are analyzed using ultraviolet (UV) spectrophotometric method at 204.6 nm. The results were shown in [Table 6]. The zero order drug release profiles of all formulations were shown in [Figure 3].

OPTIMIZATION OF 2^3 FACTORIAL DESIGN BY STATISTICAL ANALYSIS

Multiple regression is a statistical technique that allows us to predict the effect of independent factor on dependent formulation response variables. In 2^3 factorial design, an analysis of variance (ANOVA) was performed for the situation where there are three independent variables, EC (A), Xanthan gum (B) and Carbopol (C), each with two levels (low and high). This design will have $2^3 = 8$ different experimental conditions. Buoyancy and time required for 50% of drug release were considered as the dependent response variables. After performing 8 runs of formulations, the data obtained for the response variable in all runs was subjected to multiple regression analysis using Microsoft excel 2007 software for statistical assessment. The regression statistics of ANOVA for first response variable, buoyancy are given in [Tables 7 and 8] and that of the second response variable, $T_{50\%}$ are given in [Tables 9 and 10] and line fit plots were shown in [Figures 4 and 5] respectively.

FORMULATION OF HCTZ COAT LAYER

The formulations were prepared using various disintegrants such as SSG, crospovidone and croscarmellose sodium. Pregelatinized starch was added a dry binder. Magnesium stearate was used as a lubricant. Talc was included as a glidant in the formulation. The composition of various formulations containing HCTZ is given in the [Table 11].

Evaluation of HCTZ coat tablet formulations

Powder blend of HCTZ formulations was evaluated for various pre-compression parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and Angle of repose. The results for all the HCTZ formulations were shown in [Table 12].

Table 2: Composition of captopril floating tablets based on 2^3 factorial design

Ingredients	$CF_{1 (mg)}$	$CF_{2 (mg)}$	$CF_{3 (mg)}$	$CF_{4 (mg)}$	$CF_{5 (mg)}$	$CF_{6 (mg)}$	$CF_{7 (mg)}$	$CF_{8 (mg)}$
Drug	30	30	30	30	30	30	30	30
Ethyl cellulose	60	130	60	130	60	130	60	130
Xanthan gum	—	—	5	5	—	—	5	5
Carbopol	—	—	—	—	10	10	10	10
Lactose	100	30	95	25	90	20	85	15
Talc	5	5	5	5	5	5	5	5

Table 3: Evaluation of pre-compression characteristics of captopril formulations

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
CF_1	0.175	0.243	27.98	1.39	43.08
CF_2	0.166	0.178	13.74	1.07	26.78
CF_3	0.336	0.453	25.82	1.35	35.36
CF_4	0.171	0.189	16.52	1.11	29.59
CF_5	0.348	0.508	31.49	1.46	40.96
CF_6	0.175	0.206	18.27	1.18	31.85
CF_7	0.169	0.213	20.65	1.26	47.86
CF_8	0.169	0.209	19.13	1.24	32.84

The prepared HCTZ tablets were subjected to various evaluation tests such as weight variation, hardness, friability, disintegration, wetting tests. The results of all these post-compression

characteristics of captopril were shown in [Table 13]. Comparison of disintegration time of various HCTZ formulations was shown in [Figure 6].

In vitro drug release study

The *in vitro* drug release study was performed for the formulation and pure drugs using USP type II dissolution apparatus (paddle type). The samples were withdrawn at regular intervals and are analyzed using UV spectrophotometric method at 217.6 nm. The results were shown in [Table 14].

The zero order plot of all HCTZ formulations was shown in [Figure 7].

FORMULATION OF COMPRESSION COATED TABLETS

The optimized formulations of captopril core and HCTZ coat layers were chosen for formulation of compression coated tablet. The required weight of the captopril powder blend mixed with all other ingredients (195 mg) was weighed and transferred into small die and compressed as core tablets. In the second step, a slightly larger die of 13 mm diameter was partially filled with half of the HCTZ coat material (275.5 mg) and then captopril core tablet was manually
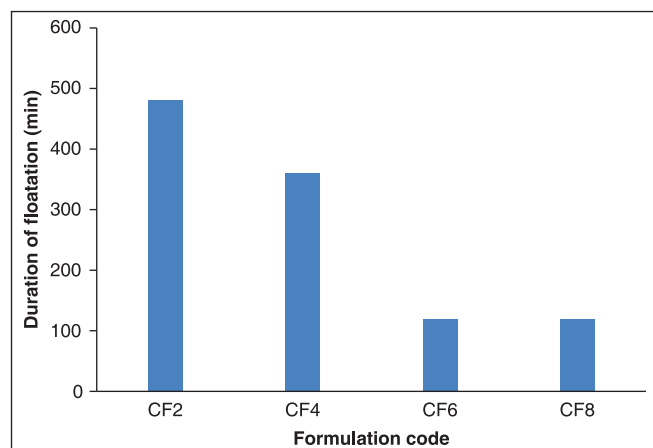
Table 4: Evaluation of post-compression characteristics of captopril formulations

Formulation code	Weight variation (mg) ($n = 20$)	Friability (%) ($n = 10$)	Hardness (kg/cm^2) ($n = 6$)
CF$_1$	195±0.298	1.03	3.0
CF$_2$	195±0.231	0.98	3.0
CF$_3$	195±0.339	1.12	2.5
CF$_4$	195±0.287	1.07	2.1
CF$_5$	195±0.456	1.32	1.8
CF$_6$	195±0.783	1.01	2.9
CF$_7$	195±0.247	0.98	2.9
CF$_8$	195±0.334	1.05	2.7

