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ABSTRACT

This study aims to optimize the concentrations of hydroxypropyl methyl cellulose (HPMC) K4M and Eudragit L100-55 (methacrylic acid) in formulation of extended-release tablets containing guanfacine hydrochloride by employing a 3^2-factorial design approach. Extended-release tablets of guanfacine hydrochloride reduce the need for frequent dosing to achieve the desired therapeutic outcomes. Cumulative drug release after 1, 8, and 20 hours of dissolution were taken as target responses and concentrations for both polymers as the variables. 3D response surface and polynomial equations were generated for choosing the optimized formulation with the most favorable response. Suitability of the drug and excipients was assessed during preliminary evaluation and compatibility studies using an accelerated thermal stress study. The release kinetics of the formulations followed Hixson Crowell and Higuchi models, indicating slow erosion of polymer to release the drug over an extended time period. Validated optimization techniques confirmed predictability of the model. The stability study verified superiority of the optimized formulation after 3 months of storage.

KEYWORDS: Guanfacine hydrochloride, extended-release tablets, hydroxypropyl methyl cellulose (HPMC), Eudragit, response surface methodology, kinetic modeling

INTRODUCTION

Guanfacine hydrochloride is an effective α-adrenergic blocker that is useful in individuals with attention deficit hyperactivity disorder (ADHD) and hypertension (1, 2). It is a BCS class I drug that gets absorbed rapidly following oral administration. Immediate-release tablets of guanfacine hydrochloride require frequent dosing (up to 4 times a day), which might reduce patient compliance and increase risks of undesirable responses. These issues can be resolved by preparing an extended-release product to be administered in a single daily dose (3). The innovator product (INTUNIV, Shire US Inc) is a once daily prolonged-release tablet of guanfacine hydrochloride. This product is FDA approved and currently indicated for the treatment of ADHD in children and adolescents (4, 5). Some studies have shown that once daily extended-release formulation of guanfacine hydrochloride is more effective than the immediate-release dosage form (6–8).

Extended-release dosage forms can reduce frequent dosing, optimize release rates, improve patient compliance, and minimize adverse effects (9, 10). Polymer matrices comprising of hydrophilic polymers are widely used in extended-release formulations. In matrix systems, the active pharmaceutical ingredient (API) is homogeneously dispersed using one or more polymers, such as microcrystalline cellulose, sodium alginate, carbopol, etc. (11, 12). Hydroxypropyl methyl cellulose (HPMC) is a type of hydrophilic polymer that is widely used in the preparation of polymer matrices to extend drug release. It remains stable at pH 3–11 and withstands enzymatic degradation (13). Eudragit L 100-55 is a versatile methacrylic acid-based synthetic polymer that is available as a solid powder with faint odor. It is used for efficient coating of tablets and other solid dosage forms to develop extended-release or controlled-release pharmaceutical products (14).

In this study, HPMC K4M and methacrylic acid (Eudragit L100-55) were used as a hydrophilic matrix to prepare extended-release tablet formulations to release drug

for 24 hours. An appropriate combination of these polymers is expected to extend the release of guanfacine hydrochloride. Eudragit L100-55 controls pH-dependent release of the drug as the polymer does not dissolve in acidic medium, while HPMC K4M retards the release rate throughout the gastrointestinal region (13, 14). The optimized combinations may also be useful in formulation of extended-release tablets containing other APIs with short half-life and low bioavailability. A 3^2-factorial design was applied in the study to investigate the effect of two independent factors, such as concentration of HPMC K4M and amount of Eudragit L100-55, on the dependent variables, i.e., drug release at 1, 8, and 20 hours. Design expert software (version 13) was employed to provide information on the values essential for generating preferred responses and probable interactions between the independent and dependent variables.

