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FORMULATION, EVALUATION AND OPTIMISATION OF SUSTAINED RELEASE FLOATING BILAYER TABLETS OF ARTEMETHER

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ABSTRACT

The present research work is aimed at formulation, evaluation and optimization of effervescent floating bilayer tablets containing Artemether as sustained release. Tablets were formulated using direct compression technology, composing of two layers, i.e. *Floating layer* containing effervescent components and a hydrocolloid forming polymer and *SR layer* containing drug and a rate controlling polymer, designed to increase the gastric residence time, thus prolong the drug release. Formulations were developed as per the standard experimental design protocol using Design Expert Software (Version7.1.6, Stat-Ease Inc, Minneapolis, MN), by varying concentrations of HPMC K100M and Carbopol 934P, a total number of thirteen formulations were prepared. Central composite design (2-factor, 3-level) was used for the optimization. Concentration of Carbopol and HPMC K100M were considered as independent variables. Total floating time and Time taken for 95% drug release were considered as dependent variables. All other formulative ingredients and processing variables were kept invariant throughout the study. The optimised formulation, suggested by Design Expert Software, F13 showed floating lag time of 45 sec, floating time of almost 12 hours and maximum drug release of 98.3 % at the end of 12 hours. It can be concluded from the study that the problem of short gastric residence time resulting in low bioavailability and poor efficacy encountered with an oral formulation of Artemether can be overcome with the sustained release bilayer floating tablets of Artemether for effective treatment of Malaria.

KEYWORDS: Sustained release, Floating bilayer tablets, Artemether, HPMC, Carbopol 934.

INTRODUCTION

Artemether (ART) is an antimalarial drug used in the treatment of both uncomplicated and severe malaria, especially in the conditions of choloroquine resistant P. falciparum, and it undergoes rapid absorption in the stomach, reaching a peak concentration within two hours, but it has short biological half life (2 to 3 hours) and hence gets completely cleared from the body within 4 to 6 hours of dosing, resulting in poor efficacy. In context of the above principles, a strong need was recognized for a system that resides and delivers Artemether in stomach over a relatively longer period of time. Rapid elimination resulting in poor bioavailability in conventional dosage forms of Artemether necessitated the design and development of sustained release gastro retentive drug delivery system of Artemether.

Currently many approaches are in practice for prolonging the gastric retention time, since most of drugs are absorbed in the upper part of the small intestine[1], like floating drug delivery systems or Hydrodynamically Balanced Systems (HBS)[2], Swelling and expanding systems[3], Bioadhesive systems, High-density systems, Floating muco-adhesive systems[4] and etc…. Among these floating drug delivery systems are simple to fabricate and attractive cost wise.[5] In the present study, an attempt has been made to develop Floating Drug Delivery System of Artemether, thereby increasing its gastric residence time and also releasing it at a sustained fashion to ensure optimum levels of the drug in the blood and minimizing its side effects.

MATERIALS AND METHODS

All the materials including Artemether, Magnesium stearate, Talc, Sodium bicarbonate, sodium lauryl sulphate, Micro crystalline cellulose, HPMCK100M, Xanthan gum, Poly vinyl pyrolidine K30 were obtained as gift sample from Saimirra Innopharm Pvt. ltd., ambattur, chennai, all the chemicals/solvents used were of AR grade.

PRE-FORMULATION STUDIES OF DRUG

Determination of Absorbance maxima

100µg/ml (stock solution) of artemether was prepared using 1N HCl, after ensuring the complete solubility of the drug, further dilution was made with distilled water to get 20µg/ml solution of artemether and the solution was then scanned in the range of 200-400nm for the determination of

absorbance maxima.[6]

Standard calibration grpah of Artemether

Dilutions of stock solution in the concentrations of 5, 10, 15, 20, 25 and 30µg/ml were prepared and scanned at 256nm against blank, 1N HCl. Caliberation curve of artemether was then plotted taking Concentration in X-axis and corresponding absorbance values of serial dilutions in Y- axis.

Compatibility study of drug and excipients

The pure drug and blend of drug and excipients were studied using Fourier transform infrared spectroscopy. The spectra were recorded at the scanning range of 400-4000cm^{-1} using FTIR–8400 S, spectrophotometer (Shimadzu, Japan).

