

Floating tablets of hydralazine hydrochloride: optimization and evaluation

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Hydralazine hydrochloride has a half-life of 2 to 4 hours with an oral bioavailability of 26-50%. Since hydralazine has a demethylating effect on various suppressor genes, it can be used in various types of cancer to support chemotherapy. The purpose of this study was to optimize and evaluate floating tablets of hydralazine hydrochloride designed to prolong the gastric residence time and to provide controlled release of the drug for 14 h. The floating tablets of hydralazine hydrochloride were prepared by the wet granulation method. Semi-synthetic polymers of hydroxy propyl methyl cellulose (HPMC K100M) and ethyl cellulose were used as the release retarding agents. A 2² factorial design was applied to systematically optimize the drug release profile. The concentrations of HPMC K100M and ethyl cellulose were optimized to provide controlled release of hydralazine for 14h. Non-Fickian diffusion release transport was confirmed as the release mechanism for the optimized formulation and the predicted values agreed well with the experimental values. Drug excipient compatibility studies were investigated by FTIR, DSC and XRD. These data indicate that there were no chemical interactions between the drug and the polymer. *In vivo* X-ray imaging showed floating tablet performance in rabbits.

Uniterms: Hydralazine/floating tablets/evaluation. Hydralazine/floating tablets/optimization. Hydralazine/floating tablets/controlled release. *In vivo* X-ray/tablets performance. Cancer/treatment.

O cloridrato de hidralazina apresenta meia-vida de 2 a 4 horas, com biodisponibilidade oral de 26-50%. Uma vez que a hidralazina possui efeito desmetilante em vários genes supressores, ela pode ser utilizada para diversos tipos de câncer, em apoio à quimioterapia. O objetivo deste estudo foi o de avaliar e otimizar comprimidos flutuantes de cloridrato de hidralazina, planejados para prolongar o tempo de residência gástrica e proporcionar liberação controlada do fármaco por 14 h. Os comprimidos flutuantes de cloridrato de hidralazina foram preparados pelo método de granulação úmida. Polímeros semi-sintéticos de hidroxipropilcelulose (HPMCK100M) e acetato de celulose foram utilizados como agente de retardamento de liberação. Aplicou-se planejamento fatorial 2² para otimizar sistematicamente o perfil de liberação do fármaco. As concentrações de HPMCK100M e de etilcelulose foram otimizadas para se obter liberação controlada de hidralazina durante 14 h. O transporte de liberação de difusão não-Fickiana foi confirmado como o mecanismo de liberação para a formulação otimizada e os valores previstos estiveram de acordo com os valores experimentais. Estudos de compatibilidade entre fármaco e excipiente foram realizados por FTIR, DSC e DRX. Estes dados indicaram que não havia interação química entre o fármaco e o polímero. Imagens de raios-X *in vivo* mostraram o desempenho dos comprimidos flutuantes em coelhos.

Unitermos: Hidralazina/comprimidos flutuantes/avaliação. Hidralazina/comprimidos flutuantes/otimização. Hidralazina/comprimidos flutuantes/liberação controlada. Raios X *in vivo*/desempenho de comprimidos. Cancer/tratamento.

INTRODUCTION

Oral drug delivery systems represent an important area of controlled drug delivery, as such dosage forms

have the major advantage of patient compliance (Dalavi *et al.*, 2010). The overall performance of oral controlled release drug delivery systems is limited by several factors such as physiological variability, gastric retention time, variation in physiological pH and a narrow absorption window. Gastric retention is useful for those drugs which (i) act locally (Zhenping *et al.*, 2001; Yuveraj, Singh *et*

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al., 2007); (ii) have a narrow absorption window in the small intestinal region (Streobel *et al.*, 2006); (iii) are unstable in the intestinal environment and (iv) have poor solubility in a high pH environment. Various dosage forms have been developed for gastric retention; these include floating tablets (Sathis *et al.*, 2011) floating beads, pellets, floating granules and floating microspheres. Hydralazine is a directly acting smooth muscle relaxant used to treat hypertension by acting as a vasodilator. It is the first-line therapy for hypertension in pregnancy along with methyldopa. The drug is insoluble in water and has a half-life of 2 to 4 hours with an oral bioavailability of 26-50%. In the recent years, more attention has been directed towards hydralazine, since it has a demethylating effect on various suppressor genes. Therefore, it can be used in various types of cancer to support chemotherapy (Melike, Benek, 2012; Song *et al.*, 2009). In the present study, an attempt was made to optimize (Singh *et al.*, 2009) the concentration of semi-synthetic polymers for the controlled release of hydralazine and to minimize its side effects by administration of a lower dose. As hydralazine can also be used as a support in cancer therapy, the controlled release formulation was prepared using various polymers. Sodium bicarbonate was used as a gas generating agent. Drug-excipient compatibility was studied by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) and X-ray diffraction (XRD). An *in vivo* X-ray imaging study was performed to show floating tablet performance in rabbits.