Table 5: Duration of floatation for various captopril formulations

Formulations	Floating time
CF$_1$	59 s
CF$_2$	>8 h
CF$_3$	1 min 20 s
CF$_4$	6 h, disintegrated
CF$_5$	55 s
CF$_6$	2 h
CF$_7$	6 min
CF$_8$	2 h

Table 6: *In vitro* drug release data of captopril formulations

Time (h)	% drug release of formulations							
	CF$_1$	CF$_2$	CF$_3$	CF$_4$	CF$_5$	CF$_6$	CF$_7$	CF$_8$
0.25	15.48±1.32	8.451±1.77	11.34±1.34	14.85±1.63	14.98±1.41	11.67±1.37	15.76±1.35	15.26±1.36
0.5	23.92±1.81	12.26±1.97	16.87±1.73	19.03±1.95	26.75±1.38	19.45±1.29	21.69±1.76	22.46±1.67
1	30.14±1.45	19.92±1.94	23.10±1.29	28.46±1.56	38.69±1.82	28.04±1.82	36.90±1.90	31.73±0.103
2	49.56±1.73	28.54±1.76	39.05±1.31	36.21±1.73	48.92±1.24	41.46±1.39	48.93±1.43	40.74±1.27
3	62.53±1.67	36.17±161	49.87±1.87	44.05±1.89	56.39±1.73	52.69±1.68	55.35±1.75	49.38±1.83
4	81.90±1.28	45.43±1.94	54.78±1.58	62.60±1.68	61.18±1.96	61.48±1.49	62.86±1.96	54.67±1.24
5	86.34±1.21	61.26±1.99	59.64±1.46	79.48±1.61	67.67±1.21	70.27±1.46	69.47±1.31	65.08±1.62
6	—	74.41±1.83	65.08±1.93	89.97±1.83	71.47±1.03	75.36±1.32	75.73±1.37	72.92±1.59
7	—	90.37±1.84	73.36±1.82	—	75.68±1.74	78.45±1.78	79.98±1.87	79.56±1.92
8		97.42±1.45	77.34±1.68	—	77.02±1.87	84.42±1.94	81.87±1.62	82.36±1.71

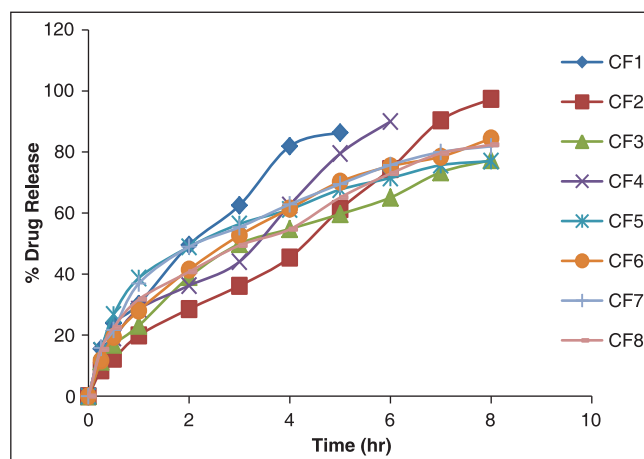**Figure 2:** Comparison of floating times of various formulations

Figure 3: Zero order plot of captopril formulations

Table 7: Estimation of significance factor of analysis of variance for response of buoyancy

Source	df	SS	MS	F	Significance F
Regression	3	189256.8	63085.61	4.920105	0.078916
Residual	4	51288.02	12822.01		
Total	7	240544.9			

Table 8: Estimation of regression coefficient of analysis of variance for response of buoyancy

Factor	Coefficients	Standard error	P value
Intercept	1.571429	0.779398	0.113989
Ethyl cellulose	0.019643	0.006916	0.046859
Xanthan gum	−0.025	0.096825	0.808994
Carbopol	−0.0875	0.048412	0.144986

Table 9: Estimation of significance factor of analysis of variance for response of T$_{50\%}$

Source	df	SS	MS	F	Significance F
Regression	3	5.34375	1.78125	3.8	0.114947
Residual	4	1.875	0.46875		
Total	7	7.21875			

Table 10: Estimation of regression coefficient of analysis of variance for response of T$_{50\%}$

Factor	Coefficients	Standard error	P value
Intercept	−138.407	128.9041	0.343405
Ethyl cellulose	3.824286	1.143839	0.028745
Xanthan gum	−5.74	16.01375	0.73813
Carbopol	−14.88	8.006874	0.136653

placed centrally and the remaining HCTZ coat material (275.5 mg) was filled on the top of the captopril core and finally compression force was applied using Elite-10 station GMP model rotary press with round biconcave punches resulting in tablet within tablet (compression/press coated tablet). The images of compression coated formulation were shown in [Figure 8].

EVALUATION OF COMPRESSION COATED TABLETS

After the compression of core tablet with coat layer, the post-compression parameters would change. So the compression coated tablets were subjected to various evaluation tests. The results of weight variation, friability, hardness, disintegration of coat, thickness, wetting time and water absorption ratio were given in [Table 15].