METHODS

Materials

Guanfacine hydrochloride was obtained from Intas Pharmaceuticals Ltd.(Ahmedabad, Gujarat). HPMC K4M (molecular weight: 1261.4 g/mol, degree of substitution: 20–24% of methoxyl and 7–12% of hydroxypropyl substitutions) was procured from Samsung Fine Chemicals Co., Ltd (Korea). Eudragit L100-55 (methacrylic acid) was purchased from Evonik Industries Signet Chemical Corporation Pvt. Ltd (Maharashtra, India). Microcrystalline cellulose PH-102 was from FMC Asia – Pacific, Inc. (Maharashtra, India). Isopropyl alcohol was obtained from Rankem (Gujarat, India). Lactose monohydrate was obtained from Tiwari Chemicals and Tiwari Pharma (Himachal Pradesh, India). Citric acid and fumaric acid were obtained from Thirumalai Chemicals (Maharashtra, India). Glyceryl behenate was obtained from Gattefosse, Ltd. (India). Lake of Indigo carmine and ferric oxide yellow were from Colorcon (West Point, PA, USA). All chemicals and reagents used were of analytical grade.

Precompression Evaluation

The ratio of the weight of powder to the bulk volume is known as bulk density. It consists of the solid portion of the particles and the space between them. Bulk density is important in determining the size of equipment needed for handling and processing. Tapped and untapped bulk density measurements can estimate the compressibility of a material. Flow rate, particle size distribution, and cohesiveness of the powder are the factors on which the compressibility of the powder is dependent. Powders that possess more than 20% of Car's index (compressibility index) value exhibit poor flow properties. From the values of bulk density and tapped density, Car's index and Hausner's ratio were calculated.

Particle size distribution and shape affects the chemical and physical properties of the drug substance. It also effects biopharmaceutical behavior, content uniformity, solubility, and stability. A Malvern analyzer (Mastersizer 3000) was used to measure the particle size distribution of guanfacine hydrochloride (15–17).

Compatibility Study

Drug-excipient compatibility studies of guanfacine hydrochloride with different commonly used excipients were carried out with an accelerated thermal stress study. The blends of the drug substance with different excipients in a 1:1 (w/w) ratio were used for the compatibility study. Samples were stored at accelerated conditions of 40 °C and 75% relative humidity (RH) in open and closed vials (Sigma Aldrich, 20 mL vial with size of 21 × 61 mm) and checked for any physical changes after 2 weeks and for chemical changes after 4 weeks (18, 19).

Preparation of Extended-Release Tablets

Formulations were prepared using a wet granulation method. All ingredients were sifted through 40 mesh. Drug and excipients were mixed uniformly and granulated using purified water. The cohesive mass was dried, and granules were sized by passing through 20 mesh. Granules were lubricated using either glyceryl palmitostearate (formulation F1 and F2) or glyceryl behenate (formulation F3–F8). Finally, the blend was compressed using an 11 × 6 mm-oval BL/BL punch and tablet compression machine (Rimek, Mini Press I) (20, 21). Each compressed tablet contained 4 mg of guanfacine hydrochloride (all formulations).

Physical Characterization of Tablets

The prepared guanfacine hydrochloride tablets were evaluated for physical parameters such as weight variation (Metter Toledo), hardness, thickness, friability (Labtronics), and content (% assay) according to *United States Pharmacopoeia* (USP) (22). Weight, friability, and drug content results were reported as mean and standard deviation.

Experimental Design

Based on the results obtained with preliminary formulations, a randomized 3^2-factorial design approach was used to identify the optimized formulation. In this design, two factors were evaluated, each at three levels, and experimental trials were performed for all nine possible combinations. The composition of all formulations is shown in the Table 1. The concentration of HPMC K4M and the amount of methacrylic acid were selected as

independent variables. As dependent variables, drug release (%) was measured after 1, 8, and 20 hours of dissolution. The release profiles of the formulations were estimated utilizing the Electrolab (Edt 08lx) dissolution tester. The outcomes of the experiment were evaluated statistically for the response variables using Design Expert (version 13, Stat-Ease Inc., Minneapolis, MN, USA).