EXPERIMENTAL DESIGN

For the purpose of experimental design and optimization Design Expert Software (Version 7.1.6, Stat – Ease Inc., Minneapolis, MN) was brought in, Central composite design (2-factor, 3-level) was chosen as it was appropriate for the present study[7], Concentration of HPMC K100M (A) and CP934P (B) were considered as independent variables and the dependent variables were total floating time (TFT), and time duration for 95% drug release (T95).

The Design Expert Software suggested thirteen (13) model formulations. Table 1 and 2 summarizes the actual values of the independent variables and an account of the all experimental runs suggested by The Design Expert Software.

Table 1: Maximum and minimum levels of independent variables.

FACTOR	NAME	LOW LEVEL	HIGH LEVEL	SD	CODING
A	CARBOPOL	45.0	75.0	0.000	ACTUAL
B	HPMC	30.0	90.0	0.000	ACTUAL

Table 2: DOE suggested by design expert in central composite design (2-factor, 3-level) of Actual values of independent variables.

RUN	B: C A: CARBOPOL	B:HPMC
1	38.79	60
2	75	30
3	60	60
4	60	60
5	60	60
6	60	60
7	60	60
8	45	30
9	45	90
10	60	102.43
11	60	60
12	60	17.57
13	75	90

All other ingredients and processing conditions were kept invariant.

The composition details of bilayer floating tablets are given in Table 3.

Table 3: Composition details of floating bilayer tablets of Artemether.

ING. (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
EFFERVESCENT FLOATING LAYER (300 mg)													
CA	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
SB	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5
MCC	137.5	101.2	95.0	116.2	116.2	116.2	116.2	131	131	116.2	116	116	101
C934	38.8	75	81.2	60	60	60	60	45	45	60	60	60	75
XG	15	15	15	15	15	15	15	15	15	15	15	15	15
CMC	15	15	15	15	15	15	15	15	15	15	15	15	15
MS	3	3	3	3	3	3	3	3	3	3	3	3	3
ROI	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
ARTEMETHER SUSTAINED RELEASE LAYER (300 mg)													
ART	40	40	40	40	40	40	40	40	40	40	40	40	40
MCC	180	210	180	180	180	180	180	210	150	138	180	150	150
HPMC	60	30	60	60	60	60	60	30	90	102	60	57	90
PVP	15	15	15	15	15	15	15	15	15	15	15	15	15
ASIL	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**

***CA-Citric acid** ***SB-Sodium bicarbonate**

***MCC-Micro Crystalline Cellulose**
***XG-Xanthan Gum**
***MS-Magnesium Stearate**
***ART-Artemether**
***PVP-Poly Vinly Pyrollidine**
***C934-Carbopol 934P**
***CMC- Carboxy Methyl cellulose**
***ROI-Red Oxide Iron**
***HPMC-Hydoxy Propyl Methyl Cellulose**
***ASIL-Aerosil.**

PREPARATION OF BILAYER FLOATING TABLETS

Tablets were prepared by direct compression technology using clit single punch machine.[8] Preparation of bilayer floating tablet is carried out in two stages. First stage was formulation of floating layer tablets. The effervescent ingredients such as citric acid & sodium bicarbonate and other formulative ingredients were mixed geometrically and compressed to produce floating layer tablets. Second stage was formulation of bilayer floating tablets. The drug, Polymer and other ingredients were mixed separately for sustained release layer. Floating layer was placed in the punching die and the contents of sustained release layer were placed over the floating layer tablet and compressed to produce bilayer floating tablets.

EVALUATION

Pre compression parameters

The blends were subjected to several analyses including bulk denity, tapped desnsity, compressibility and flow property.

Post compression parameters

The prepared bilayer tablets were tested for weight variation, drug content uniformity, friability (Koshiash Industries, Mumbai) thickness and hardness (Monsanto tablet hardness tester, Secor India Laboratory Instruments, Delhi).

Drug content

Accurately weighed 20 tablets were powdered and weighed a quantity of powder equivalent to 40mg of artemether and transferred to 100ml volumetric flask. 20ml of 0.1 M Sodium hydroxide was added and mixed with the aid of ultrasound and diluted to with 0.1M Sodium Hydroxide. Centrifugation was done for 5 minutes and diluted 5.0ml of the clear supernatant liquid to 50.0ml with the phosphate buffer pH 6.8. The resulting solution is then analyzed by using UV Spectrophotometer at λ max 256 nm.