In vitro drug release study

The optimized formulation was evaluated for drug release study using USP type II dissolution apparatus (paddle type). A total volume of 5 ml sample solution was withdrawn from the dissolution apparatus at regular time intervals and the sample solution was replaced with fresh dissolution medium to maintain sink conditions. The samples were withdrawn at regular intervals of at 5, 10, 15, 20 and 25 min for HCTZ and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h. for the captopril. The sample solutions were filtered through 0.45 μm Whattman filter paper and analyzed using UV spectrophotometric method at 204.6 nm for captopril and 271.6 nm for HCTZ. The kinetic models used were a zero order equation, first order, Higuchi release
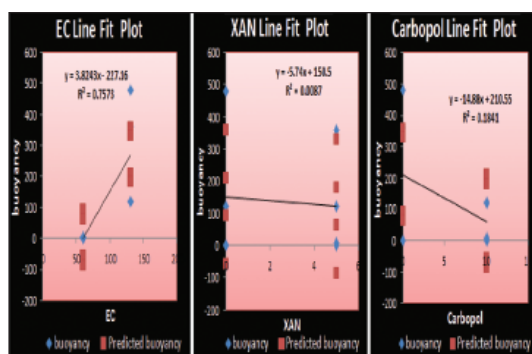
Table 11: Various formulations of hydrochlorothiazide coat layer

Material (weight in mg)	F$_1$	F$_2$	F$_3$	F$_4$	F$_5$	F$_6$	F$_7$	F$_8$	F$_9$
Hydrochlorothiazide	12	12	12	12	12	12	12	12	12
SSG	27.75	—	—	55.5	—	—	83.25	—	—
Crospovidone	—	27.75	—	—	55.5	—	—	83.25	—
Croscarmellose sodium	—	—	27.75	—	—	55.5	—	—	83.25
MCC	495.25	495.25	495.25	467.5	467.5	467.5	439.75	439.75	439.75
Pregelatinized starch	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

SSG: Sodium starch glycolate, MCC: Microcrystalline cellulose

Figure 4: Line fit plots for response of buoyancy

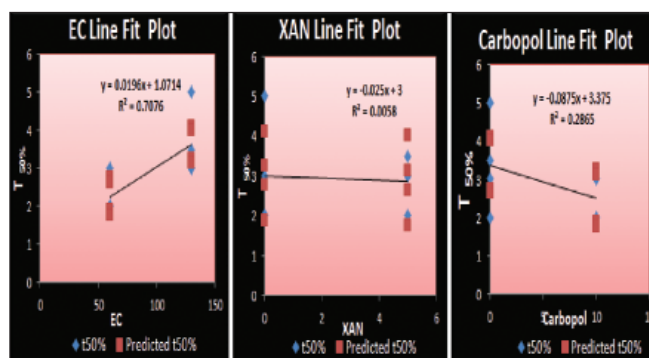**Figure 5:** Line fit plots for the response of T50%

and Korsmeyer-Peppas models. [Table 16] shows correlation coefficients of the formulation.

Estimation of drug content

A total of 20 tablets from each batch were crushed in mortar and the powder equivalent to 100 mg each of captopril and HCTZ was shaken with 100 ml of 0.1 N Hcl in a100 ml volumetric flask and sonicated for 15 min and filtered through 0.45 μm Whatman filter paper. After necessary dilutions, sample was measured at 271.6 nm for HCTZ and 204.6 nm for captopril using UV-visible spectrophotometer and the results were shown in [Table 17].
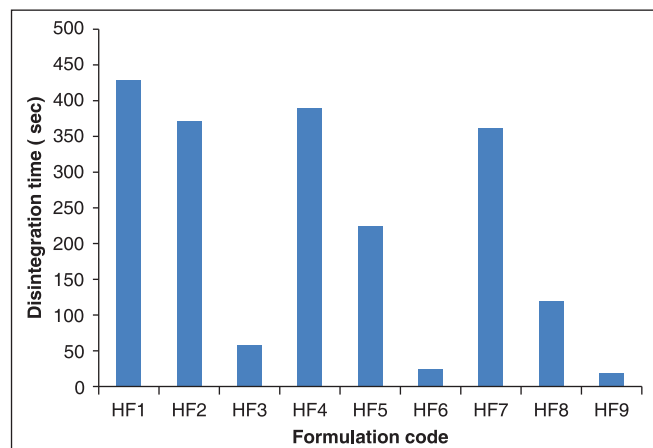
Figure 6: Comparison of disintegration time of various hydrochlorothiazide formulations
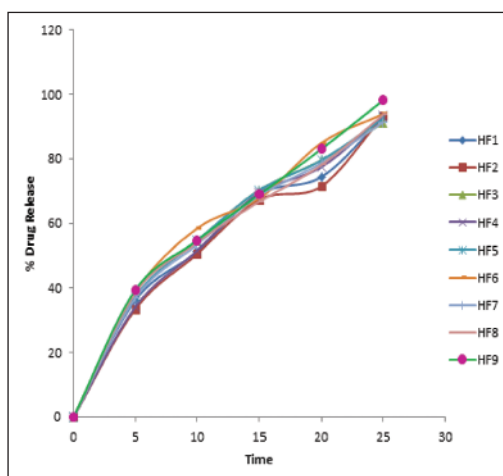
Figure 7: Zero order plot of all hydrochlorothiazide formulations

Table 12: Evaluation of pre-compression characteristics of hydrochlorothiazide formulations