MATERIAL AND METHODS

Hydralazine was donated by Hetero Drugs Ltd., Hyderabad, India. HPMC K100M and ethyl cellulose were obtained as gift samples from Matrix Labs, Hyderabad. Other ingredients used were of analytical grade.

Optimization of formulation

The optimization technique encompassed designing a set of experiments that could reliably measure the response variables, fitting a mathematical model to the data, conducting appropriate statistical tests to assure that the best possible model was chosen, and determining the values of the independent formulation variables to produce the optimum response (Gupta *et al.*, 2008).

Experimental design

In the preliminary studies, eight formulations with different drug/polymer ratios were formulated based on a 2² factorial design (Madan *et al.*, 2009). The design

included two factors each evaluated at two levels. The proportion of the retardant materials HPMC K100M (X₁) and ethyl cellulose (X₂) were selected as the independent variables. Drug release at 1.5 (Y₁), 4 (Y₂), 8 (Y₃) and 14 hours (Y₄) was selected as the dependent variable in this study. The plan of the experiment is given in Table I.

TABLE I - Plan of the experiments with coded levels of the variables

Sl. No.	Variables	X ₁	X ₂
1	X ₀	- 1	- 1
2	X ₁ (HPMC K100M)	1	- 1
3	X ₂ (Ethyl cellulose)	-1	1
4	X ₁ X ₂ (Interaction)	1	1
5	Midpoint		
6	Midpoint		
7	Midpoint		
8	Midpoint		

Preparation of tablets

The formulations were prepared by the wet granulation method (Garget *et al.*, 2009) at random following a 2² factorial design. The various excipients used are listed in Table II. All the ingredients, except magnesium stearate and talc, were thoroughly mixed and passed through a no.60 sieve. Granulation was performed with a solution of 0.5% PVP K 30 in ethyl alcohol. The wet mass was passed through a no.40 sieve and dried at 50 °C for 10 min. The dried granules were lubricated with magnesium stearate and talc and compressed into tablets using a Cadmach 21 station rotary tablet compression machine.

In vitro buoyancy studies

The tablets were placed in a 100 mL beaker containing 0.1N HCl at a temperature of 37± 0.5 °C. The time taken for the tablet to rise to the surface is called the floating lag time. The total period of time the dosage form remains on the surface of the media is called the total floating time.

Dissolution studies

In vitro dissolution study of hydralazine was performed using a USP Type I basket dissolution apparatus in 900 mL of 0.1N HCl at 37 °C (50 rpm) (Sameer, Singh *et al.*, 2011). Samples were withdrawn, filtered, suitably diluted and assayed at 302 nm on a UV spectrophotometer. The samples were then replaced with fresh dissolution medium.

TABLE II - Formulation of floating tablets of hydralazine

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Hydralazine	50	50	50	50	50	50	50	50
HPMCK100M	100	150	100	150	125	125	125	125
Ethyl cellulose	20	20	40	40	30	30	30	30
NaHCO ₃	45	45	45	45	45	45	45	45
Mgstearate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Lactose	58	8	38	3	38	38	38	38
Total wt.	300	300	300	300	300	300	300	300

All values are in given in mg

Kinetic modeling of drug release

The dissolution profile of all the batches was fitted to zero order, first order, Higuchi, Korsmeyer and Peppas models to ascertain the kinetic modeling of drug release (Dave *et al.*, 2004).

Drug-polymer compatibility

FT-IR analysis

FT-IR was carried out to assess the interaction between the drug and the tablet excipients. For this, sufficient amounts of the pure drug and powdered hydralazine tablets were scanned over a wavenumber range of 4000 to 650 cm⁻¹ at a resolution of 4 cm⁻¹ on a BRUKER Alpha FT-IR spectrometer (serial number:200218). The system was operated in transmission mode.

DSC analysis

Thermal analysis were carried out using a differential scanning calorimeter (Perkin Elmer DSC Pyris-1, Perkin Elmer Inc.).

XRD studies

Diffraction patterns of the drug, HPMC and floating tablets were obtained using a Philips PW 1830 X-ray diffractometer.