In- vitro buoyancy determination

The tablets were placed in 900ml dissolution vessel containing 0.1N HCl (pH=1.2). The time required for the tablets to rise to the surface was detemined to be the floating lag time and the total floating duration was determined as total floating time.

In- vitro drug release

The in vitro dissolution studies were performed by using the USP type II (paddle) apparatus at 37±0.5^{0}C and at 50rpm and 0.1 N HCL (pH 1.2) as dissolution media. The samples were removed at predetermined intervals and replaced with media, maintaining sink condition. Each removed sample was filtered through 0.45µ filter. The samples were analyzed at 256 nm for estimation of Artemether by UV/VIS spectrophotometer.

Mechanism of drug release

The different mathematical models were applied for describing the kinetics of drug release from tablets. The drug release kinetics from tablet formulations were determined by finding the best fit release data to Zero order, first order, Hixon crowell, Higuchi, Kors-meyer peppas and Hixson plots.

RESULTS AND DISCUSSION

Determination of Absorbance maxima

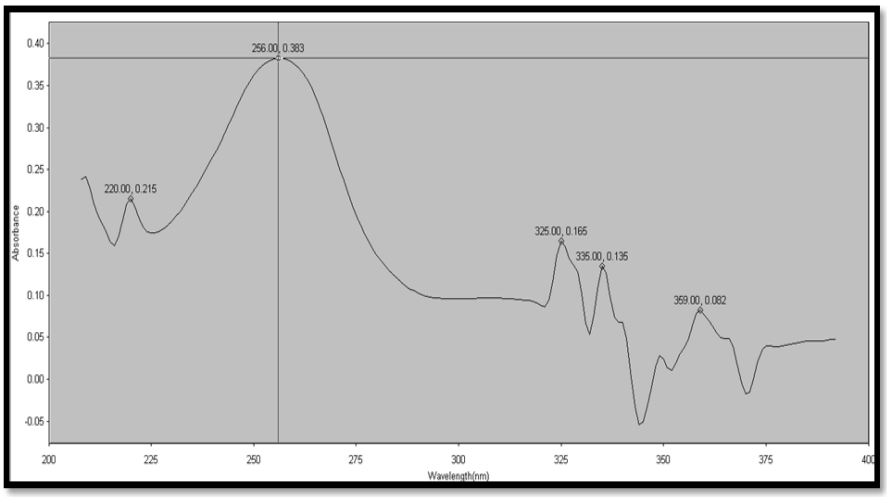

Figure 1: Determination of Absorbance maxima.
Inference: Lambda max is observed at 256 nm.

Standard graph of Artemether

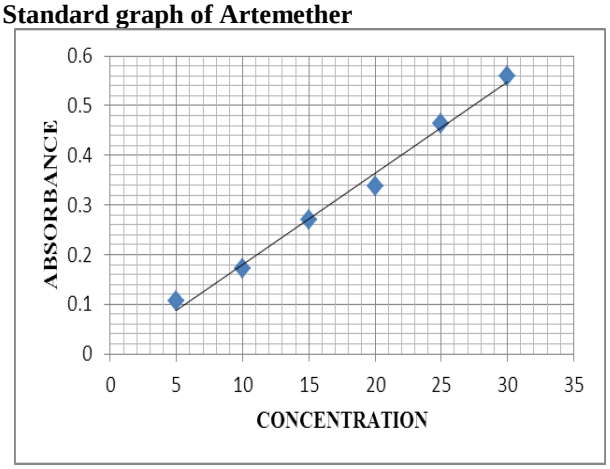

Figure 2: Standard graph of Artemether.

Inference: 5-30µg/ml Solutions of Artemether obeys Beer-Lamberts law

Drug – Excipients compatibility studies

The FTIR spectra of physical mixture of drug-polymer blend showed neither significant nor disappearance of characteristic peaks when compared with FTIR spectrum of pure sample suggesting that there was no interaction between drug and excipients and drug was stable without undergoing any physical change.