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
HF$_1$	0.431	0.523	17.6	1.21	39.84
HF$_2$	0.424	0.520	18.5	1.23	35.91
HF$_3$	0.428	0.524	18.3	1.22	35.08
HF$_4$	0.425	0.523	18.7	1.23	39.32
HF$_5$	0.420	0.528	20.5	1.24	37.45
HF$_6$	0.432	0.521	17.1	1.21	33.67
HF$_7$	0.420	0.528	20.4	1.24	37.32
HF$_8$	0.438	0.521	15.9	1.19	34.89
HF$_9$	0.441	0.516	14.53	1.17	33.26

Table 13: Evaluation of post-compression characteristics of hydrochlorothiazide formulations

Formulation code	Weight variation (mg) (n = 20)	Friability (%) (n = 10)	Hardness (kg/cm^2) (n = 6)	Thickness (mm) (n = 6)	Disintegration time (s)	Wetting time (s)
HF$_1$	555±1.29	0.93	3.1±0.5	3.9±0.5	429	12
HF$_2$	555±1.32	0.88	3.1±0.5	3.9±0.5	372	10.58
HF$_3$	555±1.27	0.82	2.9±0.5	3.9±0.5	58	9.34
HF$_4$	555±1.26	0.92	2.9±0.5	3.8±0.5	390	10.89
HF$_5$	555±1.34	0.94	2.8±0.5	3.9±0.5	225	9.56
HF$_6$	555±1.23	0.82	2.9±0.5	3.8±0.5	24	8.63
HF$_7$	555±1.29	0.98	2.9±0.5	3.4±0.5	362	9.89
HF$_8$	555±1.28	0.83	3.0±0.5	3.8±0.5	119	7.63
HF$_9$	555±1.26	0.78	3.0±0.5	3.5±0.5	19	6.12

Table 14: *In vitro* drug release data of hydrochlorothiazide formulations

Time (min)	% drug release								
	HF$_1$	HF$_2$	HF$_3$	HF$_4$	HF$_5$	HF$_6$	HF$_7$	HF$_8$	HF$_9$
5	36.25±0.73	33.50±0.78	39.05±0.87	34.23±0.38	37.34±0.87	38.82±1.11	36.93±0.72	38.57±1.12	39.46±0.87
10	51.32±0.94	50.65±0.57	54.56±0.94	51.65±0.83	54.56±0.94	58.38±1.15	53.49±0.93	54.08±0.99	54.71±1.24
15	69.13±1.01	67.34±0.92	70.23±1.21	69.43±1.16	70.23±1.21	67.69±0.81	68.54±1.32	66.67±0.85	68.90±0.79
20	74.35±1.03	71.45±1.50	79.54±1.03	77.45±1.25	79.54±1.03	84.92±1.09	78.67±1.13	78.07±1.24	83.02±1.18
25	94.75±0.94	93.31±0.74	96.17±0.94	94.36±0.82	95.49±0.49	96.89±1.27	94.37±0.86	97.68±0.96	98.18±1.04

Comparison of drug release profiles of pure drug, marketed formulation and optimized formulation of captopril and HCTZ

The drug release profiles of optimized formulation were compared with that of respective pure drugs and their marketed formulations. Based on the results of dissolution profiles of captopril and HCTZ, the graphs were given in [Figures 9 and 10] respectively. The similarity factor was calculated as a part of model independent kinetics by comparing the drug release profiles of optimized compression formulation of HCTZ with that of marketed formulation of HCTZ. Similarity factor was calculated using the following equation:

$$F_2 = 50 + \log \{[1 + (1/n) \sum_{t=1} {}^*n(R_t - T_t)2]^{-0.5}\}{}^*100$$

Where R_t and T_t are the cumulative percentage dissolved at each of the selected *n* time points of reference and test product respectively

The *f* value was found to be in the acceptable range of 50-100 according to US Food and Drug Administration (FDA).

Fourier transform infrared spectroscopy (FTIR)

FT-IR spectrometry was found to be most reliable technique for predicting the possible interaction between the drugs. The spectra was recorded for captopril, HCTZ, EC, pregelatinized starch, croscarmellose sodium, lactose, microcrystalline cellulose, talc individually and for optimized formulation using FTIR (bruker), model 10048657 Alpha-T., AT-001 opus software. The samples were scanned from 1000 to 3500/cm and the obtained spectra were shown in [Figures 11-13].

Differential scanning calorimetry (DSC)

DSC was carried out to find out the presence of any interaction between the drug and excipients. Pure drugs (captopril, HCTZ)
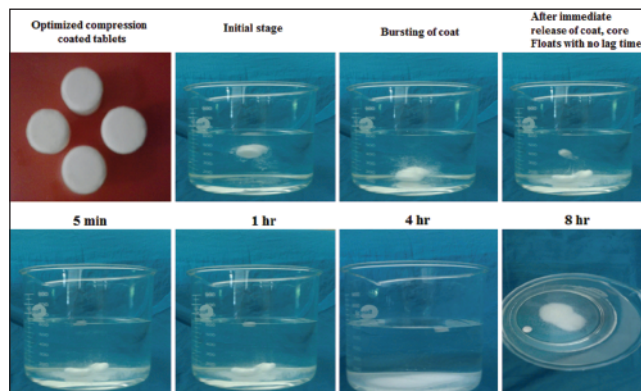