Kinetic Modeling and Similarity Factor Analysis

Dissolution profiles for each formulation were fitted to various kinetics models including zero order, first order, Higuchi, Hixson Crowell, and Korsmeyer-Peppas to ascertain the kinetics of drug release (23–25). The best fitting kinetic model of drug release was determined based on the regression coefficient. Kinetic modeling is a model-dependent approach. In controlled drug delivery formulations, swelling, diffusion, erosion, and dissolution-controlled drug release are the most important rate-limiting mechanisms. The diffusion system, dissolution system, and osmotic system are mechanisms for delivering the drug in a controlled manner. Formulations containing swelling polymers show swelling as well as diffusion mechanism because the kinetics of swelling includes relaxation of polymer chains and imbibition of water, causing the polymer to swell and changing it from a glassy to rubbery state.

For modified-release dosage forms, SUPAC guidelines use the similarity factor (f_2), which is used to compare dissolution profiles. The dissolution profiles of all formulations were compared to the innovator using a f_2. An f_2 value between 50 and 100 indicates similarity among the dissolution profiles (26).

In Vitro Drug Release of the Optimized Formulation

The drug release profile of the optimized formulation was measured in dissolution media representing three distinct pH conditions, i.e., HCl buffer pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8. A sample (10 mL) of each solution was withdrawn at 1-hour intervals for 24 hours, with the replacement of fresh dissolution medium at each timepoint.

The samples were passed through a 0.45-µm membrane filter and diluted to a suitable concentration with the specific medium. The absorbance of these solutions was measured at 220 nm using a UV-Vis scanning spectrophotometer (Shimadzu UV-1800, Japan). The dissolution test was performed using USP apparatus 2 (paddle method) (Model: TDT-08L1202085, Electrolab, India).

Stability Study

The optimized formulation was subjected to stability study according to ICH guidelines (27). The stability study was conducted using the Thermo Fischer Scientific stability chamber (model no. 3940). All tablets were packed in aluminum foil at the end of every week. The tablets were visually examined for any physical changes and for chemical changes in drug content for 3 months. During this period, aluminum foils were subjected to different storage conditions including 40 °C and 75% RH, 30 °C and 65% RH, and 25 °C and 60% RH (27). The tablets were evaluated for drug content, loss on drying (LOD), hardness, weight, and impurities (single and total) at the end of each month.

Table 1. Composition of Formulations as per Factorial Designs

Ingredients	Amount (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Guanfacine hydrochloride	4	4	4	4	4	4	4	4	4
Avicel PH 102	60.21	80.21	90.21	80.21	70.21	75.21	65.21	85.21	70.21
HPMC K4 M	35	25	25	35	35	30	30	30	25
Eudragit L 100-55	80	70	60	60	70	70	80	60	80
Ludipress	40	40	40	40	40	40	40	40	40
Fumaric acid	18	18	18	18	18	18	18	18	18
Glyceryl behenate	26	26	26	26	26	26	26	26	26
Lake of Indigo carmine	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Ferric oxide yellow	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
%DR$_1$	16	22	23	15	18	20	26	24	26
%DR$_8$	66	75	82	86	87	71	75	85	69
%DR$_{20}$	85	101	102	92	95	98	91	100	85

%DR$_1$, %DR$_8$, and %DR$_{20}$ are percent drug release in 0.1 N HCl at 1 h, 8 h, and 20 h, respectively. HCL: hydrochloric acid.

RESULTS AND DISCUSSION

Precompression Evaluation
Results from the precompression evaluation showed that guanfacine hydrochloride exhibits poor flow properties because Carr's index and Hausner's' ratio were 37.44% and 1.5, respectively. The particle size distribution of guanfacine hydrochloride indicated that around 90% of powder exhibited particle size higher than 355 μm, i.e., within coarse size range.