In vivo radio imaging study

The optimized floating tablets excluding the drug and containing barium sulfate (50 mg per tablet) were prepared and studied for *in vivo* X-ray imaging study to establish the product performance in rabbits

RESULTS AND DISCUSSION

The floating tablets containing hydralazine hydrochloride were prepared by the wet granulation method at random following a 2² factorial design. According to this trial proposal, eight experimental formulations of floating tablets containing hydralazine hydrochloride were prepared. An overview of the experimental plan and observed response values are presented in Table III. The Design-Expert 7.1.6 software

TABLE III - Experimental plan and observed response values from randomized runs in a 2² factorial design for the development of floating tablets containing hydralazine hydrochloride

Std	Run	Factor 1	Factor 2	Response 1	Response 2	Response 3	Response 4
		HPMC K100 (X ₁)	EC (X ₂)	Dissolution 1.5 h	Dissolution 4 h	Dissolution 8 h	Dissolution 14 h
8	1	125	30	17	49	70	92
6	2	125	30	20	52	71	94
5	3	125	30	19	49	69	92
7	4	125	30	17	50	72	95
2	5	150	20	8	49	68	92
4	6	150	40	27	46	63	87
3	7	100	40	25	52	75	98
1	8	100	20	28	61	72	97

provided suitable model equations involving the individual main factors and interaction factors for each investigated response after fitting these data. These models were evaluated statistically by applying one-way ANOVA. All these models were found to be significant ($p < 0.05$).

The model equations in terms actual factors generated by the Design-Expert 7.1.6 software are given below:

Dissolution after 1.5 h = $115.00 - 0.84 X_1 - 2.35 X_2 + 0.022 X_1 X_2$ [$R^2 = 0.9181$; $p = 0.0388$];

Dissolution after 4 h = $83.50 - 0.18 X_1 - 0.30 X_2$ [$R^2 = 0.8954$; $p = 0.0338$];

Dissolution after 8 h = $61.00 + 0.08 X_1 + 0.95 X_2 - 0.008 X_1 X_2$ [$R^2 = 0.9204$; $p = 0.0372$]; and

Dissolution after 14 h = $94.00 + 0.02 X_1 + 0.65 X_2 - 0.006 X_1 X_2$ [$R^2 = 0.9420$; $p = 0.0231$]

The main effects of factors X_1 and X_2 were larger compared to the effects of their interaction, i.e. $X_1 X_2$. The curvature effect was insignificant and the steepest ascent method was chosen for optimization. X_1 was the major factor; an increased polymer concentration reduced drug release, while ethyl cellulose had a negligible effect on drug release. Ethyl cellulose and HPMC K100M interaction was insignificant.

The limit for the estimated response for the preparation of optimized floating tablets of hydralazine hydrochloride was considered to be for 1.5 h: NMT 25%; 4 h: 50-60%; 8 h: 60-70; and 14 h: NLT 80%. The overlay plot indicating the region of optimal process variable settings is presented in Figure 1.

ANOVA study

The coefficients of X_1 were found to be significant at $p < 0.05$, confirming the significant effect on the selected responses. Increasing the concentration of HPMC K100M resulted in a decrease in the release of hydralazine. This was found to be close to unity, indicating good estimation of the coefficient. Similarly, R_i -squared was close to zero, which led to a good model. The values of Prob>F were less than 0.05, which indicated that the model terms were significant. In all cases, "Pred R-squared" values were in reasonable agreement with the "Adj R-squared" values. Adeq-Precision is a measure of the signal to noise ratio; a ratio > 4 is desirable. In this case, the Adeq-Precision values were 9.41, 9.29, 10.39 and 11.60 for 1.5 h, 4 h, 8 h and 14 h, respectively, which indicated an adequate signal. However, both the variables favored the preparation of controlled release floating tablets of hydralazine. The statistical approach for formulation (optimization) is a useful tool, particularly when simultaneously evaluating several variables. The observed responses were in close agreement with the predicted values of the optimized formulations, demonstrating the feasibility of the optimization procedure for developing floating tablets of hydralazine hydrochloride.

According to the overlay plot (Figure 1), the optimum concentrations are 130 mg for X_1 and 30 mg for X_2 .

In vitro buoyancy

All floating tablets of hydralazine hydrochloride floated well over a long period of time (not less than