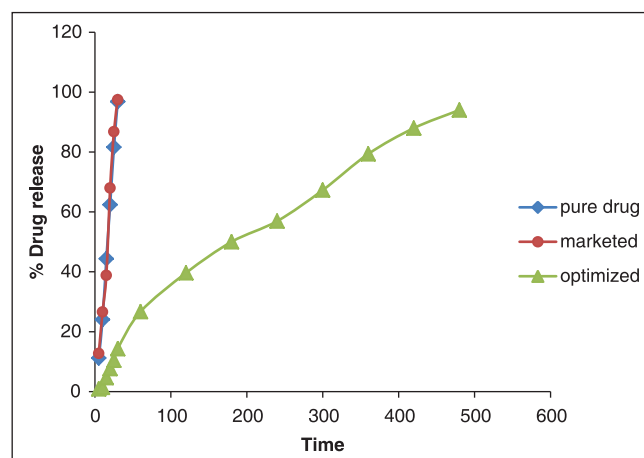**Figure 8:** The images of compression coated formulation

Table 15: Post-compression parameters of compression coated tablets

Parameter	Value
Weight variation	750±0.231 mg
Thickness	7.5 mm
Hardness	3 kg/cm^2
Friability	0.94 %
Disintegration time of coat	19 s
Wetting time	25.92 s
Water absorption ratio	20.5 %

Table 16: Correlation coefficients of the formulation

Kinetics	R^2 of captopril	R^2 of hydrochlorothiazide
Zero order	0.9728	0.9407
First order	0.9411	0.9917
Higuchi model	0.9870	0.9827
Korsmeyer-Peppas model	0.9802	0.8979

Table 17: Drug content of optimized formulation

Name of the drug	Label claim (mg)	Amount of drug estimated (mg)	Percentage of label claim
Captopril	30	29.79	99.30
Hydrochlorothiazide	12	12.03	100.30

Figure 9: Zero order plot of pure drug, marketed and optimized compression coated formulation of captopril
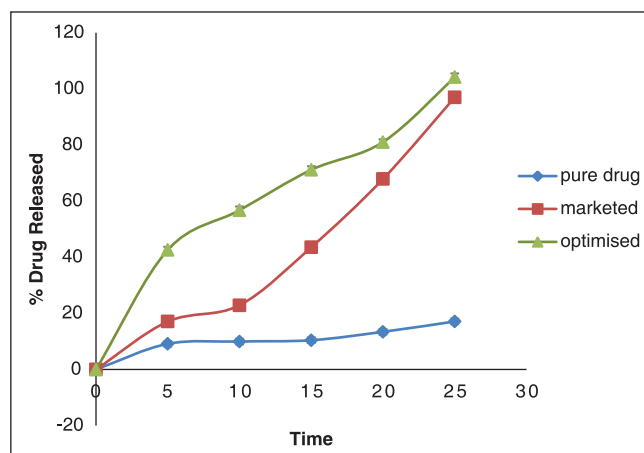

Figure 10: Zero order plot of pure drug, marketed and optimized compression coated formulation of hydrochlorothiazide

and optimized formulation were subjected to DSC analysis. Samples were taken in the pierced DSC aluminum pan and scanned in the temperature range of 0-350°C for captopril pure drug, 0-290°C for HCTZ pure drug and 0-400°C for optimized formulation at a heating rate of 2°C/min using differential thermal analyzer (Mettler Toledo) with STARe SW 9.01 Thermal Analysis Excellence software and the resulting thermo grams were shown in [Figures 14 and 15].

Thermo gravimetric analysis (TGA)

TGA is a technique in which the mass of a substance is monitored as a function of temperature or time as the sample specimen is subjected to a controlled temperature program in a controlled atmosphere. TGA were performed for pure drugs and the optimized formulation using Inkarp TGA at a temperature range of 30-550°C at a heating rate of 2°C/min in an aluminum pan using nitrogen gas. The results were shown in [Figures 16 and 17].

RESULTS AND DISCUSSION

Calibration curves were plotted for both captopril and HCTZ using UV spectrophotometric method. All the process was analyzed and based on obtained concentration and linearity it was found that obtained drug was pure and within the standards specified in IP.

