RESEARCH ARTICLE

Formulation and Evaluation of Propranolol Hydrochloride Floating Tablets by 3^2 Factorial Design

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ABSTARCT

The goal of current work is to develop Propranolol HCl floating tablets. Floating tablets of Propranolol HCl were designed basing on the idea of gas generation. Using sodium bicarbonate ($NaHCO_3$) as a gas-generating agent, xanthan gum, polyox WSR 303a as a matrix-forming polymer, and HPMC K4 M and K15 M as matrix-forming polymers, matrix tablets totalling 40 mg of propranolol HCl were created.Among the four polymers namely HPMCK4M, HPMCK15M, Xanthan gum and Polyox WSR, HPMC K4M gave good release and was selected for formulation of propranolol HCl floating tablets by 3^2 factorial design. Propranolol HCl release from the manufactured floating tablets occurred gradually over the course of 12 hours and was contingent upon the tablet's composition. The percentage that the independent variables HPMC K4M and $NaHCO_3$ were utilised in the formulation of propranolol HCl floating tablets is described by a chosen three level, two factors experimental designs (3^2 factorial designs). Floating lag time (FLT), percent drug released in 8h were selected as dependent variables. The equations for Floating lag time (FLT) and drug release in 8 hr in ($PD_{8)}$ drug dissolved are as follows. $Y_1= 23.89 +4.17X_1 -8.33 X_2-0.75X_1X_2 +0.17X_1^2 +2.67X_2^2$ (FLT), $Y_2= 81.06 -1.86X_1 - 4.10X_2 -0.14 X_1X_2 – 0.21X_1^2 + 6.57 X_2^2$ (DR_{8h}). The Y1 equations' co-efficient of X2, which has a negative sign, shows that floating lag time increases as sodium bicarbonate concentration falls. The findings indicatethat the amount of $NaHCO_3$ (X2) and the amount of HPMCK4M (X1) both have an impact on how long it takes for a medication to release and floating lag time.All manufactured floating tablet drug release followed first order kinetics, with the exception of F7, F8, and F9. Drug release from all the floating tablets prepared followed first order kinetics except in case of F7, F8 and F9. All manufactured floating tablets had their drug release regulated by non-Fickian diffusion, which served as the floating tablet's release mechanism. For FLT and DR 8h, the proximity between the predicted and observed values supports the rationality of the consequent equations for the dependent variables. Among the nine formulations F9 formulation is considered as best formulation basing on floating lag time and medication release parameters. It can be inferred from the findings that the floating tablets of propranolol HCl can be obtained successfully using optimization by 3^2 factorial design using HPMC K4M and sodium bicarbonate.

Keywords: Propranolol hydrochloride, Sodium bicarbonate, Floating delivery.

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INTRODUCTION

Oral medicine delivery is commonly preferred due to its ease of administration and ability to improve patient adherence. Research has indicated that there are two physiological aspects that affect the oral route: varied gastric emptying times (GET) and short gastric residence periods (GRT) might lead to varied delays to peak plasma levels and unexpected bioavailability. Furthermore, due to inadequate drug release from the delivery mechanism, the efficiency of the amount given may be diminished by humans' comparatively short gastric emptying time (GET), which typically averages two to three hours throughout the principal absorption zones (upper intestine and stomach). Thus, localized drug delivery, enhanced absorption capacity and therapeutic efficiency, and possible dosage reduction are all benefits of directing a method for administering medication to a certain section from the gastrointestinal system.[1] These elements resulted in the development of oral controlled-release dose formulations that can remain in the stomach. Gastroretentive systems have the capacity for continue being in the stomach territory for protractedintervals of time, which can significantly prolong the time that drugs spend there. Prolonged stomach retention increases the solubility, reduces medication waste, and increases bioavailability of medications that improved bioavailability are all benefits of prolonged stomach retention. Floating drug delivery systems (FDDS) haveless mass density than the fluids found in the stomach, which allows for them to stay afloat in the stomach for extended periods of time without slowing down the rate of stomach evacuation. Although the medication floats atop the contents of the stomach, it is

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Table 1: Formulae of Propranolol HCl Floating Tablets (PF1-PF8)