Compatibility Study
The accelerated thermal stress study indicated no significant physical changes in the excipients compared to guanfacine hydrochloride alone. The level of impurities found in the blend after completion of 4 weeks was also not significantly different from the initial levels.

Physical Characterization of Tablets
All formulations conformed to pharmacopeial specifications. The average weight and hardness of all formulations were 265 mg and 110 N, respectively. Tablet thickness was 4.2–4.7 mm. The assay results varied among batches, i.e., 100.2 ± 5.01% for F6 to 79.82 ± 3.99 for F3. Friability results were less than 1% for all formulations, indicative of optimum physical strength.

Kinetic Modelling and Similarity Factor Analysis
Release rate kinetics and outcomes of the f_2 analysis are displayed in the Table 2. The dissolution profile for F6–F9 were best fitted to that the Innovator, with f_2 values of 68–85. The F9 formulation showed superior fit ($f_2 = 85$) in comparison with the release profiles of the other tablets.

On the basis of linearity, the in vitro release of guanfacine hydrochloride from the innovator tablet and all test formulations was best delineated by the Hixson Crowell equation, followed by Higuchi and Korsmeyer–Peppas. This means that dissolution predominantly takes place through gradual decrease in surface area of the tablets as per Hixson Crowell equation, and subsequently slow diffusion of drug from the formulation is explained by Higuchi's equation. The diffusion exponent (np) of all the formulations and the innovator are within the range of 0.7454 to 0.966, which depicts that the release of drug follows anomalous diffusion, i.e., the drug release occurs by both erosion and diffusion mechanisms.
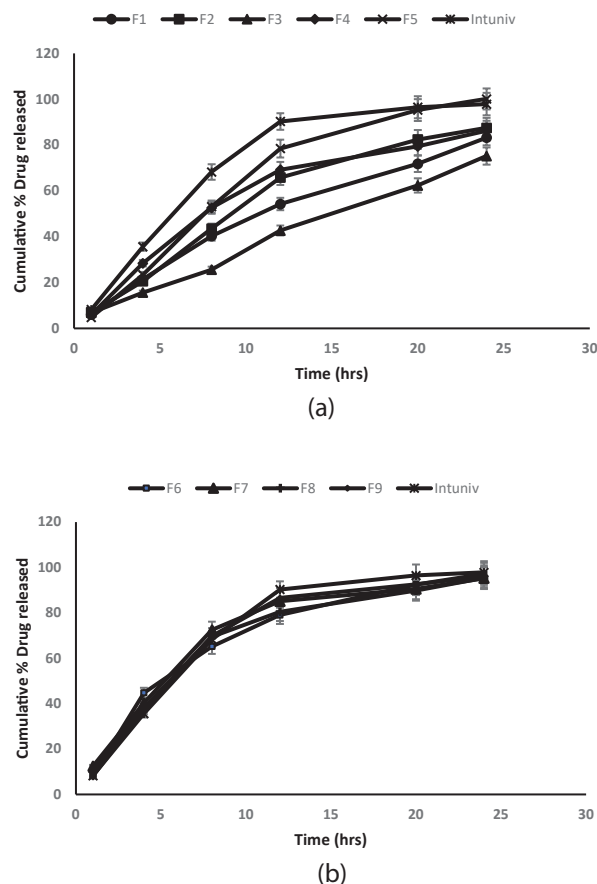

(a)

(b)

Figure 1. Dissolution profiles for formulations F1–F5 (a), F6–F9 (b), and INTUNIV.