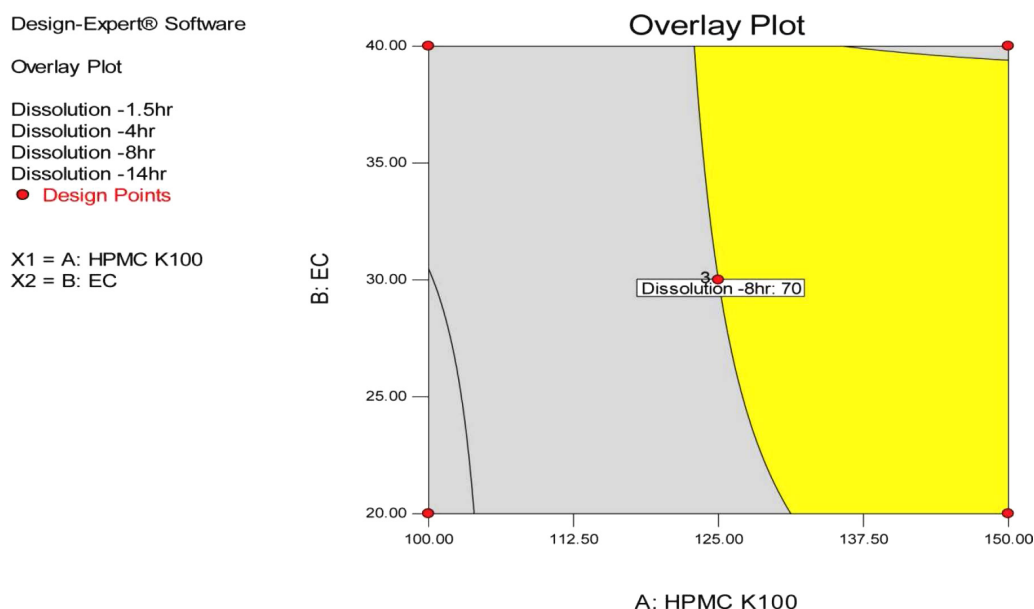


FIGURE 1 - Overlay plot indicating the region of optimal process variable settings in the development of floating tablets of hydralazine hydrochloride.

TABLE IV - Evaluation of the physicochemical parameters of hydralazine hydrochloride

Formulation code	Weight (mg) n = 20	Hardness ± SD (kg/cm ²) n=10	Drug content % ± SD (n=3)	Friability (%)	Thickness (mm)	Floating lag time	Floating duration (h) n=3
F1	300.54±1.28	5.63±0.42	98.25±3.01	0.13	3.45±0.05	16 sec	24±1.00
F2	300.05±1.12	5.85±0.65	102.03±2.4	0.12	2.97±0.02	12 sec	24±0.05
F3	300.15±1.10	6.91±0.34	99.70±3.51	0.14	3.71±0.09	20 sec	24±1.05
F4	299.59±1.29	6.58±0.49	100.81±0.7	0.13	3.51±0.10	16 sec	24±0.07
F5	300.00±0.92	6.11±0.36	97.23±0.25	0.16	3.13±0.03	18 sec	24±0.05
F6	299.91±1.33	6.45±0.53	99.17±0.42	0.12	3.15±0.07	30 sec	24±1.00
F7	299.61±1.47	6.63±0.54	101.47±2.8	0.13	3.45±0.11	25 sec	24±0.06
F8	299.35±1.37	6.63±0.43	100.01±3.0	0.15	3.35±0.08	20 sec	24±0.04
Optimized formulation	299.57±1.30	6.92±0.33	98.45±3.5	0.12	3.87±0.08	15 sec	24±0.08

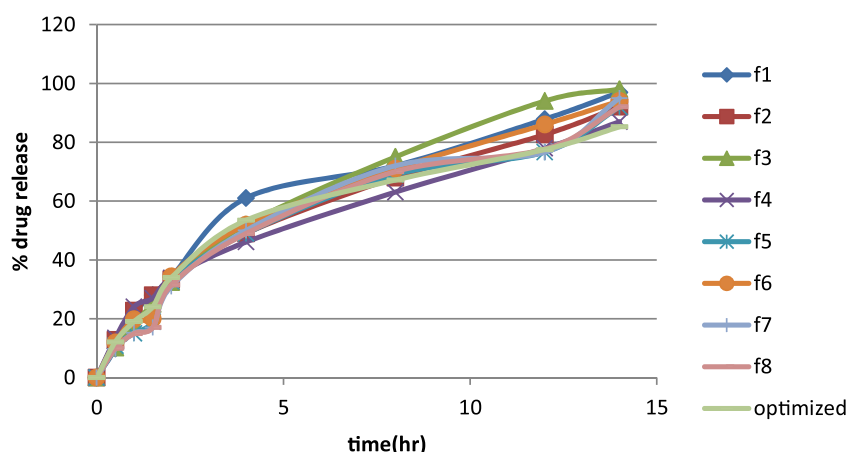


FIGURE 2 - *In vitro* hydralazine hydrochloride release from hydralazine hydrochloride floating tablets in 0.1 N HCl.

24 hours) with no minimum floating lag time (12 to 30 seconds) (Table IV). These floating tablets contained sodium bicarbonate as an effervescent agent. An effervescent agent generally produces CO₂, which reduces the density of the system and makes it float on an aqueous medium.

In vitro dissolution

In vitro hydralazine hydrochloride release from various hydralazine hydrochloride floating tablets in 0.1 N HCl is presented in Figure 2. The drug release was found to be sustained over a prolonged period of time (14 h). In these floating tablets, HPMC K100M and ethylcellulose were used as release retardant materials. The greater viscosity due to HPMC K100M may promote the formation of a highly viscous gel upon contact with aqueous fluids. This would retard the drug release rate from these floating tablets. A comparison of the percentage

of drug release using the Experimented (E) and Predicted (P) values for the most probable optimal formulation are given in Table V.