Ingredient (mg/tab)	PF_1	PF_2	PF_3	PF_4	PF_5	PF_6	PF_7	PF_8
Propranolol HCl	40	40	40	40	40	40	40	40
HPMC K4 M	75	100	-	-	-	-	-	-
HPMC K15 M	-	-	75	100	-	-	-	-
Xanthan gum	-	-	-	-	75	100	-	-
Polyox WSR							75	100
Sodium bicarbonate	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Dicalcium phosphate	92.5	67.5	92.5	67.5	92.5	67.5	92.5	67.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight (mg)	250	250	250	250	250	250	250	250

gradually and at the appropriate rate eliminated from the body. Upon the medicine is released, its leftover system is evacuated from the stomach.[2]

That leads to a longer stomach residence duration and improved management of the plasma drug concentration fluctuation. A floating chamber filled with air, vacuum, or inert gas can be used to make a medication delivery device float in the stomach. To keep the medication in the stomach, several methods are now employed. Among them are the following: floating systems, systems for bioadhesion, systems for swelling and expanding, and different delayed gastric emptying devices. In order to improve the biological accessibility and acquire controlled release, the floating tablet principle provides a straightforward and useful method of achieving longer residence times in the stomach and upper gastrointestinal system. Gas generation is the foundation for the design of floating tablets.[3] To create floating tablets with various API, a variety of polymers have been used, including ethyl cellulose, calcium alginate, eudragit RL, carbopol 934P, xanthan gum, and chitosan. When making floating tablets, sodium bicarbonate is the recommended gas-generating ingredient.This study's goal is to create and assess floating tablets containing propranolol hydrochloride utilizing sodium bicarbonate and HPMC K4 M in a 3^2 factorial design. Propranolol HCl is a commonly used hypertension medication; however, due to first-pass elimination, the bioavailability of an oral dose is significantly lower than that of an IV injection. Therefore, it's a great option for making gastro-retentive floating tablets.[4] In the current investigation, floating tablets of propranolol HCl were created for twice a day administration with the goal of improving its biological accessibility and achieving sustained release over a 12-hour period.

MATERIALS AND METHODS

Propranolol HCl was the material, and the gift sample came from M/s life line pharmaceuticals Pvt. Ltd., located in Vijayawada. Dicalcium phosphate (DCP), sodium bicarbonate, Polyox WSR, and HPMC K100 and K4M were purchased from commercial suppliers. Pharmacopoeial grade materials were used for all other materials.

Analytical method

To estimate the amount of propranolol HCl in manufactured products, an ultraviolet (UV) spectrophotometric approach was used. This method measured absorbance at 290 nm in a pH 0.1N HCl buffer.[5]

FTIR studies

FTIR experiments were utilized to assess Propranolol HCl's compatibility with different excipients utilized in the floating tablet formulation. Using KBr disk, FTIR spectra of pure pharmaceuticals including propranolol HCl and formulations of physical mixtures were recorded using anBruker Optics (Model: Alpha) makes the FTIR spectrophotometer.[6]

Preparation of Propranolol HCl Floating Tablets

Diffusion control system containing 40 mg of propranolol HCl were prepared by using di calcium phosphate, $NaHCO_3$ as a gas-generating agent with Xanthan gum, Polyox WSR 303, HPMC K4 M, and HPMC K15 M as matrix-forming polymers. Using various matrix forming agents and fillers, eight distinct formulations of Propranolol HCl floating tablets were created. The formula found in Table 1 was used to create the floating tablets using the direct compression method.[7] As a result of the preformulation studies' good drug release mechanisms, swaying tablets containing 40 mg of propranolol HCl were pepared employing a 3^2 factorial design, di calcium phosphate as a filler, NaHCO3 as a gas-

Table 2: Formulae of Propranolol HCl Floating Tablets (F1-F9) as per 3^2 factorial design

Ingredient (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	VF
Propranolol HCl	40	40	40	40	40	40	40	40	40	40
HPMC K4M	75	87.5	100	75	87.5	100	75	87.5	100	92.59
Sodium bicarbonate	37.5	37.5	37.5	44	44	44	50	50	50	44.20
DCP	92.5	80	67.5	86	73.5	61	80	67.5	55	68.21
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight (mg)	250	250	250	250	250	250	250	250	250	250