Optimization of Experimental Design
The 3^2 factorial designs employed two independent factors: quantity of HPMC K4M (X_1) and quantity of methacrylic acid (X_2) varied at three levels (high [+1],

Table 2. Kinetic Modeling and Similarity Factor Analysis of Dissolution Data

Model	F1	F2	F3	F4	F5	F6	F7	F8	F9	INTUNIV
R_0	0.7979	0.9322	0.9922	0.8858	0.9095	0.8403	0.7897	0.8235	0.9702	0.9682
R_1	0.6114	0.7743	0.8939	0.6633	0.7029	0.6000	0.6322	0.6374	0.7718	0.691
R_H	0.9235	0.9755	0.9601	0.9738	0.9718	0.9542	0.9184	0.941	0.996	0.9822
R_{HC}	0.9357	0.9787	0.9901	0.9652	0.9673	0.9837	0.9288	0.961	0.9995	0.9938
R_{KP}	0.9398	0.9877	0.9827	0.963	0.9762	0.9286	0.9486	0.9513	0.9946	0.9881
n_p	0.966	0.8509	0.7856	0.864	0.7454	0.935	0.9629	0.891	0.8147	0.914
f_2	40.5	46.75	33.1	51.02	59.37	67.97	74.24	71.87	85.42	Ref

R_0, R_1, R_H, R_{HC} and R_{KP} are the correlation coefficients of the zero order, first order, Higuchi, Hixson Crowell, and Korsmeyer-Peppas equations; n_p is diffusion exponent; and f_2 is similarity factor.
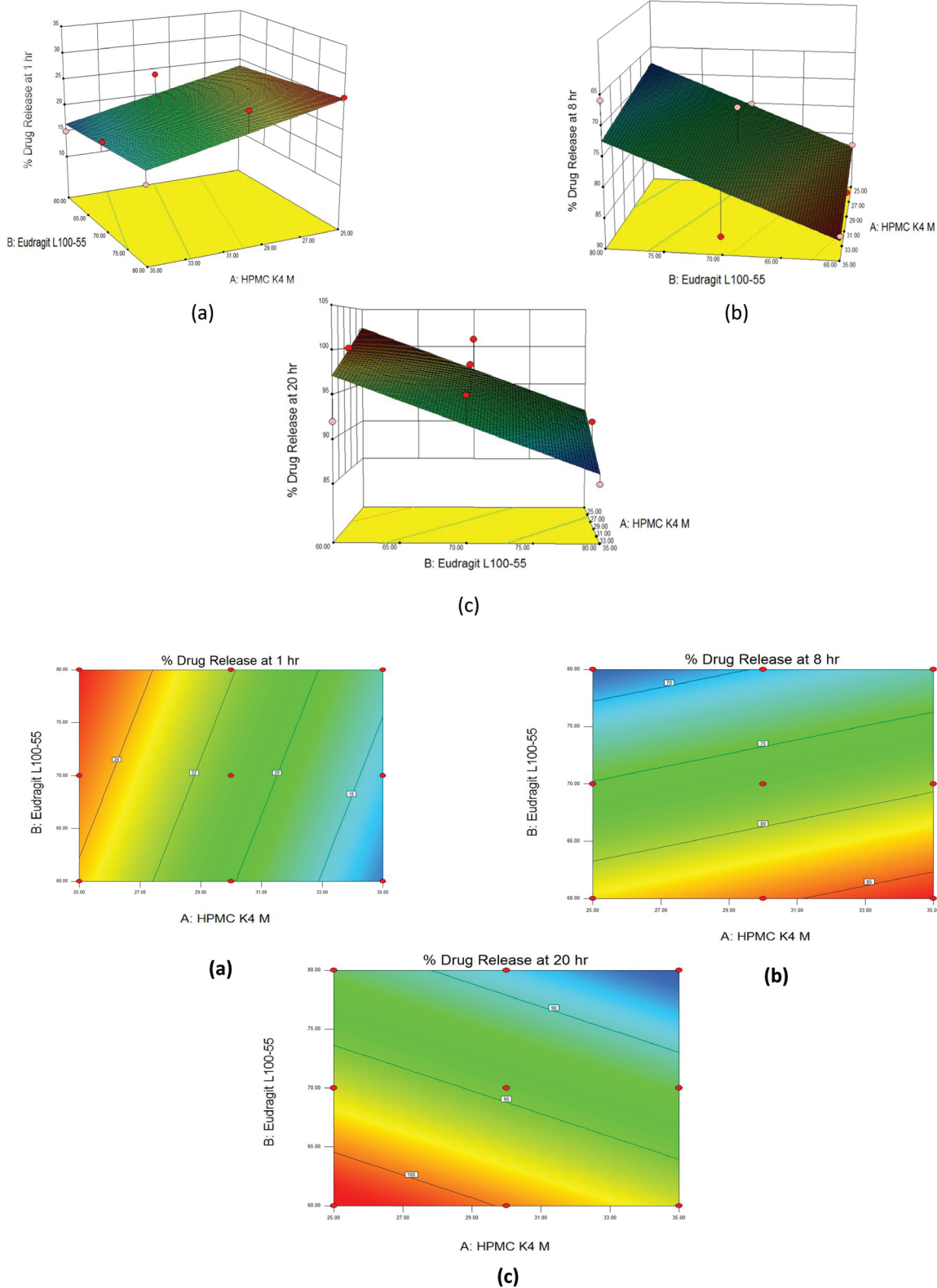
Figure 2. 3D response plots (top) and contour plots (bottom) of cumulative drug release (%) in 0.1 N HCl at 1 h (a), 8 h (b), and 20 h (c).

