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ORIGINAL RESEARCH

Quality by Design (QbD)-Based Numerical and Graphical Optimization Technique for the Development of Osmotic Pump Controlled-Release Metoclopramide HCl Tablets

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Purpose: To develop the osmotically controlled-release gastroprokinetic metoclopramide HCl tablets, using quality by design (QbD)-numerical and graphical optimization technique for the treatment of gastroparesis and prophylaxis of delayed nausea and vomiting induced by low-high emetogenic chemotherapy.

Methods: Formulations were designed by central composite design using Design Expert version 11.0.0, with osmogen concentration (X_1), orifice size (X_2), and tablet weight gain after coating (X_3) as input and in-vitro drug release at 1hr. (Y_1), 6 hrs. (Y_2), and 12 hrs. (Y_3), and the regression coefficient of drug release data fitted to zero-order, RSQ zero (Y_4) as output variables. Core tablets prepared by direct compression were coated with Opadry® CA. The experimental design was validated by the polynomial equation. A correlation between predicted and observed values was evaluated by random checkpoint analysis. The optimized formulations were characterized for drug release, pH effect, osmolarity, agitation intensity, surface morphology, and stability study, and were subjected to accelerated studies according to ICH guidelines.

Results: The interaction charts and response surface plots deduced a significant simultaneous effect of X variables on in vitro drug release and RSQ zero. The numerical optimization model predicted >90% drug release with X_1 (13.30%), X_2 (0.6 mm), and X_3 (7.96%). Random checkpoint analysis showed a good correlation between predicted and observed values. The optimized formulation followed zero-order kinetics (r^2=0.9703) drug release. Shelf life calculated was 2.8 years as per ICH guidelines.

Conclusion: The QbD-based approach was found successful in developing controlled release osmotic tablets of metoclopramide HCl, for reducing the dosage frequency, better emetic control, and improve patient compliance.

Keywords: metoclopramide, elementary osmotic tablet, EOP, central composite design, controlled release, quality by design, QbD, numerical optimization

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Introduction

Steady-state drug concentration is difficult to obtain from oral conventional dosage forms due to the wide fluctuation of plasma drug levels. This unpredictability may lead to difficulty in achieving the targeted concentration, resulting in either an undesirable drug effect or no therapeutic response. A practical approach to overcome these disadvantages is to prepare a controlled release drug delivery system

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that releases drugs in a sustainable and more predictable manner.[1] The design of an osmotically controlled drug delivery system is one of the techniques for controlling drug release with ideally zero-order kinetics comparing to other controlled release drug delivery systems. It is also independent of the different physiological factors of the gastrointestinal system, such as gastrointestinal (GI) motility, pH variation, and presence of food. In designing such a system, drugs having a broad range of solubility can be selected. Moreover, this system is also supposed to provide a high degree of in vitro and in vivo correlation (IVIVC).[2,3]

Several modifications have been made in the osmotic drug delivery system since its introduction. The first osmotic pump device introduced by Theeuwees in 1970 was an elementary osmotic pump (EOP).[4] This EOP was a single compartment osmotic system, comprised of an inner core having an active pharmaceutical ingredient with or without osmogen and coated with a semipermeable membrane with an orifice created by laser or manual technique. When the pump comes in contact with GI fluids, fluids imbibes in the core through the semipermeable membrane due to the osmotic pressure gradient, resulting in the formation of a saturated drug solution there. The saturated solution release through the orifice, as shown in Figure 1 controlled by membrane surface area A, thickness h, Lp mechanical permeability capacity of the membrane. In contrast, σ is the coefficient of reflection, the difference of osmotic pressure Δπ, and hydrostatic pressure difference Δ p across the membrane (Equation 1).