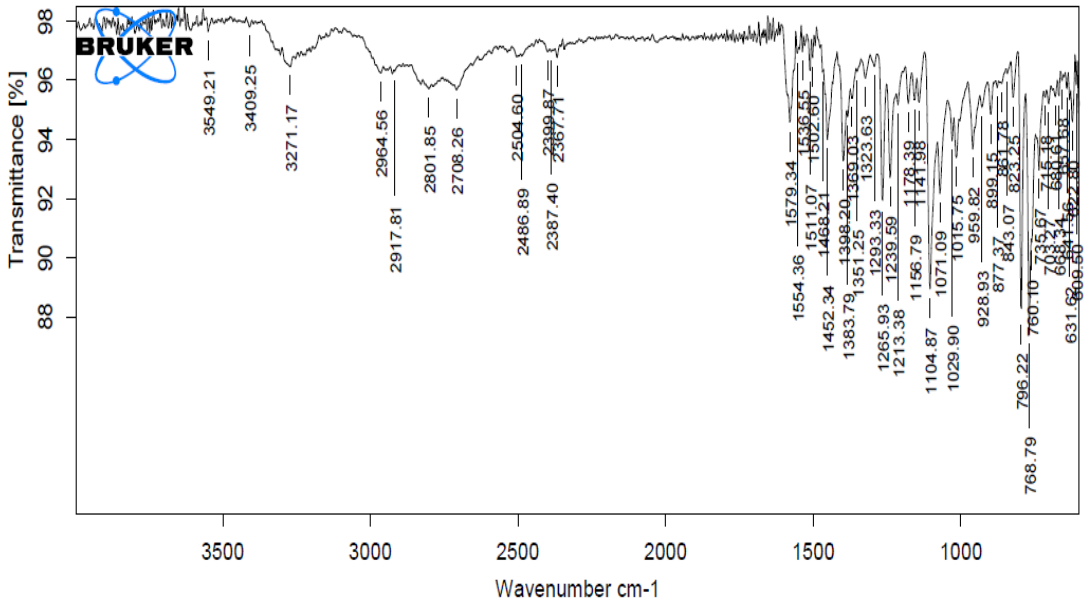

Figure 1: Propranolol HCl FTIR Spectra

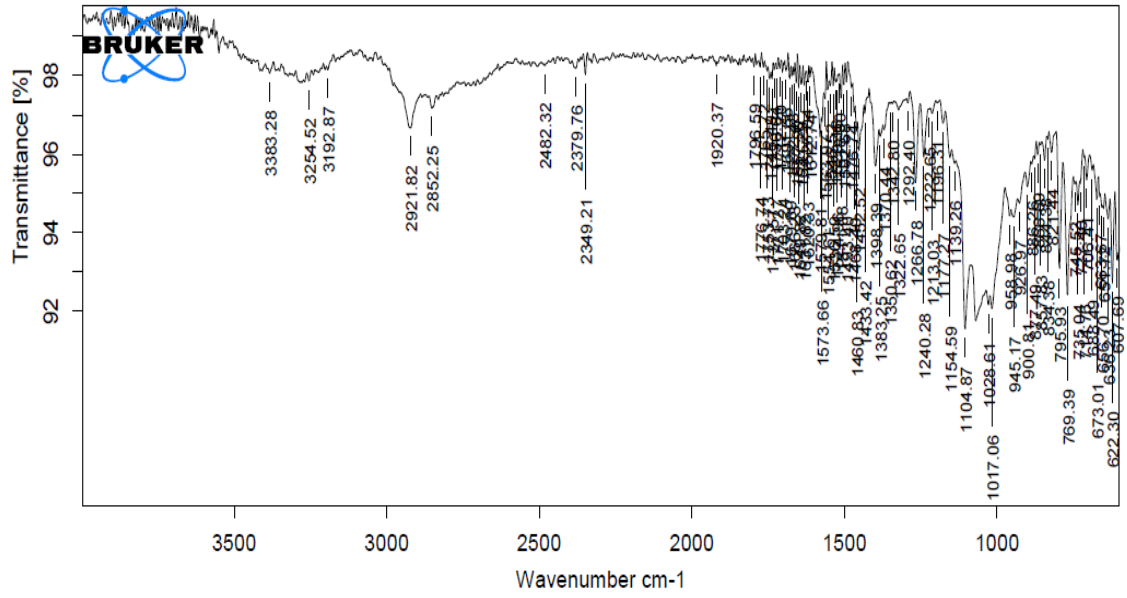

Figure 2: Propranolol HCl Formulation (F9) FTIR Spectra

creating agent, and HPMC K4 M as matrix-forming polymer.[8] Using various matrix forming agents and fillers, nine distinct formulations of Propranolol HCl floating tablets were created. The formula found in Table 2 was used to make the floating tablets using the direct compression method.

