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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[4,5]}

Captopril (\textbf{(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\textsuperscript{[6]} and congestive heart failure.\textsuperscript{[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.\textsuperscript{[8,9]} The drug is susceptible to produce stability problems.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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 antihypertensive 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

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

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

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 2³ 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 2³ 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 as a dry binder. Magnesium stearate was used as 
the 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 2³ factorial design

| Ingredients       | CF₁ (mg) | CF₂ (mg) | CF₃ (mg) | CF₄ (mg) | CF₅ (mg) | CF₆ (mg) | CF₇ (mg) | CF₈ (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 (°) |
|------------------|---------------------|-----------------------|------------------|----------------|---------------------|
| CF₁              | 0.175               | 0.243                 | 27.98            | 1.39           | 43.08               |
| CF₂              | 0.166               | 0.178                 | 13.74            | 1.07           | 26.78               |
| CF₃              | 0.336               | 0.453                 | 25.82            | 1.35           | 35.36               |
| CF₄              | 0.171               | 0.189                 | 16.52            | 1.11           | 29.59               |
| CF₅              | 0.348               | 0.508                 | 31.49            | 1.46           | 40.96               |
| CF₆              | 0.175               | 0.206                 | 18.27            | 1.18           | 31.85               |
| CF₇              | 0.169               | 0.213                 | 20.65            | 1.26           | 47.86               |
| CF₈              | 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 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 compressed to form a bilayer.

### Table 4: Evaluation of post-compression characteristics of captopril formulations

| Formulation code | Weight variation (mg) (n = 20) | Friability (%) (n = 10) | Hardness (kg/cm²) (n = 6) |
|------------------|-------------------------------|-------------------------|---------------------------|
| CF₁              | 195±0.298                     | 1.03                    | 3.0                       |
| CF₂              | 195±0.231                     | 0.98                    | 3.0                       |
| CF₃              | 195±0.339                     | 1.12                    | 2.5                       |
| CF₄              | 195±0.287                     | 1.07                    | 2.1                       |
| CF₅              | 195±0.456                     | 1.32                    | 1.8                       |
| CF₆              | 195±0.783                     | 1.01                    | 2.9                       |
| CF₇              | 195±0.247                     | 0.98                    | 2.9                       |
| CF₈              | 195±0.334                     | 1.05                    | 2.7                       |

### Table 5: Duration of floatation for various captopril formulations

| Formulations | Floating time |
|--------------|---------------|
| CF₁          | 59 s          |
| CF₂          | >8 h          |
| CF₃          | 1 min 20 s    |
| CF₄          | 6 h, disintegrated |
| CF₅          | 55 s          |
| CF₆          | 2 h           |
| CF₇          | 6 min         |
| CF₈          | 2 h           |

### Table 6: in vitro drug release data of captopril formulations

| Time (h) | CF₁ | CF₂ | CF₃ | CF₄ | CF₅ | CF₆ | CF₇ | CF₈ |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|
| 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±1.61  | 49.87±1.87  | 44.05±1.89  | 56.39±1.73  | 52.69±1.68  | 55.35±1.75  | 49.39±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±1.31  | 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
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...
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 a 100 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](image)

![Figure 7: Zero order plot of all hydrochlorothiazide formulations](image)

| 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 (°) |
| HF1    | 0.431 | 0.523 | 17.6 | 1.21 | 39.84 |
| HF2    | 0.424 | 0.520 | 18.5 | 1.23 | 35.91 |
| HF3    | 0.428 | 0.524 | 18.3 | 1.22 | 35.08 |
| HF4    | 0.425 | 0.523 | 18.7 | 1.23 | 39.32 |
| HF5    | 0.420 | 0.528 | 20.5 | 1.24 | 37.45 |
| HF6    | 0.432 | 0.521 | 17.1 | 1.21 | 33.67 |
| HF7    | 0.420 | 0.528 | 20.4 | 1.24 | 37.32 |
| HF8    | 0.438 | 0.521 | 15.9 | 1.19 | 34.89 |
| HF9    | 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/cm²) (n = 6) | Thickness (mm) (n = 6) | Disintegration time (s) | Wetting time (s) |
| HF1    | 555±1.29 | 0.93 | 3.1±0.5 | 3.9±0.5 | 429 | 12 |
| HF2    | 555±1.32 | 0.88 | 3.1±0.5 | 3.9±0.5 | 372 | 10.58 |
| HF3    | 555±1.27 | 0.82 | 2.9±0.5 | 3.9±0.5 | 58 | 9.34 |
| HF4    | 555±1.26 | 0.92 | 2.9±0.5 | 3.8±0.5 | 390 | 10.89 |
| HF5    | 555±1.34 | 0.94 | 2.8±0.5 | 3.9±0.5 | 225 | 9.56 |
| HF6    | 555±1.23 | 0.82 | 2.9±0.5 | 3.8±0.5 | 24 | 8.63 |
| HF7    | 555±1.29 | 0.98 | 2.8±0.5 | 3.4±0.5 | 362 | 9.89 |
| HF8    | 555±1.28 | 0.83 | 3.0±0.5 | 3.8±0.5 | 119 | 7.63 |
| HF9    | 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 |
| HF1 | HF2 | HF3 | HF4 | HF5 | HF6 | HF7 | HF8 | HF9 |
| 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 | 58.39±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:

\[ F_2 = 50 + \log \left\{ \left[ 1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right]^{\frac{1}{2}} \right\} \times 100 \]

Where \( R_i \) and \( T_i \) are the cumulative percentage dissolved at each of the selected \( n \) time points of reference and test product respectively.

The \( F_2 \) 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)

Table 15: Post-compression parameters of compression coated tablets

| Parameter                  | Value      |
|----------------------------|------------|
| Weight variation           | 750±0.231 mg|
| Thickness                  | 7.5 mm     |
| Hardness                   | 3 kg/cm²   |
| 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                   |
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 STARé 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 Inkaip 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 CF₂, CF₄, CF₆, CF₈ formulations have acceptable flow
properties. The post-compression results indicates that CF₂, CF₄, CF₆, CF₇ 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 CF₂ 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, CF₂ formulation showed better drug release profile of 97.42%.

**Optimization of 2³ 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 response variable buoyancy, R² 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 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 R² 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 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 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$_{8}$ 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 t 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 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 showed a sharp peak at 105.10°C which indicates the melting point of captopril and the TGA curve of HCTZ showed a sharp peak at 274.9°C. The TGA curve of compression coated tablet 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.

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