Analysis of drug release data

The drug release kinetics was evaluated using the linear regression method (Table VI). The best fit with

TABLE V - Comparison of percentage of drug release between the experimented (E) and predicted (P) values for the most probable optimal formulation

Time interval	Predicted value	Experimental value
1.5h	NMT 25%	24.05
4h	50-60%	53.49
8h	60-70%	67.17
14h	NLT 80%	85.26

TABLE VI - Drug release kinetics of floating tablets of hydralazine hydrochloride

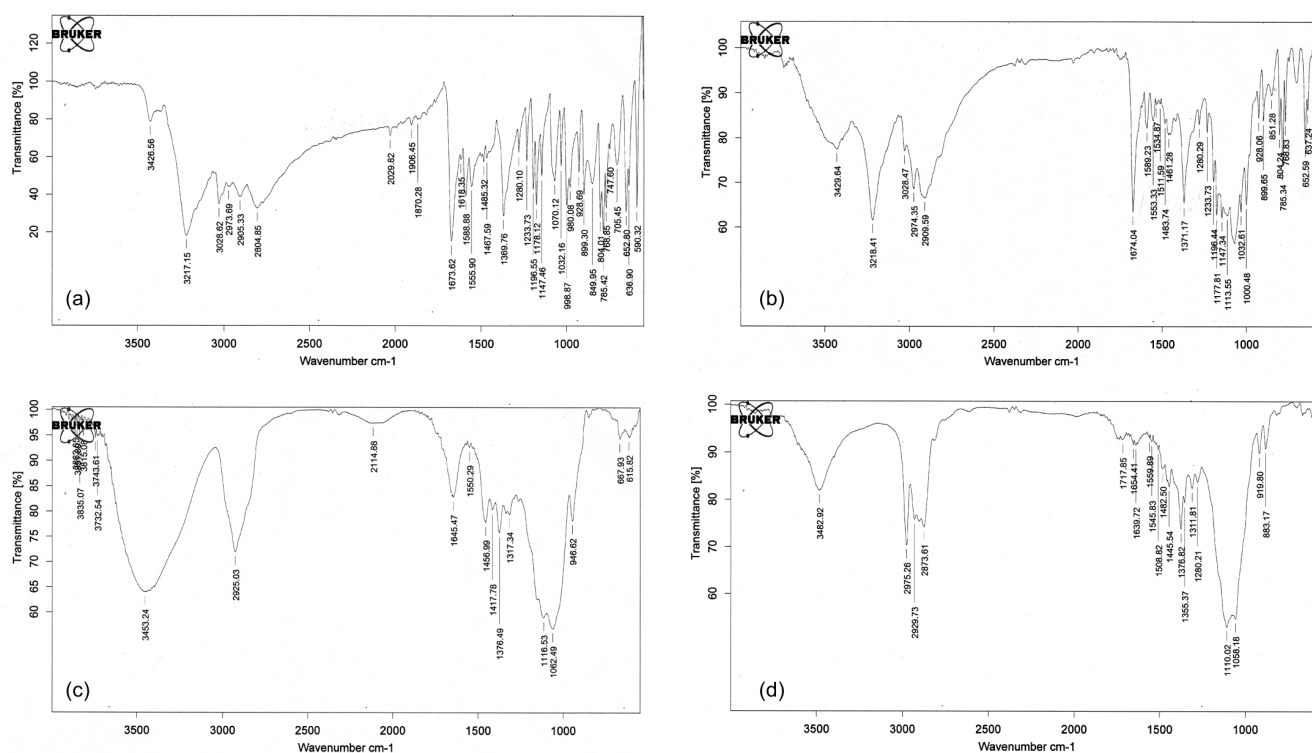
Formulation code	Zero order	First order	Higuchi kinetics	Korsmeyer-Peppas equation	
	R ²	R ²	R ²	n	R ²
F1	0.881	0.971	0.981	0.494	0.986
F2	0.911	0.947	0.995	0.489	0.996
F3	0.846	0.972	0.954	0.550	0.948
F4	0.914	0.896	0.996	0.461	0.999
F5	0.899	0.924	0.990	0.513	0.982
F6	0.864	0.964	0.976	0.516	0.972
F7	0.907	0.904	0.992	0.536	0.983
F8	0.905	0.913	0.991	0.533	0.983
Optimized formulation	0.931	0.975	0.995	0.480	0.991

the highest coefficients of determination (R²) was shown by both the Higuchi and first order models followed by zero order, which indicates that drug release followed the diffusion mechanism. The results of the *in vitro* release data were fitted to the Korsmeyer-Peppas equation to analyze the release pattern of the drug from the polymeric system. The values of “n” were in the range of 0.48-0.55, indicating that drug release followed Fickian diffusion.