RESULTS AND DISCUSSION

The floating tablet approach provides a simple and effective way to get prolonged residence periods throughout the upper digestive tract and stomach to produce regulated release and improve bioavailability. The current investigation aims to formulate a floating tablet containing propranolol hydrochloride.

FTIR Analysis of Propranolol Hydrochloride

Figure 1 and 2 displays the infrared spectra of propranolol HCl and physical mixes of formulations. Propranolol HCl's infrared spectra displayed the following distinctive absorption peaks. All of the aforementioned distinctive peaks of propranolol HCl were also seen in the infrared spectra of physical mixes of tablet formulations. Both the physical combinations and the pure medication propranolol HCl have identical infrared spectra.[9] No chemical interaction was found between the medication and the excipients utilized in the floating tablet formulation, according to these IR spectral data.

Propranolol HCl Floating Tablets

Gas-generating mechanism was used in the preparation of the Propranolol HCl tablets that float utilizing $NaHCO_3$ as a catalyst to produce gas, xanthan gum, polyox WSR 303,

Table 3: Physical Parameters of Propranolol HCl Floating Tablets (PF1-PF8)

Formulation	Hardness (Kg/cm^2)	Friability (% wt. loss)	Drug Content (%)	Floating lag time (min- sec)	Floating Time (h)
PF_1	4	0.82	99.6	0-30	>24
PF_2	5	0.75	98.2	0-54	>24
PF_3	5.5	0.65	100.3	0-40	>24
PF_4	4	0.87	99.5	0-22	>24
PF_5	5	0.77	97.3	0-10	>24
PF_6	6	0.55	99.8	0-20	>24
PF_7	5.5	0.60	98.7	0-20	>2 h
PF_8	6	0.45	99.6	0-18	>2 h

Table 4: Propranolol HCl Floating Tablets' Physical Parameters (F1-F9) according to the 3^2 factorial design

Formulation	Hardness (Kg/cm^2)	Friability (% wt. loss)	Drug Content (%)	Floating lag time (min- sec)	Floating Time (h)
F_1	4	0.82	99.6	0-30	>24
F_2	5	0.75	98.2	0-35	>24
F_3	5.5	0.65	100.3	0-40	>24
F_4	4	0.87	99.5	0-20	>24
F_5	5	0.77	97.3	0-24	>24
F_6	6	0.55	99.8	0-28	>24
F_7	5.5	0.60	98.7	0-22	>24
F_8	6	0.45	99.6	0-18	>24
F_9	6	0.34	101.2	0-15	>24
VF	5.5	0.32	99.6	0-25	>24

Table 5: Release Parameters of Propranolol HCl Floating Tablets (PF1-PF6)

Formulation	Release Rate		Release Exponent (n)
	K_0 (mg/h)	$K_1(h^{-1})$	
PF_1	7.94	0.33	0.57
PF_2	7.81	0.19	0.77
PF_3	6.95	0.17	0.48
PF_4	6.25	0.127	0.52
PF_5	5.86	0.12	0.50
PF_6	6.20	0.10	0.77

HPMC K4 M and K15 M as matrix-forming polymers.[10] Using the formula in Table 1, the compression technique method was utilized to create eight different formulations of floating tablets containing propranolol HCl. Every manufactured floating tablet was assessed in terms of drug release parameters, hardness, friability, floating lag time, and floating time. The results are given in Table 3 and 4. The tablets' hardness fell between 4.0 and 6.0 kg/cm^2. In every instance, the reduction in weight was recorded in the friability assessment smaller than 0.87%. Within 100±3% of the claimed amount, propranolol HCl was present in every tablet that was manufactured. With the exception of tablets made with polyox WSR 303 (F7 & F8), all floating tablets that were preparedwere discovered not to disintegrate in acidic in water (1.2) or alkaline (7.4) solutions. This made the produced floating tablets friable, rigid, and with a good drug content, making them suitable for controlled release.[11] The varying floating lag times of various tablets in the in vitro buoyancy testing ranged from 10 to 54 seconds. With the exception of the tablet made with polyox WSR 303, floating times ranged from 20 to 24 hours for different floating tablets. Due to their rapid disintegration, these tablets were deemed unsuitable for use while creating tablets with prolonged liberation of drug.[12] The Propranolol HCl medication release from the manufactured floating tablets was investigated in 0.1N HCl. Figure 3 and 4 displays the drug releaseprofiles among the manufactured floating tablets. Table 5 and 6 provides a summary of the drug release parameters of the produced tablets. Propranolol HCl release from the tablets was gradual over a period of 12 hours, contingent upon the tablet's composition. A decrease in polymer concentration was accompanied by a rise in the release of drug. Using a 3^2 factorial design, HPMC K4M was chosen from among four polymers - HPMCK4M, HPMCK15M, Xanthan gum, and Polyox WSR for the creation of floating tablets containing propranolol HCl. Propranolol HCl floating tablet formulation used two independent variables, HPMC K4M and sodium bicarbonate, to varying degrees, as described by a 3^2 factorial design, a three level, two factor experimental design. As dependent variables, percent of the medication released in eight hours (DR8h) and floating lag time (FLT) were used. For the Final Equations, significance terms were selected at a 95% confidence interval ($p<0.05$). Factor X1 (HPMC K4M) has three concentration levels of 30%, 35%, and 40%, while factor X2 (sodium bicarbonate) has three concentration levels of 15%, 17.5%, and 20%. The strategy of the Propranolol HCl floating tablet preparation was created on (%) relative to the average weight of the tablet, which is 250 mg. Using