$$\frac{dm}{dt} = \frac{A}{h} Lp(\sigma \Delta \pi) \cdot C \quad (1)$$

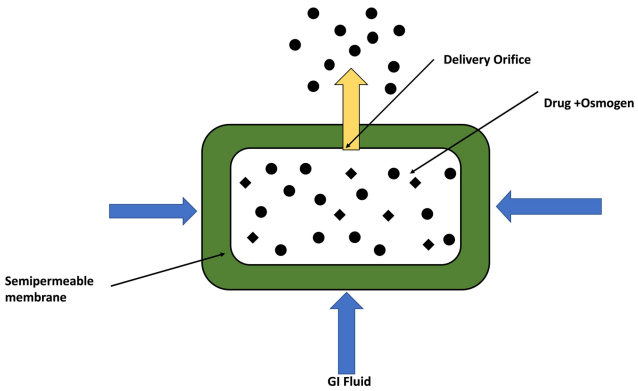


Figure 1 Elementary osmotic pump.

With the increased sized of the delivery orifice hydrostatic pressure system within the system is minimized ($\Delta\pi \gg \Delta P$). The osmotic pressure within the core is higher than the osmotic pressure of the environment so that the product $Lp\ \sigma$ is replaced by constant k (Equation 2)

$$\frac{dm}{dt} = \frac{A}{h} k\pi.C \quad (2)$$

The pump ideally should follow zero-order release kinetics ($Q_t=K_o t$) depending upon the intrinsic solubility of the compound.[5] Designing osmotically controlled pumps following the zero-order release rate for highly soluble drugs like MCP is a challenging task.[6] Opadry® CA is a semipermeable membrane former that contains cellulose acetate as an insoluble component and polyethylene 3350 as water-soluble component.[2]

Metoclopramide hydrochloride (MCP), (4-amino-5-chloro-2-methoxy-N-(2 diethylaminoethyl)), is a gastro prokinetic drug, which has an antagonist effect on dopamine receptors of the central nervous system and gastrointestinal smooth muscles.[7] It increases the threshold for vomiting at the chemoreceptor trigger zone and thus is considered as a drug of choice against chemotherapy-induced emesis, especially in adults receiving low-high emetogenic chemotherapy. According to the updated consensus of the Multinational Association of Supportive Care in Cancer by the European Society for Medical Oncology (MASCC/ESMO) in 2016, MCP is the antiemetic drug of choice in advanced cancers, and its dose is titrated to its effect. MASCC/ESMO recommended oral antiemetic dose of MCP is 20 mg 4 times daily for 2–4 days. Therefore, osmotically controlled oral metoclopramide HCl tablets following zero-order release kinetics, can provide better control of nausea and vomiting caused by chemotherapeutics agents like cisplatin, mechlorethamine, streptozocin, cyclophosphamide, carmustine, dacarbazine, and their combinations.[8] MCP is also useful for the treatment of a variety of gastrointestinal disorders such as dyspepsia, esophageal reflux disease. Currently, it is the only Food and Drug Administration (FDA) approved drug for the treatment of gastroparesis.[9–11]

Metoclopramide is a well-tolerated drug at usual therapeutic doses; generally, side effects are infrequent; however, long-term use of MCP can cause extrapyramidal effects,[12] especially in elderly females, patient with liver and kidney disease, diabetes, or those on antipsychotic drug therapy. For gastroesophageal reflux disease, the immediate-release tablet, in a dose of 10 mg, is administered 3 to 4 times a day.[13]

The Design of Experiments (DoE) is a widely used technique for the implementation of quality by design (QbD) approach in both industrial and research settings. It is also suggested by FDA because "it provides a structured, organized method for determining the relationship between factors affecting a process and the response of that process".[14] Drug screening, development, and analysis have traditionally been carried out by "one factor at a time' (OFAT) approach, now has mostly been replaced by QbD technique. QbD provides better results with fewer experimental runs and includes both screening and optimization designs; it not only describes the main effect of different input variables but also their interaction in a cost-effective manner.[15]