Drug-polymer compatibility

FT-IR analysis

The FT-IR spectra of pure hydralazine hydrochloride, the optimized formulation, HPMC K100M and ethyl cellulose are presented in Figure 3. The characteristic peaks were at 3218.41 cm⁻¹ (N-H stretching), 3028.47 cm⁻¹ (aromatic C-H stretching), 2974 cm⁻¹

**FIGURE 3** - FTIR spectra of a. Pure drug b. Optimized formulation C.HPMC K100M d.Ethyl cellulose.

(CH stretching due to methyl groups), 2904-1674 cm^{-1} (aromatic C-H vibrations), 2804 cm^{-1} (C-H stretching), 2029-1870 cm^{-1} (C=C stretching) and 1673-1467 cm^{-1} (C-C stretching due to the aromatic ring). In the optimized formulation, the main bands of hydralazine were detected at a lower intensity due to the polymers. The characteristic peaks present in the FT-IR spectrum of both HPMC K100M and ethylcellulose also appeared in the spectra of floating tablets of hydralazine hydrochloride. These phenomena indicate that there was an absence of any chemical interaction between the drug and the excipients.

DSC analysis

DSC thermograms of pure hydralazine hydrochloride, the optimized formulation, HPMC K100M and ethyl cellulose are presented in Figure 4. The DSC of pure hydralazine hydrochloride showed an endothermic peak at 282.5 °C, indicating the melting point of drug. In the DSC of HPMC K100M, broad endotherm at 83.9 °C was observed, which may have been due to evaporation of absorbed water, as well as a broad endotherm at 352.8 °C indicated the absence of a sharp melting point. In ethyl cellulose, a broad endotherm at 332.8 °C indicated the absence of a sharp melting point. The characteristic peaks that appeared in pure hydralazine hydrochloride were present in the optimized formulation and were absent

in the DSC thermograms of both HPMC K100M and ethylcellulose. These results indicate the absence of any chemical interactions between the drug and the excipients used in the formulation.

XRD analysis

The XRD pattern of pure hydralazine hydrochloride, the optimized formulation, HPMC K100M and ethyl cellulose are presented in Figure 5. The XRD pattern of hydralazine hydrochloride indicated crystalline characteristics, which was similar to the pattern of the optimized floating tablets of hydralazine hydrochloride; the polymer diffractograms showed an amorphous pattern.

In vivo radio imaging study

The optimized floating tablets excluding the drug and containing barium sulfate (50 mg per tablet) were prepared and studied in an *in vivo* X-ray imaging study to establish product performance in rabbits. An X-ray image is shown in Figure 6. X-ray images were taken at 0.5, 2 and 6 h. The presence of the floating tablet in the upper gastrointestinal tract was clearly observed in these X-ray images. The *in vivo* X-ray imaging study clearly indicated that the prepared optimized floating tablet was retained in the rabbit stomach over a prolonged period of time and had good *in vivo* performance. Ethical clearance for