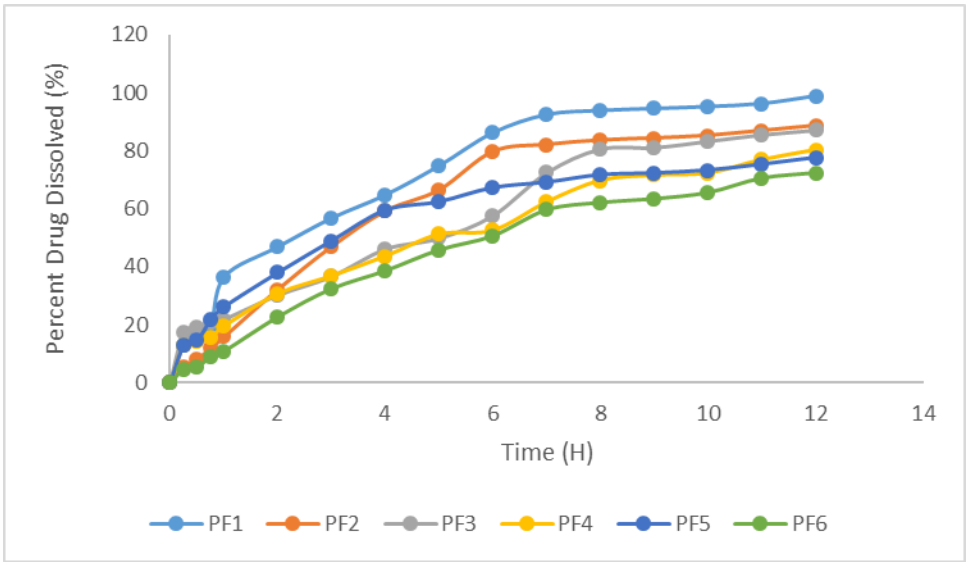

Figure 3: Propranolol HCl Floating Tablets Dissolution Profiles (PF1-PF6)

chosen X1, X2, combos of the two elements according to the 3^2 Factorial, nine different formulations of propranolol HCl floating tablets were prepared.[13] These formulations were then assessed to determine the importance of the mixed results of X1, X2, in order to determine the optimal blend as well as the focus needed to achieve the desired drug release in 12 hours. Three concentration levels of HPMCK4M were chosen and assigned the codes -1 = 30%, 0 = 35%, and +1 = 40%. Using DESIGN EXPERT 7 software, polynomial equations were produced for the FLT and DR8h. Figure 5-8 displays the response surface and contour plots for the percent medication released in 8 hours and the floating lag time (FLT) applying X1 and X2, respectively, on both axes. The formula $Y= b0 + b1 X1 + b2 X2 + b12 X1 X2 + b11 X1^2 + b22 X2^2$ is the polynomial equation for 3^2 full factorial designs.[14] If Y represents the dependent variable, b0 is the nine batches' mathematical mean answer, and b1 is the factor X1 estimated co-efficient. The average effect of adjusting each factor one from a low to a high value over time is represented by the primary effects (X1 and X2). When two factors are altered at the same time, the response changes as indicated by the interaction term (X1X2). The polynomial expressions ($X1^2$ and $X2^2$) are included in order to explore non-linearity. The correctness of the obtained equations was proved by generating one check point formulations of intermediate concentration (VF).The following are the formulae for the floating lag time (FLT) and drug release in 8 hours in (DR8h) drug dissolved.