The study aims to design and develop an osmotically controlled tablet of highly soluble drug metoclopramide HCl (MCP) by numerical and graphical optimization technique, using central composite design (CCD). The zero-order release kinetics of the oral osmotic system of MCP will be suitable for the better prophylaxis of delayed nausea and vomiting caused by low and high emetogenic chemotherapeutic agents, moreover, it will also reduce the frequency of administration in gastroparesis and gastroesophageal reflux disease for better patient compliance. The directly compressed core tablets, were coated by Opadry® CA as a semipermeable membrane former. The effect of the NaCl concentration (osmogen), orifice size and, tablet weight gain after coating was studied on cumulative drug release (% CDR) and regression coefficient of release data fitted to zero (RSQ zero). The targeted attributes were obtained by numerical and graphical optimization. FTIR (Fourier Transform Infrared Spectroscopy) was used to evaluate the MCP and excipients interaction. The SEM (Scanning electron microscopy) was applied to study the surface morphology of the tablet before and after drug release. The optimized formulation was subjected to stability study as per ICH guidelines.

Materials and Methods

Chemicals

Metoclopramide Hydrochloride was gifted from GSK. (336.3 g/mol, 98.0%-101% w/w, Batch number IMGAB), with the expiry of 03–2024. Colorcon Limited (Kent, UK) provided Opadry® CA. Avicel pH 101 (226 g/mol, 97% w/w), Magnesium stearate (591.257 g/mol, ≥99.5% w/w) and Aerosil (60.08 g/mol, 99.8% w/w), were purchased from Sigma-Aldrich, Germany. Sodium chloride (58.44 g/mol, ≥99.5% w/w), Sodium hydroxide (40.00 g/mol, ≥99% w/w), Potassium Dihydrogen phosphate (136.08 g/mol, ≥99.5% w/w), Acetone (58.08 g/mol, ≥99.8% w/w) Acetonitrile (41.05 g/mol ≥99.9), and Hydrochloric acid (36.458 g/mol, 37–38% w/w) were obtained from Merck, Germany.

Experimental Design for Metoclopramide Osmotic Tablets

Central composite design (CCD) provides a feasible and accurate way to analyze three factors at three levels statistically.[16] A three-factor, three levels of central composite design was applied for the optimization of the MCP osmotic system using Design-Expert Software 11.0.0. The factors affecting drug release from osmotic systems are the amount of NaCl (5–15%) (osmogen), orifice size (0.2–08 mm), and tablet weight gain after coating (4–12%), were selected as independent variables X_1, X_2, and X_3 respectively.[2,17] The experiment runs were 14 with six center point formulations (Table 1). All other formulations and processing variables were kept constant throughout the study. The cumulative amount of drug release (% CDR) at 1 hr. (Y_1), 6 hrs. (Y_2), 12 hrs. (Y_3). Moreover, the regression coefficient of release data fitted to zero order equation, ie, RSQ zero (Y_4) were selected as response variables.[18]

Statistical analysis of the experimental design was performed by multiple regression analysis to evaluate the contribution of each factor with different levels to the response; two-way analysis of variance (ANOVA) was performed using the Design Expert version 11.0.0 software. To graphically demonstrate the influence of each factor on the response, the response surface plots were generated. Polynomial models, including interaction and quadratic terms, were generated for four response variables using multiple linear regression analysis (MLRA) approach. Using a 5% level of significance, if the P-value was less than 0.05, the model and the model terms were considered significant. The general form of the MLRA model is best represented by the following equation,

$$Y = A + AX_1 + BX_2 + CX_3 + AXB_1X_2 + AXC_1X_3 + BCX_2X_3 + AX_1^2 + BX_2^2 + CX_3^2 \quad (3)$$

The coefficients of variables and interaction terms are designated as A, B and C, whereas A_o is the intercept.