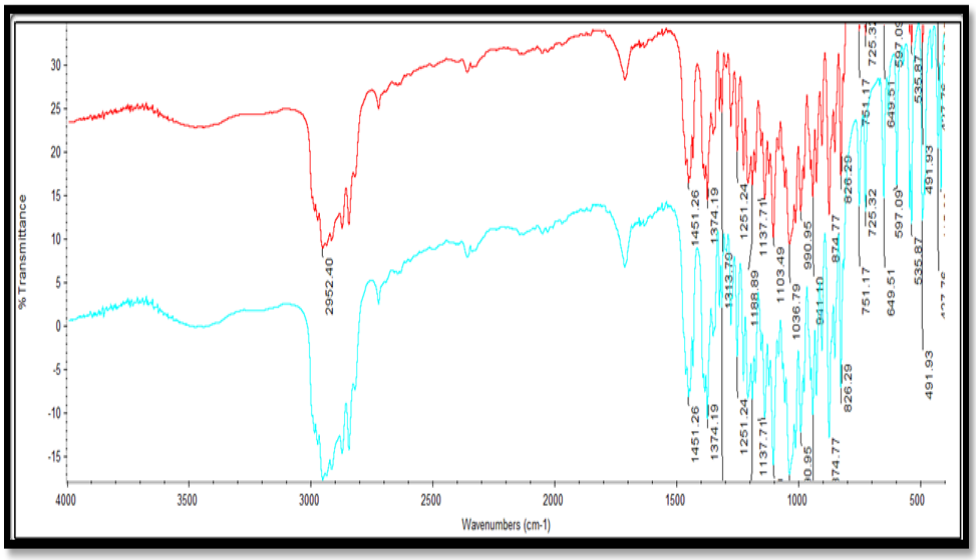

Fig. 3: FTIR spectras of Artemether and Artemether + Excipients.

Pre compression parameters

All the parameters were within the acceptable limits for the powder blend with good flow properties without much deviation while compressing the formulations ranging from F1 to F13. The official and unofficial tests carried out on these formulations showed compliance with the specified guidelines. Numerical values are given in table 4.

Post compression parameters

The physical evaluation of the tablets revealed hardness values between 5 and 8.5kg/cm^2 and low friability values (below 0.9%) across all formulations indicated that the tablets had sufficient mechanical strength. Further uniform thickness and weight of all the tablets were observed with low % relative standard deviation values. In all the formulations, the drug content was found to be uniform among the different batches of tablets, and ranged from 97.88±1.92 to 101.55 ± 2.01% which is within acceptable pharmacopoeial limits. Numerical values are given in table 5.

Table 4: Pre compression parameters of formulations F1 to F13.

CODE	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose	CI (%)	Hausner's ratio
F1	0.57	0.68	43.15	16.17	1.19
F2	0.47	0.73	41.81	35.61	1.55
F3	0.54	0.72	28.60	18.51	1.29
F4	0.58	0.78	27.34	10.00	1.34
F5	0.56	0.78	40.10	28.20	1.39
F6	0.58	0.77	48.23	24.67	1.32
F7	0.58	0.70	26.56	17.14	1.20
F8	0.61	0.72	32.46	15.20	1.18
F9	0.56	0.78	40.10	28.20	1.39
F10	0.57	0.68	43.15	16.17	1.19
F11	0.54	0.72	28.60	18.51	1.29
F12	0.56	0.78	40.10	28.20	1.39
F13	0.58	0.70	26.56	17.14	1.20

- **CI - COMPRESSABILITY INDEX**

Table 5: Post compression parameters of formulations F1 to F13.

CODE	Hardness (kg/cm2)	Friability (%)	Uniformity of wt (mg)	Drug content
F1	3.2	0.89	600±5%	98.35
F2	3.3	0.76	600±5%	97.88
F3	3.8	0.72	600±5%	99.20
F4	3.8	0.40	600±5%	99.20
F5	4.3	0.43	600±5%	99.20
F6	2.9	0.12	600±5%	99.12
F7	3.3	0.10	600±5%	102.3
F8	3.4	0.21	600±5%	105
F9	3.9	0.13	600±5%	101.55
F10	4	0.36	600±5%	100
F11	4	0.12	600±5%	99.80
F12	4	0.10	600±5%	99.23
F13	4.3	0.10	600±5%	99.69

***In Vitro* Buoyancy Studies**

The floating lag time for formulations containing carbopol 934P and HPMC K100M were found to be less than a minute, with varying total floating time. Floating lag time and Total floating time of various formulations are given in Table below.

Table 6: *In Vitro* Buoyancy.