Evaluation of captopril core tablets

The pre-compression results of captopril formulations indicates that CF_2, CF_4, CF_6, CF_8 formulations have acceptable flow
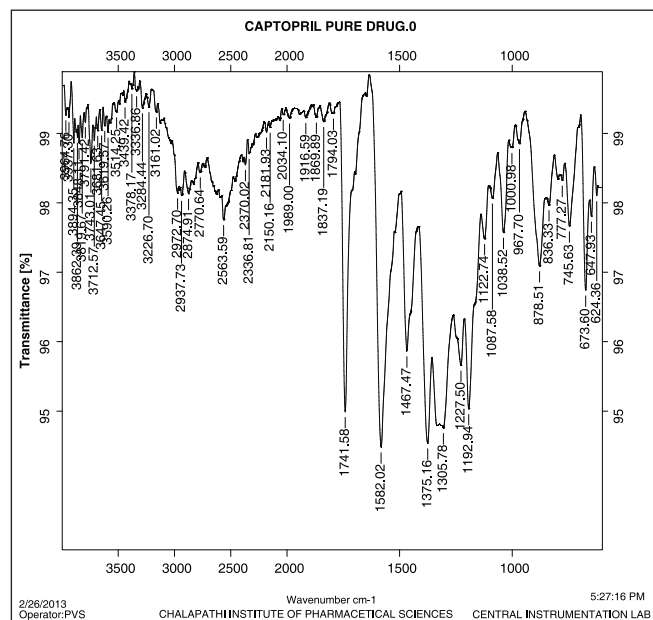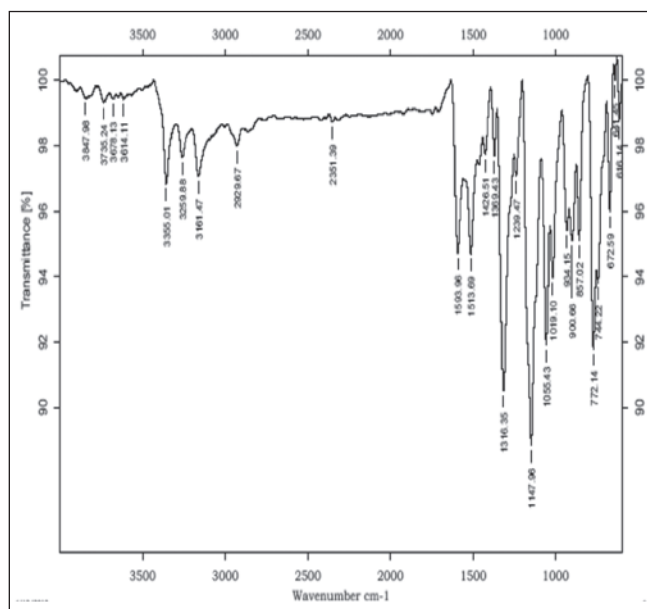

Figure 11: Fourier transform infrared spectroscopy spectra of captopril

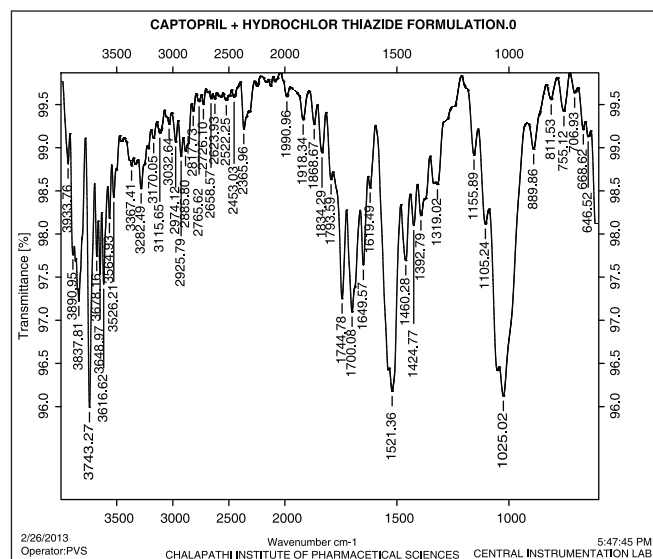**Figure 13:** Fourier transform infrared spectroscopy spectra of optimized compression coated formulation

Figure 12: Fourier transform infrared spectroscopy spectra of hydrochlorothiazide
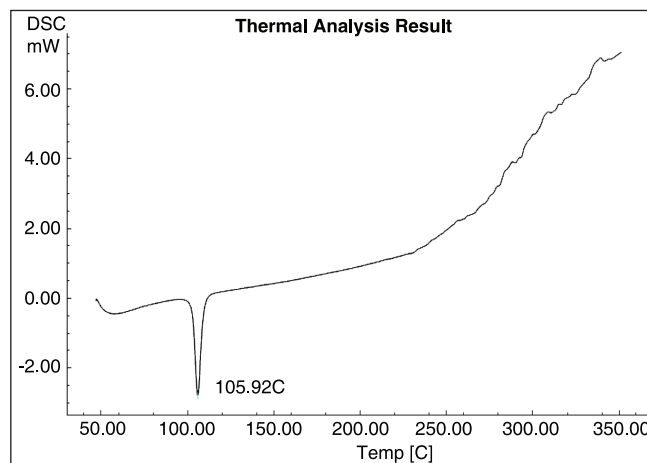

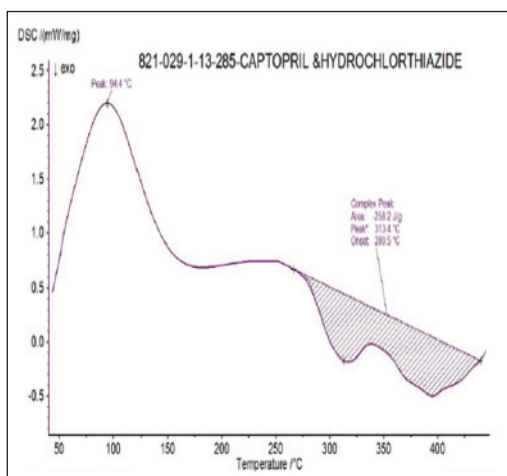**Figure 14:** Differential scanning calorimetry of pure captopril