Table 1 Composition of Batches and Experimental Values of Responses Y_1, Y_2, Y_3, and Y_4

Formulation	X_1	X_2	X_3	A:X_1%	B:X_2 mm	C:X_3%	Y_1%	Y_2%	Y_3%	Y_4
F-1	0.000	0.000	1.682	10	0.5	14.72	9.26	42.23	70.95	0.915
F-2	1.000	1.000	−1.000	15	0.8	4	31.29	72.23	100	0.5946
F-3	0.000	0.000	0.000	10	0.5	8	13.95	38.12	79.43	0.9498
F-4	0.000	1.682	0.000	10	1.00	8	28.93	55.23	85.74	0.6422
F-5	−1.000	1.000	1.000	5	0.8	12	9.29	17.92	44.76	0.9009
F-6	0.000	0.000	0.000	10	0.5	8	8.79	40.55	80.43	0.9813
F-7	−1.000	−1.000	−1.000	5	0.2	4	27.04	51.98	100	0.8191
F-8	1.682	0.000	0.000	18.40	0.5	8	12.05	60.02	97.23	0.9578
F-9	−1.000	−1.000	1.000	5	0.2	12	6.09	12.23	40.2	0.9238
F-10	0.000	0.000	0.000	10	0.5	8	9.04	41.55	77.34	0.9594
F-11	0.000	0.000	−1.682	10	0.5	1.27	31.65	55.71	99	0.8072
F-12	0.000	0.000	0.000	10	0.5	8	12.47	37.08	81.04	0.9582
F-13	−1.000	1.000	−1.000	5	0.8	4	21.26	60.12	100	0.7949
F-14	1.000	1.000	1.000	15	0.8	12	10.37	51.55	99.59	0.9955
F-15	1.000	−1.000	1.000	15	0.2	12	10.75	49.88	98.37	0.9944
F-16	0.000	0.000	0.000	10	0.5	8	11.01	37.12	79.43	0.9542
F-17	0.000	0.000	0.000	10	0.5	8	10.36	36.15	76.49	0.9702
F-18	−1.682	0.000	0.000	1.59	0.5	8	3.06	21.04	30.06	0.9249
F-19	0.000	−1.682	0.000	10	−0.004	8	0	0	0	0
F-20	1.000	−1.000	−1.000	15	0.2	4	29.87	65.84	100	0.7417

Notes: X_1=concentration of osmogen (%), X_2=Orifice size (mm), X3=Tablet weight gain after coating (%), Y_1=%CDR at1 hrs., Y_2=%CDR at 6 hrs., Y_3=%CDR at 12 hrs. and Y_4= regression coefficient of release data fitted to zero order.

Preparation of the Core Tablets

The formulations (F1-F20), as shown in Table 1 and Table S1 containing 30 mg dose of the MCP, were prepared by direct compression technique, using a single punch tablet press (Korch Erweka, Frankfurt, Germany), with B-Type bi convex toolset of 8.6mm. For the preparation of core tablets, the crystals of sodium chloride were first triturated, and all the ingredients were passed through sieve No. 30 separately. Accurately weighed quantities of MCP and sodium chloride (osmogen) were thoroughly mixed by tumbling for 5 minutes; Avicel pH 101 (diluent) was then added to the mixture and mixed for 10 min further. Finally, weighed quantities of magnesium stearate (lubricant) and Aerosil (wicking agent) was added and mixed for an additional 3 minutes. The pre-compression parameters (Hausner's ratio, angle of repose, Carr's index, bulk and tapped densities) were determined to assure the free-flowing nature of the powder mixture.[19]

The deformation time study of the center point formulation (core tablet) was conducted using Natoli NP-RD10A bench-top tablet press, with the application of Natoli AIM TM Pro Plus Software (Natoli Engineering Inc. MO, USA) at 3000, 4000. 5000, 6000, 7000, 8000, 9000 and 10,000 N (n=3) compressional force. For Heckel analysis, parameters calculated for included the determination of weight and volume of compacted tablets, whereas the true density was calculated using additive procedure using the density values supplied by the respective chemical manufacturer. Finally, mean data was plotted as compression pressure "P" (MPa) vs ln(1-(1/D)) and compression pressure "P" (MPa) vs tablet hardness (N). Where "D" is the relative density, P is the applied pressure in MPa. The yield value was calculated, and tablets of all trial formulation (core tablets) F1-F20 were then compressed on single punch machine (see Supplementary Figure S1 and S2).[20]