FORMULATION CODE	FLOATING LAG TIME (Sec)	TOTAL FLOATING TIME (Hours)
F1	59	4
F2	45	12
F3	48	11
F4	50	9
F5	51	9
F6	53	9
F7	51	9
F8	58	6
F9	56	6
F10	52	9
F11	55	9
F12	56	9
F13	45	12

The formulations F2 and F13 containing maximum amount of Carbopol 934P floated for 12 hrs and it was inferred from the study that Carbopol has significant role in floating characteristics due to its high water swallability and hydro colloid forming tendency. Further it was revealed that as the concentration of carbopol is increased, the floating lag time is decreased due to the more imbibitions of water on the surface of the tablet and

the total floating time is increased due to swelling of the tablet which keeps it intact for a longer period of time.

***In Vitro* Drug release**

All the tablet formulations showed more than 12 % release within 1hour, After 12 hours study, it was found that formulations F2, F7 and F12 released 95% of drug within 5 hours (with HPMC < 35mg) and formulation F13 containing maximum amount of HPMC K100M (HPMC 90mg) showed maximum drug release of 98.3% compared to other formulations at the end of 12 hrs.

Table 7: *In Vitro* Drug release

TIME HOURS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	18.3	26.2	24.5	25.5	25.1	24.4	35.8	24.0	13.3	24.9	25.1	43.2	28.1
2	29.2	48.5	32.4	32.3	33.5	31.1	49.6	32.8	18.3	32.5	33.5	67.9	36
3	38.5	67.8	36.3	38.5	41.2	36.1	69.2	40.5	26.2	36.9	41.2	95.1	40.5
4	48.9	95.2	44.4	54.2	49.3	48.9	95	46.9	32.5	44.1	49.3		51.7
5	55.4		59.7	62.5	63.3	56.9		54.2	38.9	49.5	53.3		59
6	61.9		63.8	67.1	79.7	65.6		60.8	45.4	63.2	59.7		68.5
7	69.4		73.7	76.4	85.7	71.0		65.7	51.9	73.9	65.7		72
8	77.8		81.3	82.9	91.6	83.9		70.9	61.4	81.5	71.6		82.5
9	95.3		95.3	96.9	95.2	95.5		76.2	67.8	95.3	75.2		88.8
10								80.8	75.3		82.4		91.7
11								85.7	81.9		87.1		94.2
12								95.1	89.3		92.4		98.3
13									95.1				

Drug release kinetics

The mechanism of release for the formulations was determined by finding the R^2 value for each kinetic model like, zero-order, first-order, Higuchi etc. corresponding to the release data of each formulation, given in Table 6.

For all most all the formulations the R^2 value of Higuchi's model is very near to one than the R^2 values of other kinetic models. Thus, it can be said that the drug release follows Higuchi's release mechanism. Further the 'n' values of Korsmeyer – Peppas model for the formulations were in the range of 0.55-0.65. Therefore, the most probable mechanism of release was non-Fickian diffusion or anomalous diffusion.

Table 8: R^2 Values of formulations

FORMULATION CODE	R^2 VALUES				
	Zero order	First order	Higuchi	Peppas	Hixson
F1	0.943	0.987	0.995	0.931	0.977
F2	0.979	0.010	0.967	0.910	0.002
F3	0.910	0.949	0.963	0.849	0.943
F4	0.919	0.969	0.975	0.872	0.958
F5	0.943	0.916	0.951	0.941	0.853
F6	0.925	.966	0.972	0.862	0.959
F7	0.942	0.006	0.971	0.846	0.000
F8	0.932	0.982	0.997	0.881	0.970
F9	0.984	0.994	0.963	0.926	0.993
F10	0.925	0.947	0.973	0.842	0.948
F11	0.912	0.972	0.998	0.868	0.956
F12	0.982	0.024	0.977	0.809	0.044
F13	0.932	0.973	0.984	0.857	0.968

OPTIMISATION STUDIES

The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The sign and magnitude of the main effects signifies the relative influence of each factor over the response.

MATHEMATICAL MODELING

Final Equation in Terms of Coded Factors: *Total Floating Time*

TFT = + 9.13 + 2.74 * A - 0.59 * $A^{2.}$

Final Equation in Terms of Actual Factors

TFT = -11.21062+0.49554*CARBOPOL-2.60870E-003*$CARBOPOL^2$.

Final Equation in Terms of Coded Factors: *Release Time (t95)*
RELEASE TIME = +8.91 +3.77* B -0.61* B^2.

Final Equation in Terms of Actual Factors
RELEASE TIME =-1.05727+0.20675*HPMC-6.76329E-004*$HPMC^2$.