$Y1 = 23.89 + 4.17 X1 -8.33 X2-0.75 X1 X2 + 0.17 X12 + 2.67 X 22$(FLT)

$Y2= 81.06–1.86X1–4.10X2–0.14 X1X2–0.21X12 + 6.57 X22$ (DR8h)

The Y1 equations' negative sign for the co-efficient of X2 shows that floating lag time increases as sodium bicarbonate concentration falls. The results illustrated that

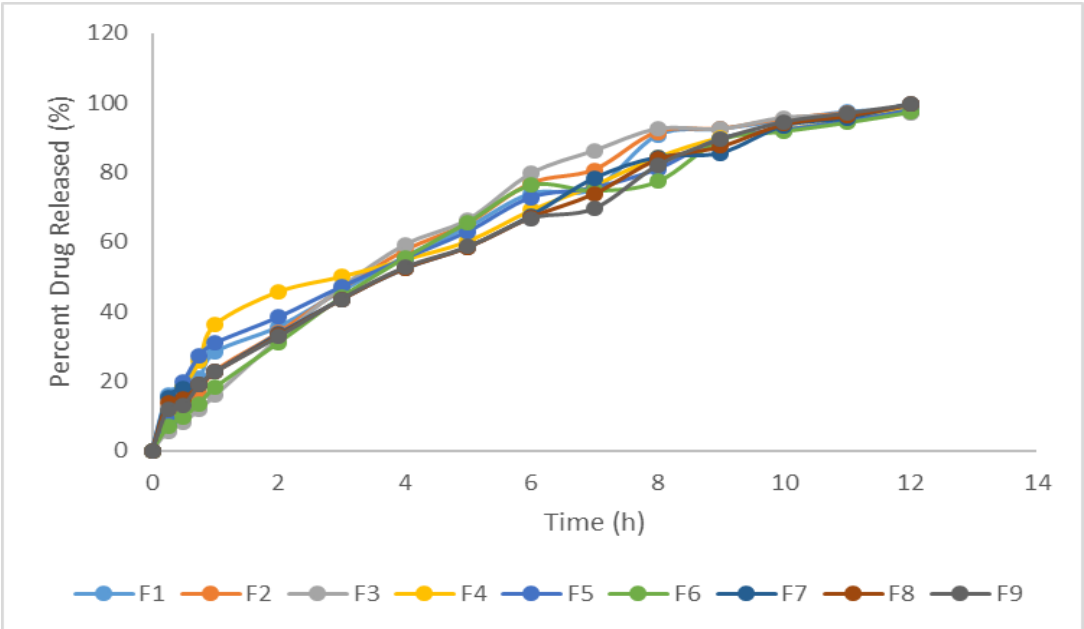

Figure 4: Propranolol HCl Floating Tablets Dissolution Profiles (F1-F9) as per 3^2 factorial design