medium [0], and low [-1]). The impact of these factors was studied on response parameters (dissolution at 1, 8, and 20 h; Y_1 [%DR$_1$], Y_2 [%DR$_8$], and Y_3 [%DR$_{20}$], respectively) in the present investigation. The outline of trials and response outcomes are presented in Table 2. The polynomial model equations were generated from the software, including the main factors and interaction factors after putting the data. The optimized equations are given below in Equations 1–3, respectively.

$$Y_1 = 4.94 - 4.02\,X_1 - 1.05\,X_2 + 0.42\,X_1X_2 + 1.30\,X_1^2 + 0.025\,X_2^2 \quad \text{Eq. (1)}$$

$$Y_2 = 96.02 + 4.08\,X_1 + 0.82\,X_2 - 0.45\,X_1X_2 - 1.63\,X_1^2 - 0.75\,X_2^2 \quad \text{Eq. (2)}$$

$$Y_3 = 45.18 + 3.83\,X_1 + 0.97\,X_2 - 0.43\,X_1X_2 - 1.39\,X_1^2 - 0.14\,X_2^2 \quad \text{Eq. (3)}$$

Coefficients β_1 and β_2 were significant for Y_1, Y_2, and Y3; β_1 and β_2 were negative for Y_1, but positive for Y_2 and Y_3. Drug release in HCl Buffer pH 2.2 decreased with increasing concentration of X_1 and X_2. ANOVA results are depicted in the Table 3, showing that all models were significant for all the studied responses. Design Expert software was employed to produce 3D response surface plots (Figure 2), which show a downward inclination of the wire mesh at higher level (+1) and upward inclination at the lower level (-1) for the concentration of both X_1 and X_2. The plot trend showed the combined effect of X_1 and X_2 in retardation of drug release in the acidic medium. However, higher concentrations of X_1 and X_2 increased drug release owing to increased elasticity of the film and pore formation.

Table 3. Analysis of Variance for Dependent Variables from Full Factorial Design

Source	Degrees of Freedom	Sum of Squares	Mean Square	F-ratio	P-value
Cumulative drug release(%) in 0.1 N HCl at 1 h					
Linear Model	2	86.67	43.33	5.391	0.0457
X_1	1	80.66	80.66	10.036	0.0194
X_2	1	6.00	6.00	0.746	0.0408
Cumulative drug release (%) in 0.1 N HCl at 8 h					
Linear Model	2	336.33	168.16	6.241	0.0342
X_1	1	28.16	28.16	1.045	0.0360
X_2	1	308.16	308.16	11.437	0.0148
Cumulative drug release (%) in 0.1 N HCl at 20 h					
Linear Model	2	224.16	112.08	5.805	0.0395
X_1	1	42.66	42.66	2.210	0.0177
X_2	1	181.50	181.50	9.401	0.0220

To optimize the responses, contour plots were generated (Fig. 2). Interestingly, the associated degrees from zero outside of the bounds is within the range of at least one goal. The concentrations of independent variables that depicted maximum desirability are close to 1.