Figure 15: Differential scanning calorimetry of optimized compression coated formulation
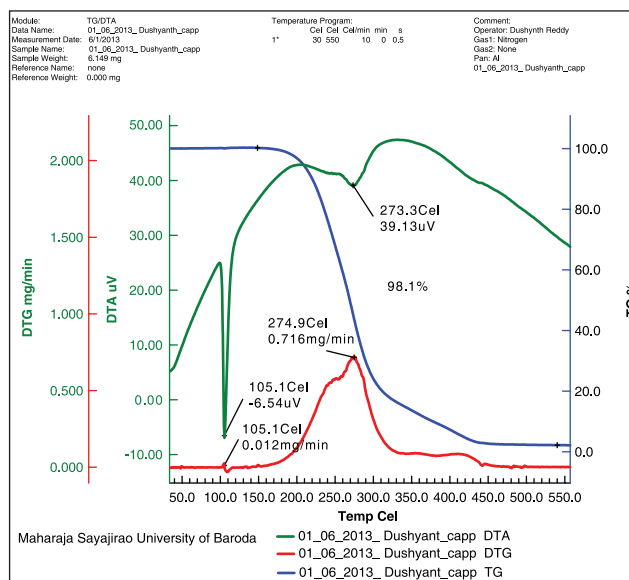

Figure 16: Thermo gravimetric analysis of pure captopril, graph generated by V. Dushyanth reddy, Maharaja Sayajirao University of Baroda
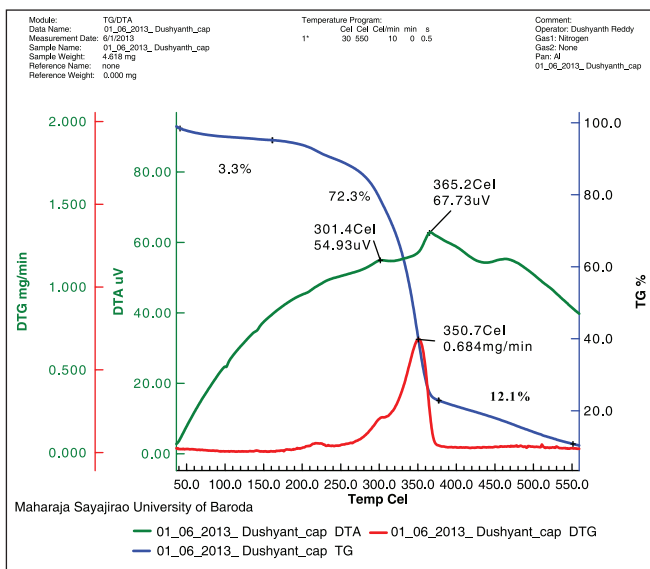

Figure 17: Thermo gravimetric analysis of optimized compression coated formulation, graph generated by V. Dushyanth reddy, Maharaja Sayajirao University of Baroda

properties. The post-compression results indicates that CF_2, CF_4, CF_6, CF_7 formulations have sufficient hardness and friability of all formulations was found to be <1% which was within the range specified in IP. Among all the formulations CF_2 formulation showed better floating time of > 8 h, which fits for the present study. Some other formulations showed good floating tendency but got disintegrated. Among all the formulations, CF_2 formulation showed better drug release profile of 97.42%.

Optimization of 2^3 factorial design by statistical analysis

The data obtained for response variables of buoyancy and $T_{50\%}$ were subjected to regression analysis using Microsoft excel for statistical assessment. According to the regression statistics of ANOVA for the response variable buoyancy, R^2 value was found

to be 0.786784. From the ANOVA results it was observed that the F value is much greater than significance F value, which indicates that the null hypothesis can be rejected and thereby concludes that that this design has a significant effect on the prediction of considered level of factors on buoyancy. The regression coefficient of EC was found be positive which indicates that there is an increase in response of buoyancy with increase in level of concentration which was shown in the line fit plot of EC. The negative regression coefficients obtained for line fit plots of xanthan gum indicates that there is no significant effect on buoyancy and that of carbopol indicates that there is a decrease in response on buoyancy with an increase in corresponding levels of concentrations.

According to the regression statistics of ANOVA for response variable drug release ($T_{50\%}$), the R^2 value was found to be 0.7403. From the ANOVA results, it was observed that the F value is greater than significance F value which indicates that the null hypothesis can be rejected and thereby concludes that that this design has a significant effect on the prediction of considered level of factors on drug release. The regression coefficient of EC was found be positive which indicates that there is an increase in response on drug release ($T_{50\%}$) with increase in level of concentration which was shown in the line the line fit plot of EC. The negative regression coefficients obtained for line fit plots of xanthan gum indicates that there is no significant effect on drug release ($T_{50\%}$) and that of carbopol indicates that there is a decrease in response of drug release ($T_{50\%}$) with an increase in corresponding levels of concentrations.

The P values for EC was found to be <0.05 which indicates that this factor has statistically significant effect on buoyancy and drug release ($T_{50\%}$) and the presence of this factor at a high level

is recommended in the formulation. The *P* values of xanthan gum and carbopol were found to be >0.05 which indicates that these factors are not statistically significant and can be dropped out from the formulation.

From the statistical analysis it was proved that single factor EC has a significant dual action on buoyancy and drug release and this formulation can be used as optimized formulation for further work.

Evaluation of HCTZ coat layer

The pre-compression results of HCTZ formulations indicate that the HF_9 formulation has good flow properties but all the formulations have acceptable flow properties. The post-compression results of HCTZ formulations indicate that HF_8, HF_9 formulations have sufficient hardness and all other formulations have acceptable hardness. Friability of all the formulations was <1% which was within the range specified in IP. The rapid disintegration and wetting were seen in HF_9 formulation containing 15% concentration of croscarmellose sodium as superdisintegrant rather than the formulations containing crospovidone and SSG.