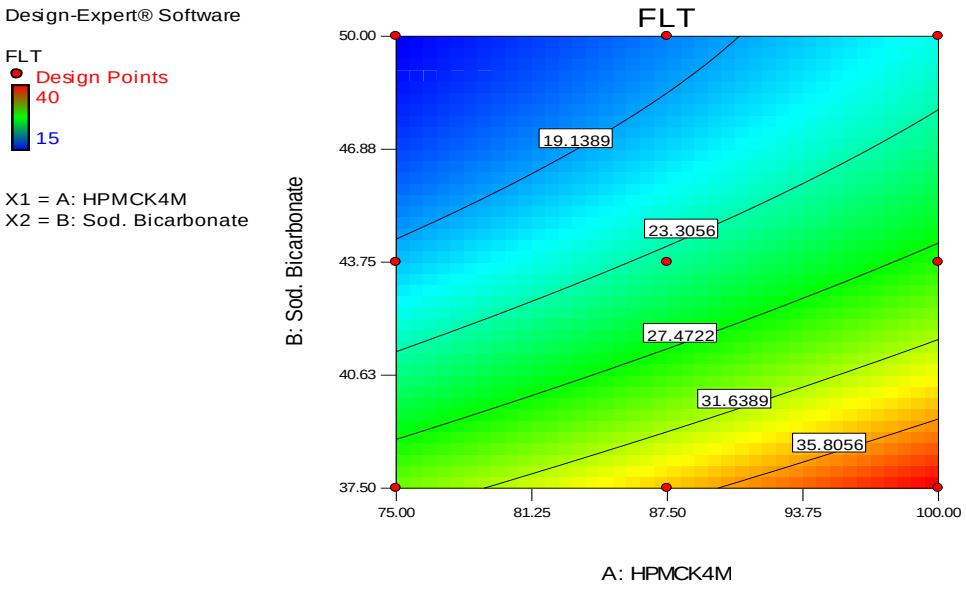

Figure 5: Contour Plot for Floating Lag Time

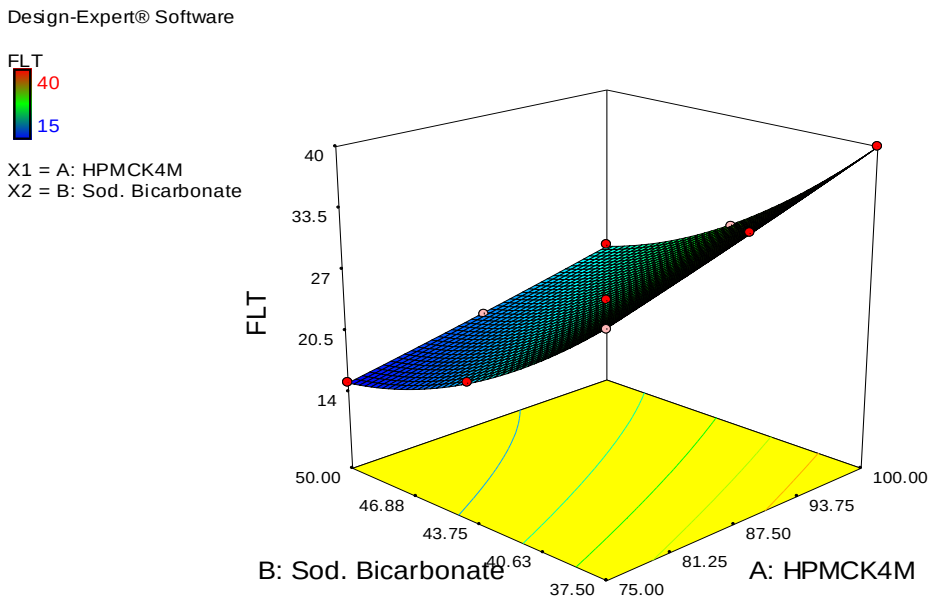

Figure 6: 3D surface Plot for Floating Lag Time

the amounts of $NaHCO_3$(X2) and HPMCK4M (X1) have an impact on how long it takes for a medication to release and floating lag time. The release data were analyzed using the Higuchi and Korsemeyer-Peppas kinetic models at zero order and first order, respectively. With the exception of F7, F8, and F9, Every floating tablet that was made had drug release that adhered to first order kinetics. Formulations F7, F8, and F9 showed a zero order release.[15] The linear Higuchi graphs show that the drug release from every floating tablet created was diffusion regulated withthe release method from these floating tablets is described as non-Fickian diffusion.[16] As the findings indicate that the time needed for the dosage form to float decreases with an increase in sodium bicarbonate content, and that the sequence of medication release could altered by carefully choosing the X1 and X2 levels. To display consequences of X1 and X2 on FLT and DR8h, Plots of response surfaces were displayed. The reliability of the developed equations for the dependent variables is indicated by the proximity of the observed and predicted values for FLT and DR8h. The floating lag time was set at 25 seconds, and the percentage of drug release was set at 80% in 8 hours, in order to validate the validity equation. The verification formula produced an 80% in drug release in 8-hour having a 25-seconds floating lag time. Based on floating parameters for drug release and lag time, the F9 formulation is deemed the best formulation out of the nine. The results showed that 3^2 factorial design optimization