Tablet Coating and Orifice Formation

After 48 hours of resting period to ensure the completion of elastic stress relaxation time, the trial batches (F1-F20) were coated in a conventional laboratory-scale tablet coating pan by Opadry® CA. A clear solution of Opadry ® CA (7% w/w) was prepared in a mixture of 90 parts of acetone and ten parts by weight of distilled water. The coating was carried out in a coating pan, having a diameter of 12 inches attached to a drive motor, rotating at a speed of 12 rpm. The tablet cores were heated at 40 °C and, the Opadry® CA solution was sprayed at the rate of 7–9 mL/min with a spray

gun fitted to an air compressor (Atomization pressure of 1kg/cm2). When the desired coating weight gain (4–12%) was attained (see Supplementary Table S1), the coated tablets were subjected to drying for 16 hours at 40°C in a hot air oven.[21]

The Micro drill (Proxxon MF 70 Germany) was used to create an orifice in the center (at one side only) of size 0.2–0.8mm.

Pharmaceutical Quality Evaluation of Metoclopramide Osmotic Tablet

Weight Variation

To study the weight variation in core and coated tablets, a set of 20 tablets from each formulation were weighed using an electronic balance, and the test was performed according to the official method, considering a limit of ±7.5%.[22]

Thickness and Diameter

The thickness and diameter of the core tablets and coated tablets were measured by using a Vernier caliper. Twenty tablets from each formulation were randomly selected and, their thickness and diameter were measured in millimeters.

Hardness and Friability

The hardness of randomly selected core and coated tablets (n=20) were determined as per the USP method, using hardness tester. Friability of core tablets (n=20) was determined by Roche Friabilator (Electrolab EF-2).[22]

Content Assay

A validated reveres phase HPLC method proposed by Khan et al[23] was used to quantify MCP in trial batches. Twenty tablets from each batch containing 30 mg of the drug were selected randomly, accurately weighed, and grounded to a fine powder. Chromatographic separation was performed on a C18 (3.9 × 300mm, Bondapak RP column) at 25°C using HPLC (LC-10 AT VP Shimadzu Japan). The mobile phase containing Acetonitrile and buffer (Potassium dihydrogen phosphate pH 3) in the 40:60 ratio was flown at a rate of 2mL/min. The MCP response was recorded at 275 nm using a UV detector (LC 10a VP, Shimadzu, Japan).

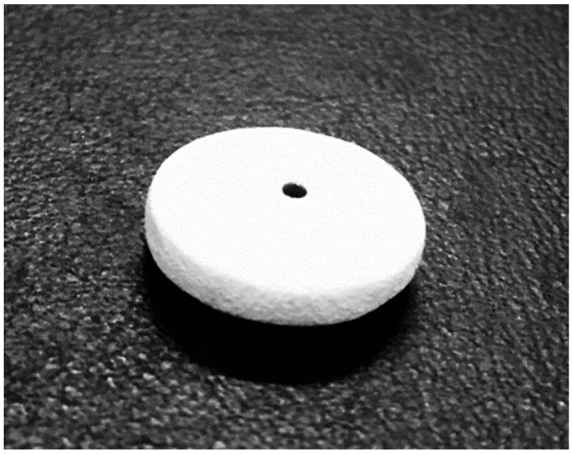
In vitro Drug Release

The release rate of MCP from trial formulations (F1-F20) was determined using USP apparatus II (Erweka, DT 600 Heusentamn, Germany). The dissolution test was conducted in 900 mL of acidic buffer (pH 1.2) for the first 2 hours at a paddle speed of 50 rpm, followed by the testing in phosphate buffer (pH 6.8).[24] During the test, the temperature of the medium was maintained at 37°C ± 0.5°C. A sample of 10 mL was drawn at fixed time intervals and filtered through 0.45µm membrane filter paper. An equal volume of fresh medium replaced the volume of each sample drawn. Cumulative drug release was determined by a validated HPLC method[23] has already been described in Content Assay.

