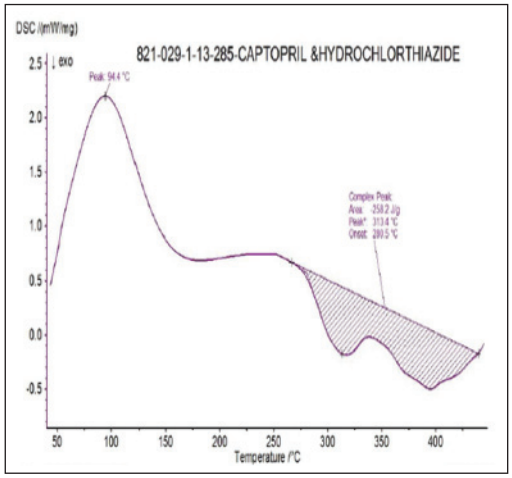

Figure 15: Differential scanning calorimetry of optimized compression coated formulation

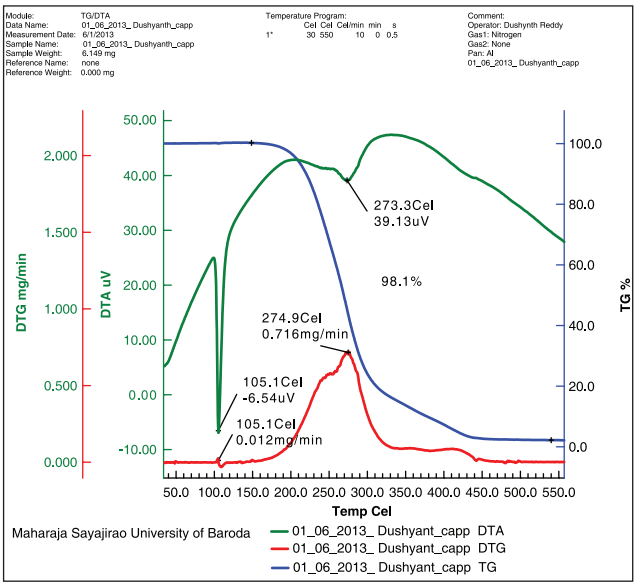

Figure 16: Thermo gravimetric analysis of pure captopril, graph generated by V. Dushyanth reddy, Maharaja Sayajirao University of Baroda

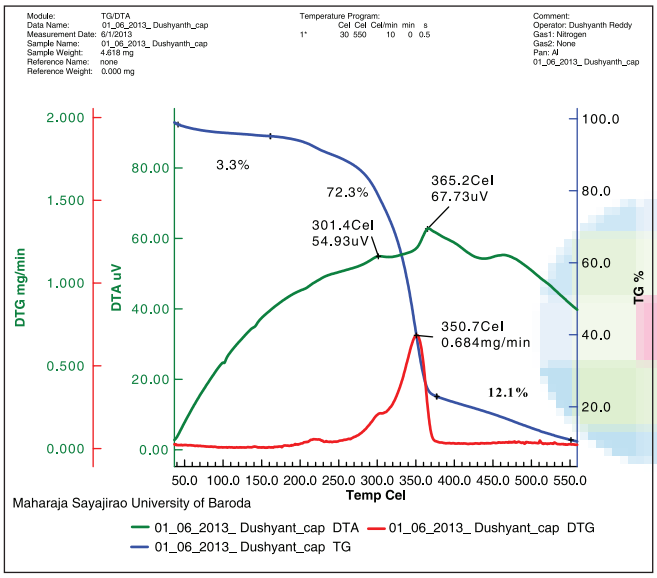

Figure 17: Thermo gravimetric analysis of optimized compression coated formulation, graph generated by V. Dushyanth reddy, Maharaja Sayajirao University of Baroda

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

The authors are grateful to V. Dushyanth Reddy, Maharaja Sayajirao University of Baroda, India for thermogravimetric instrumental facilities and technical support. Authors are highly thankful to Nishka Labs, Hyderabad, India for DSC studies and for Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India for FTIR facilities.

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How to cite this article: Sirisha PL, Babu GK, Babu PS. Conceptuation, formulation and evaluation of sustained release floating tablets of captopril compression coated with gastric dispersible hydrochlorothiazide using 2^3 factorial design. Int J Pharma Investig 2014;4:77-87.
Source of Support: Nil. **Conflict of Interest:** None declared.