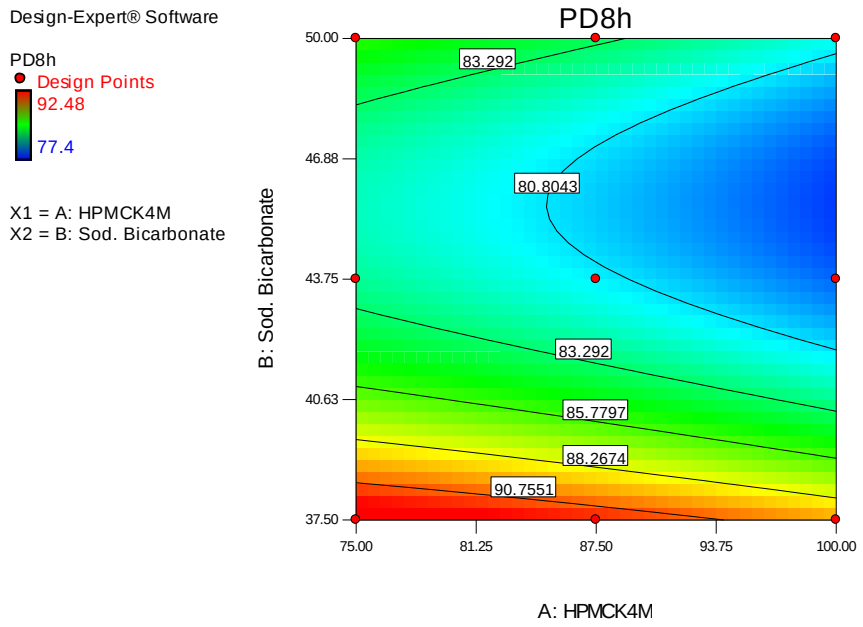

Figure 7: Contour Plot for PD 8h

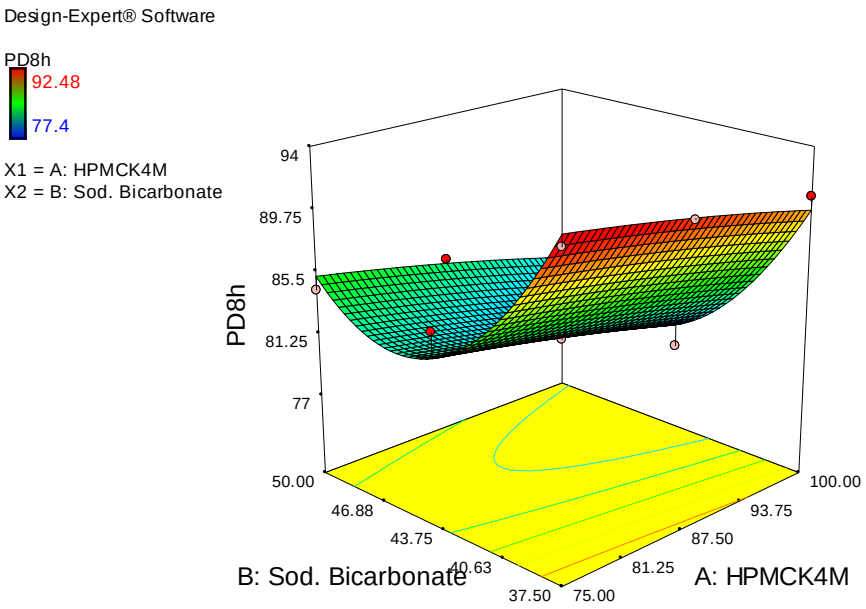

Figure 8: 3D Surface Plot for PD 8h

can be used to successfully achieve the necessary medication release for propranolol HCl.

CONCLUSION

The study successfully formulated and evaluated floating tablets of propranolol hydrochloride using a 3^2 factorial design. The research demonstrated that both the amount of HPMC K4M and sodium bicarbonate significantly impacted the floating lag time and drug release rate. The optimal formulation (F9) showed desirable properties with a short floating lag time and consistent drug release over 12 hours. The floating tablets adhered to first-order kinetics, except for some formulations which exhibited zero-order release. Overall, the study concluded that propranolol HCl floating tablets can be effectively optimized using the 3^2 factorial design to achieve the desired release profile and floating characteristics, making them suitable for prolonged gastric retention and improved bioavailability.

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Table 6: Propranolol HCl Floating Tablets (F1-F9) as per 3^2 factorial design

Formulation	Release Rate		Release Exponent
	K_0 (mg/h)	$K_1(h^{-1})$	(n)
F_1	7.91	0.31	0.52
F_2	8.31	0.30	0.63
F_3	8.74	0.31	0.80
F_4	7.46	0.27	0.53
F_5	7.56	0.26	0.55
F_6	8.22	0.266	0.72
F_7	7.90	0.34	0.54
F_8	8.00	0.33	0.57
F_9	9.28	0.333	0.59
VF	7.15	0.26	0.49

played a pivotal role in the successful completion of the present study.

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