As a dependent variable cumulative drug release at 1hr., 6hrs and 12hrs were observed. The results were grouped into four based on low, medium, and high levels of Sodium Chloride concentrations and center point formulations, with different orifice sizes, and % weight gain of tablet after coating. Low-level group (−1) bears F-5, F-7, F-9, F-13, and F-18, the medium-level group (0) contains F-1, F-4 and F-11whereas, F-2, F-8, F-14, F-15and F-20 were grouped into high-level concentration of NaCl (+1). The remaining formulation F-3, F-6, F-10, F-12, F-16, and F-17 were center point batches with the

Table 2 Selection of Factors, Levels, and Responses for Central Composite Design

Independent Variables	**Levels**	
	Low	**High**
X_1 =Osmogen Conc. (%) X_2=Orifice Size (mm) X_3=Tablet weight gain after coating (%)	5 0.2 4	15 0.8 12
Dependent Value		**Constraints**
	Y_1= Cumulative % drug Release in 1hr. Y_2= Cumulative % drug Release in 6hrs. Y_3= Cumulative % drug Release in12hrs. Y_4= r^2 (RSQ Zero)	0%<Y1<20% 50%<Y2<60% 85%<Y3<100% Y4Maximum (>0.9)



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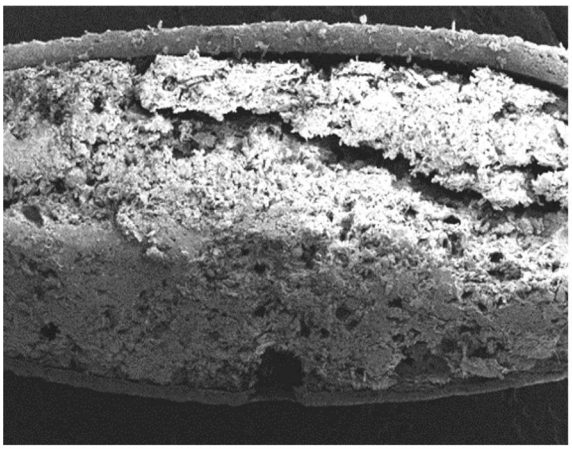

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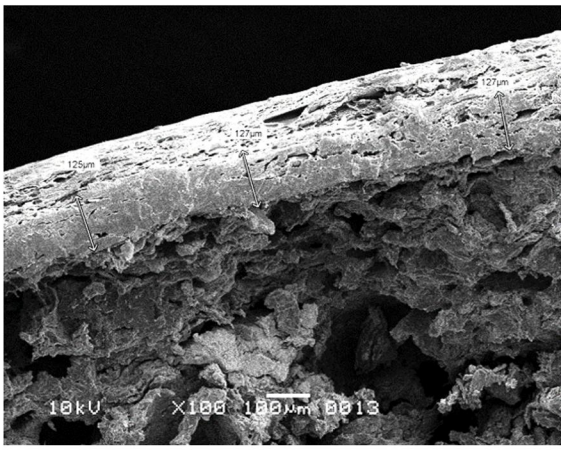

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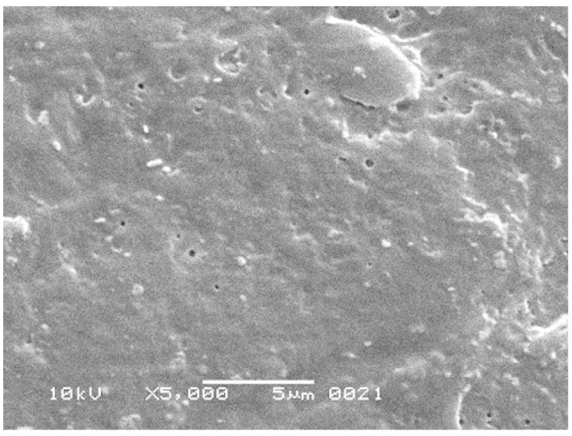