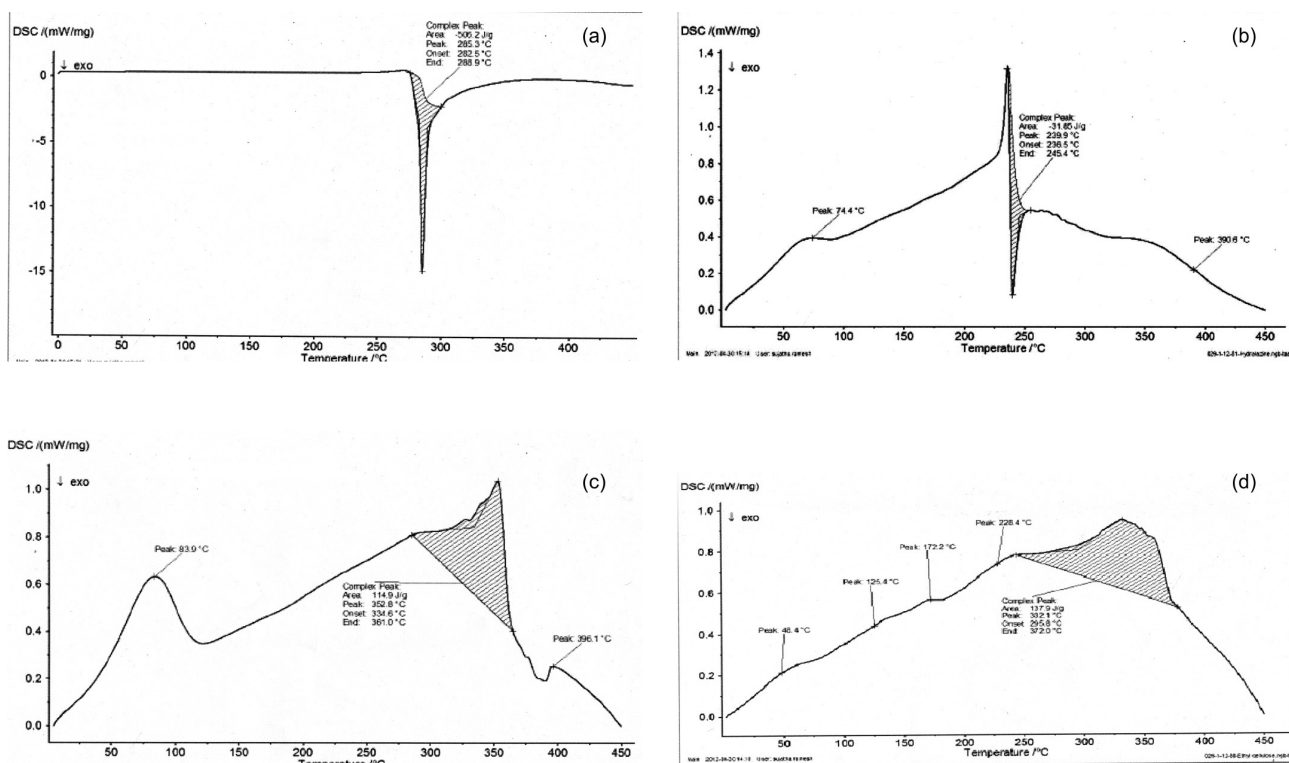


FIGURE 4 - DSC thermograms of the pure drug (a), the optimized formulation (b), HPMC K 100M (c) and ethyl cellulose (d).

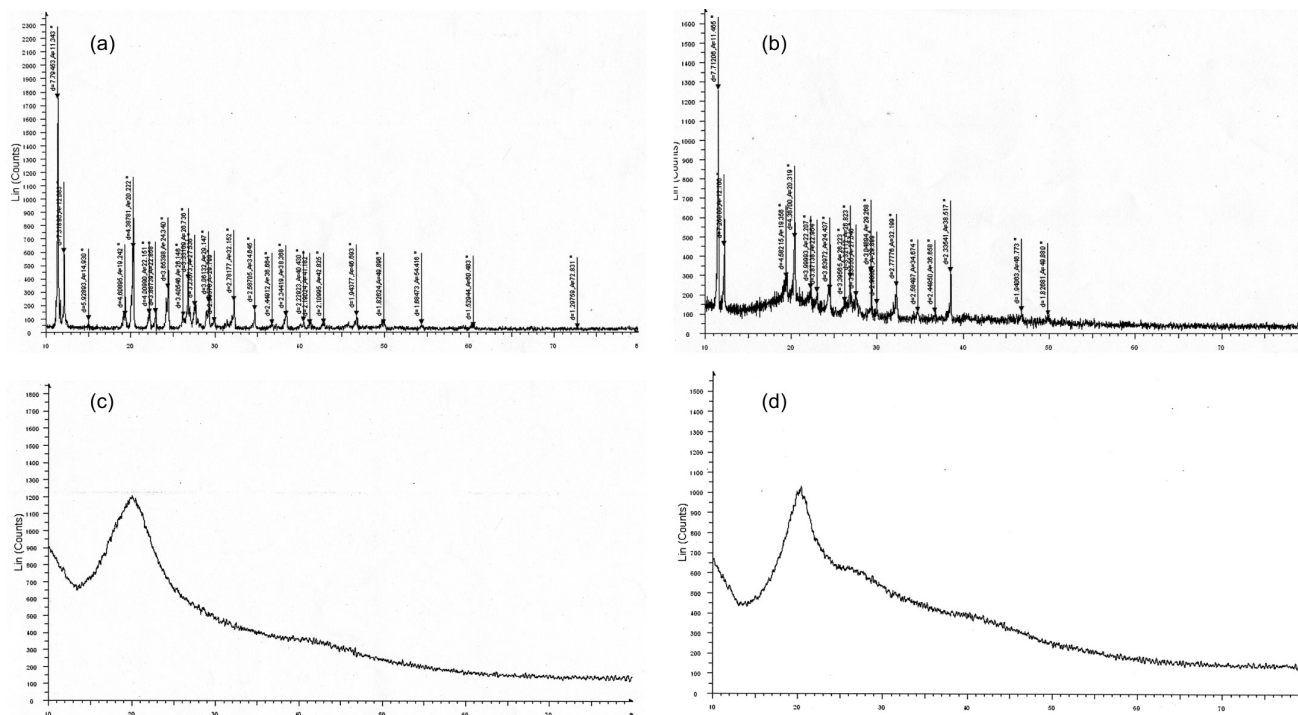


FIGURE 5 - XRD pattern of the pure drug (a), the optimized formulation (b), HPMC K100M (c) and ethyl cellulose (d).

the handling of experimental animals was obtained from the Vishnu institutional animal ethical committee (IAEC No.1358/ac/10/cpcea) constituted for this purpose.