ANOVA for Response Surface Reduced Quadratic Model
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F-Value	p-Value Prob > F	
Model	62.39	2	31.19	162.37	< 0.0001	***significant***
A-CARBOPOL	59.95	1	59.95	312.06	< 0.0001	
A^2	2.44	1	2.44	12.69	0.0052	
Residual	1.92	10	0.19			
Lack of Fit	1.92	6	0.32			
Pure Error	0.000	4	0.000			
Cor Total	64.31	12				

The Model F-value of 162.37 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

ANOVA for Response Surface Reduced Quadratic Model
Analysis of variance table [Partial sum of squares - Type III.

Source	Sum of Squares	df	Mean Square	F-Value	p-Value Prob >F	
Model	116.19	2	58.10	558.53	< 0.0001	**significant**
A-CARBOPOL	113.57	1	113.57	1091.84	< 0.0001	
A^2	1	2.62	25.21	0.0005	0.0052	
Residual	1.04	10	0.10			
Lack of Fit	1.04	6	0.17			
Pure Error	0.000	4	0.000			
Cor Total	117.23	12				

The Model F-value of 558.53 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.
Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

INFERENCE
Coefficients X1 and X2 bear a positive sign over TFT and Release time respectively. Hence it can be cocluded that, under given set of levels, maximum levels of all two independent variables are optimal for development of floating bilayer tablets containing artemether as sustained release.

RESPONSE SURFACE ANALYSIS
Figure 4 to Figure 7 shows the 3D surface plots and contour plots of the effect of amount of HPMC K 100M and Carbopol over the total floating time and duration of drug release.

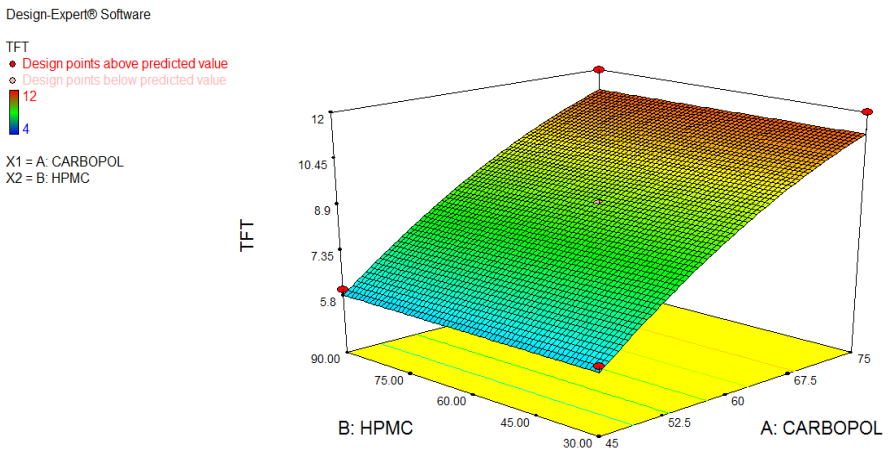

Fig. 4: Response surface plot (3D) showing the effect of amount of HPMC and amount of carbopol on total floating time.

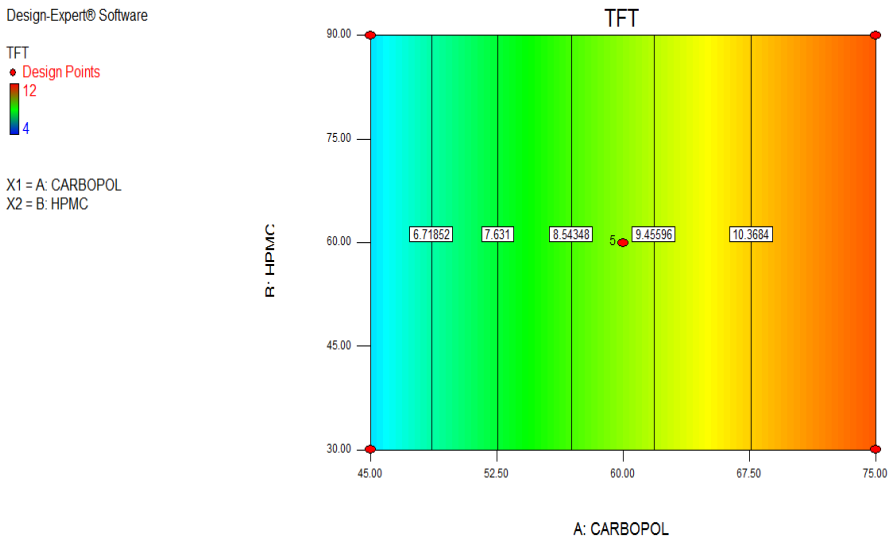

Fig. 5: Contour plot showing the effect of amount of HPMC and amount of carbopol on floating lag time.