CF_2 was selected as optimized captopril core formulation as it complied with the requirements such as prolonged buoyancy and better drug release which was also proved by ANOVA and HF_9 was selected as optimized HCTZ coat formulation as it complied with the requirements such as rapid disintegration time and better drug release.

Evaluation of compression coated tablet

The results showed weight variation of 750 ± 0.231 mg. Thickness was found to be 7.5 mm. Hardness and friability were found to be 3 kg/cm^2 and 0.94% respectively. The coat layer showed a rapid disintegration within 19 s. The wetting time of formulation including core and coat was found to be 25.92 s. The formulation showed water absorption ratio of 20.5%. The results of all the evaluation tests for the optimized compression coated tablet were satisfactory and reproducible and were found to within the acceptable limits according to IP.

In vitro drug release study

The results of HCTZ coat layer of compression coated tablet showed that the Q value of HCTZ layer is achieved within 20 min following first order release whereas the Q value of captopril was obtained at 6.5 h following Higuchi model. From the Q values it is proved that the rapid release HCTZ and slow release of captopril is achieved. The mechanism of drug release was analyzed using the exponent *n* value of Peppas equation which showed an *n* >0.90 confirming case II transportation mechanism for drug release.

Drug content

Drug content of the optimized formulation was determined. The drug content was found to be 97.03% of label claim for captopril and that of 100.3% of label claim for HCTZ.

Comparison of drug release profiles of pure, marketed and optimized formulations of captopril and HCTZ

The drug release profiles of optimized formulation were compared with that of corresponding pure drug and marketed formulations. The results of captopril showed a drug release of 96.83% for pure drug within 30 min and 94.03% for optimized compression coated tablet for a period of 8 h. The results of HCTZ showed a drug release of 17.09% for pure drug and 89.64% for marketed formulation.

The similarity factor was calculated as a part of model independent kinetics by comparing the drug release profiles of optimized compression formulation of HCTZ with that of marketed formulation of HCTZ. The similarity factor was found to be 71.2%. The *f* value was found to be in acceptable range of 50-100 according to US FDA.

FTIR

The IR spectra of pure captopril showed characteristic bands at 2874-2972/cm indicating C-H stretching. A prominent peak was obtained at 2770/cm indicating SH stretch. A peak was observed at 1741/cm indicating C = O of — COOH group, 1582/cm indicating C = O of Amide. Peaks were shown at range 1305-1375/cm indicating OH bending, 1227.5/cm indicating C-O stretching, 1192/cm indicating CN stretching. The IR spectra of pure HCTZ showed characteristic bands at 1316.35-1369.43/cm indicating the N = C stretch, Bands at 1379.1-1319.4/cm (N = C stretch), 1601.6-1589.8/cm (C = O stretch), 676.8/cm (aliphatic C-H band), 3362/cm (NH stretch), 1019-1166/cm (aromatic C = H stretch), 1603/cm (N = H bend), 1473.3-1461.8/cm (S = O) stretch. A prominent sharp peak was observed at 744/cm indicating the benzene ring deformation. Thus it is evident that all the characteristic peaks that were present in the spectra of pure drugs replicated in the same region in the spectra of compression coated tablet indicating that there is no significant interaction between the drugs and the polymers.

DSC

The DSC thermogram of captopril showed endothermic peak at 104.63°C which indicates the melting point of captopril and the DSC thermogram of HCTZ showed endothermic peak at 265.94°C indicating the melting point of HCTZ and exothermic peak at 285.70°C. In DSC thermogram of compression coated tablet, a complex peak was obtained and peaks were obtained nearly at same temperatures as that of pure drugs indicating no significant interaction between the drugs and other excipients.

TGA

The TGA curve of pure captopril shows a sharp peak at 105.10°C and a small peak were observed in the TGA curve of compression coated formulation at 105-107°C which indicates the melting point of captopril. The peak of onset of decomposition was found at 274.9°C in TGA curve of pure captopril whereas the TGA curve of compression coated formulations showed the corresponding peak at 350.7°C. It was observed that weight loss

of optimized compression coated formulation was found to be 72.3% which is less when compared to pure drug showing 98.1% weight loss, indicating that the formulation is more stable than the pure drug.

CONCLUSION

The present study was targeted to develop sustained release floating formulation of captopril compression coated with gastric dispersible HCTZ layer for effective treatment of hypertension in non-dipping hypertensive patients. To prepare sustained release floating tablets various polymers were screened among which EC was selected as the suitable polymer. To formulate rapidly disintegrating coat layer various superdisintegrants were screened among which croscarmellose was chosen as a suitable superdisintegrant. The present study succeeded in maintaining the drug concentration in long term treatment of captopril and short term treatment of HCTZ. The multiple regression analysis (ANOVA) results obtained clearly indicate that EC is a better polymer for the formulation of sustained release floating tablets of captopril. The present study succeeded in obtaining both better release profile of drug and enhancement in buoyancy rate by using a single polymer (EC). Therefore the present formulation can be scaled up for the effective treatment of non-dipping hypertensive patients. Hence, this formulation advantageous in terms of cost-effectiveness decreases the bio burden and binary action of a single polymer.

ACKNOWLEDGMENTS

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