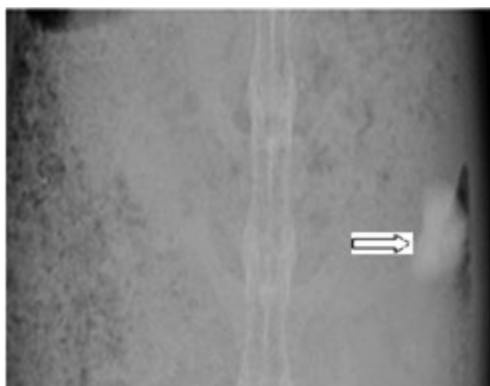


FIGURE 6 - X ray photograph of the optimized formulation in a rabbit after 6 h.

CONCLUSION

A floating drug delivery system is a promising approach to achieve *in vitro* buoyancy and extended drug release using the synthetic polymer HPMCK100M, ethyl cellulose and gas generating agent sodium bicarbonate. A systematic study using a 2^2 factorial design revealed that, by selecting a suitable composition of HPMCK100M and ethyl cellulose, the desired dissolution profile could

be achieved. The regression coefficient (R^2) values of the release data of all the formulations were obtained by the curve fitting method for the zero order, first order, Higuchi and the Korsmeyer-Peppas models. Most of the formulations followed the Korsmeyer and Higuchi models. The R^2 value of the optimized formulation was 0.991 and the n value was 0.48, indicating Fickian release governed by drug diffusion and the absence of an interaction between the drug and the polymer. An *in vivo* X-ray imaging study clearly indicated that the prepared optimized floating tablet was retained in the rabbit stomach over a prolonged period of time and showed good *in vivo* performance.

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REFERENCES

- DALAVI, V.V.; PATIL, J.S. Statistical optimization and development of gastro retentive system of an antiretroviral drug using a 3^2 factorial design. *Indian J. Pharm. Educ. Res.*, v.44, p.236-242, 2012.

- DAVE, B.S.; AMIN, A.F.; PATEL, M.M. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *In Vitro* evaluation. *AAPS Pharmscitech.*, v.5, p.77-82, 2004.
- GARG, R.; GUPTA, G.D. Preparation and evaluation of gastroretentive floating tablets of Silymarin. *Chem. Pharm. Bull.*, v.57, p.545-549, 2009.
- GUPTA, R.; PATHAK, K. Optimization studies on floating multiparticulate gastroretentive drug delivery system of famotidine. *Drug Dev. Ind. Pharm.*, v.34, p.1201-1208, 2008.
- MADAN MOHAN, K.; NITA, M.; LAKSHMI KANTA, G.; BIJAN KUMAR, G. Multiunit floating drug delivery of rosiglitazone maleate: development, characterization, statistical optimization of drug release and *In Vivo* evaluation. *AAPS Pharmscitech.*, v.10, p.887-899, 2009.
- MELIKE, U.; BENEK, C. Design of hydralazine hydrochloride matrix tablets based on various polymers and lipids. *Indian J. Pharm. Educ. Res.*, v.46, p.75-87, 2012.
- SAMEER, S.; KALPANA, P.; PATHAK, A.K.; MISHRA, A. Formulation and evaluation of floating tablet of captopril. *Int. J. Pharm. Technol. Res.*, v.13, p.333-341, 2011.
- SATHIS KUMAR, D.; SANTHOS, K.; DAVID, B.; HARANI, A.; VENKATESHWAR, R. Formulation and evaluation of bi-layer floating tablets of ziprasidone HCl and trihexyphenidyl HCl. *Braz. J. Pharm. Sci.*, v.47, p.545-553, 2011.
- SINGH, B.; PAHUJA, S.; KAPIL, R.; AHUJA, N. Formulation development of oral controlled release tablets of hydralazine: optimization of drug release and bioadhesive characteristics. *Acta Pharm.*, v.59, p.1-13, 2009.
- SONG, Y.; ZHANG, C. Hydralazine inhibits human cervical cancer cell growth *in vitro* in association with APC demethylation and re-expression. *Cancer Chemother. Pharmacol.*, v.63, p.605-613, 2009.
- STREOBEL, A.; SIEPMANN, J.; BODMEIER., R. Gastroretentive drug delivery systems. *Expert. Opin. Drug Del.*, v.3, p.217-233, 2006.
- YUVERAJ SINGH, T.; PUSHPENDRA SINGH, N.; GARIMA RANI, O. Development and evaluation of floating microspheres of verapamil hydrochloride. *Braz. J. Pharm. Sci.*, v.43, p.529-534, 2007.
- ZHENPING, W.; ZHANFENG, Y.; DIANZHOU, B. Design and evaluation of a two layer floating tablet for gastric retention using cisalpine as a model drug. *Drug Dev. Ind. Pharm.*, v.27, p.469-474, 2001.

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