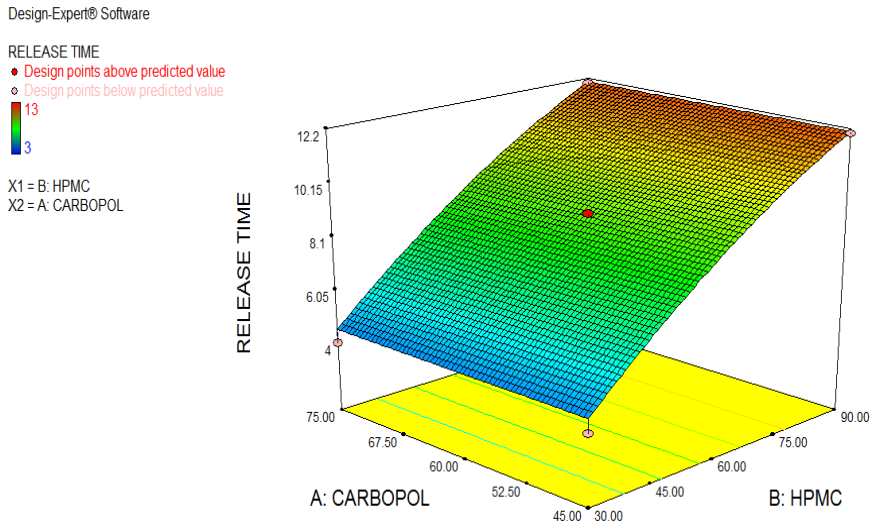

Fig. 6: Response surface plot (3D) showing the effect of amount of HPMC and amount of carbopol on time required for 95% drug release (t95).

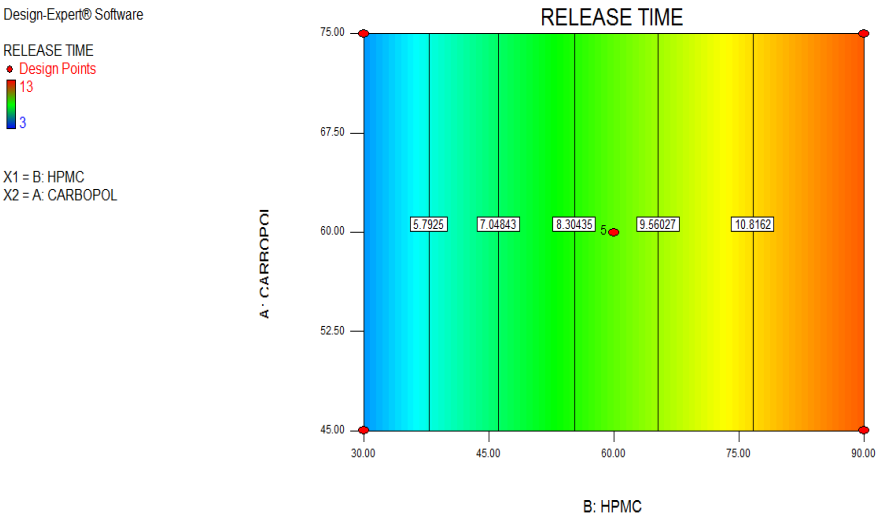

Fig. 7: Contour plot showing the effect of amount of HPMC and amount of carbopol on time required for 95 % drug release.

INFERENCE

Plots reveal that the concentration of HPMC K100M plays no part in total floating time and similarly the release time is not affected bythe varying concentrations of carbopol.

Table 9: Suggested solution.

No.	CARBOPOL	HPMC	TFT	RELEASETIME	DESIRABILITY
1	75.00	90.00	11.2809	12.071	0.909 ***Selected***

CONCLUSION

It is concluded from the present study that effervescent based floating drug delivery is a promising approach to achieve *in vitro* buoyancy by using hydrocolloid forming Carbopol 934P polymer and gas generating agents sodium bicarbonate and citric acid. HPMC (K100M) containing floating bilayer tablets of artemether is a promising sustained release system for malaria.

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