Therefore, the statistically optimized formulation was F9 with 25 mg HPMC K4M and 80 mg methacrylic acid.

Release Profile of the Optimized Formulation
The dissolution profile of the optimized formulation (F9) is presented in Figure 3. The cumulative mean ± SD amount of drug released in HCl buffer pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8 was 92.16% ± 3.59%, 92.44% ±3.12%, and 99.42% ± 3.72%, respectively, after completion of 20 hours (Fig. 3). Evidently, the percentage of drug released from the optimized tablet formulation was affected by changes in pH, primarily due to the presence of methacrylic acid as the delayed-release polymer. Methacrylic acid has low solubility at acidic pH conditions, therefore the amount of drug released was significantly lesser in acidic (pH 1.2 and 4.5) media. Its high solubility in phosphate buffer pH 6.8 resulted in almost complete release of guanfacine hydrochloride in 20 hours (Fig. 3). Thus, optimized combination of HPMC K4M and methacrylic acid as the matrix attained extended release of drug throughout the day.
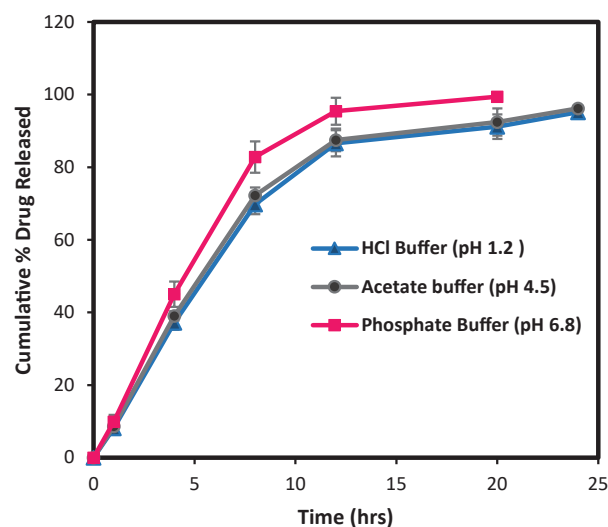

Figure 3. Comparative plot of cumulative drug release of the optimized formulation (F9).

Stability Study
The stability study of the optimized formulation (F9) showed no indications of change in the appearance of tablets, assay, % drug release in acidic medium, etc. The results of stability study in various conditions and the % drug release after 3 months.

CONCLUSION

This investigation focused on the effect of varying concentrations of HPMC K4M and methacrylic acid (Eudragit L 100-55) in designing the extended-release tablets of guanfacine hydrochloride. The precompression evaluation and compatibility studies indicated suitability of the chosen excipients. Physical characterization parameters of the compressed tablets were within the acceptable range. The release kinetics of the formulations best fit the Hixson Crowell and Higuchi's equation, owing to slow erosion of tablet surface. The optimized formulation was found by employing 3^2 factorial designs to identify the most suitable concentration of HPMC K4M and methacrylic acid in formulation F9, which met all requirements with regards to desired rate of release and high f_2 value. Dissolution of the optimized formulation was considerably higher in phosphate buffer pH 6.8 compared with HCl buffer pH 1.2 and acetate buffer pH 4.5. There were no signs of instability after 3 months of storage. The formulation was successful in delaying the release of drug, which may be useful in protecting drugs from destabilizing in the acidic environment of the stomach. The formulation is expected to show prolonged duration of action in future in vivo studies.

CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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