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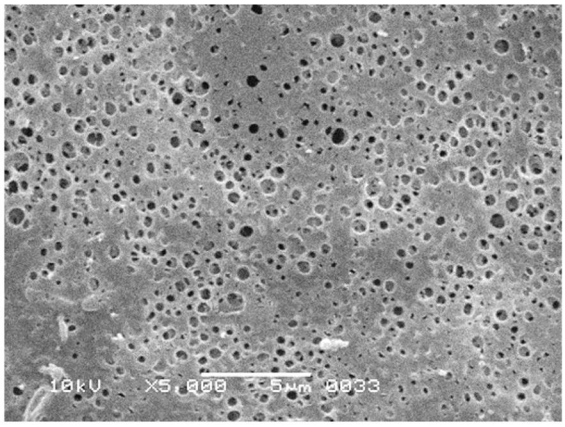


E

Figure 2 Physical evaluation and electron scan micrograph of (**A**) an image of metoclopramide osmotic tablet showing an orifice. (**B**) cross-section of the optimized formulation membrane showing uniform formation od semipermeable membrane (**C**) coating thickness of the tablet membrane structure of optimized formulation before dissolution (**D**) membrane structure of optimized formulation before dissolution (**E**) membrane structure of optimized formulation after dissolution.

same composition. F-19 is the axial formulation with no orifice.

Drug Release Kinetics

Formulations (F1-F20) dissolution data were subjected to different release kinetic models like Zero order ($Q_t = k_0 t$)[25] First Order ($\ln Q_t = \ln Q_0 - k_1 t$),[26] Higuchi ($Q_t = K_H t^{1/2}$),[27] Hixon-Crowell ($Q_0 - Q_t = k_{HC} t$)[28] and Korsmeyer- Peppas ($Qt/Q_0 = K_{KP} t^n$).[29,30]

Where Q_t is the amount of drug release at time *t,* Q_0 is the initial amount of the drug in the formulation, and k_0, k_1, k_H, k_{HC} and k_{kp} are the release rate constants for the zero-order, first-order, Higuchi model, Hixson–Crowell and Korsmeyer Peppas rate equations, respectively. The in vitro drug release plots were statistically analyzed by Design-Expert software 11.0.0 for the selection of optimized formulation.

Numerical Optimization

Numerical and graphical optimization was performed to ascertain the application of model equations and Response plots for the prediction of responses. The desirability approach was adapted for which targeted constraints are given in Table 2. The target formulations with desirable outcomes were prepared, and experimental data was obtained and compared with the predicted one. The percentage of error was calculated, which should come out to be ≤5%.[31]

Characterization of Optimized Formulation

For the confirmation of osmosis as a dominating mechanism for controlling the drug release, the dissolution test (multiple points) of the optimized formulation was conducted in dissolution media containing 1mol/L and 2 mol/L of Sodium Chloride having different osmolarity. With the higher concentration of sodium chloride, low drug release was expected.

Similarly, the dissolution test was also used to assess the pH-independent release of MCP from the optimized formulation at pH 1.2 (Hydrochloric acid buffer USP), pH 4.5, and 6.8 (Phosphate buffer USP). The effect of agitation speed on drug release was also evaluated at the paddle speed of 50, 75, and 100 rpm. The drug release profiles were compared by using similarity factor (f_2) and difference factor (f_1).

Fourier Transform Infrared Spectroscopy Study

FTIR spectroscopy technique analyses the significant changes in the position and shape of the absorbance band to provide useful information about the chemical reaction if taking place between the active pharmaceutical ingredient (API) and the excipients. Drug-Excipients compatibility of the optimized formulation was determined by Fourier Transform Infrared Spectroscopy (FTIR) (Nicolet- 6700; Thermo Scientific TM, USA). OMNIC™ Specta Software was used to record Infrared spectra in the range of 4000 to 400 cm^{-1}. Powder blend in the ratio of 1:1 (MCP: Excipient) were placed directly as a thin film for the FTIR analysis.

Scanning Electron Microscopic Analysis (SEM)

Scanning electron microscopy (SEM) (JSM- 6380A, JEOL, Japan) was used to observe the physical characteristics of the MCP osmotic tablets before and after drug release. The tablets (after 12 hours of dissolution) were dried overnight at 40°C before SEM analysis. The samples were mounted on an aluminum stud and sputter-coated with gold up to 250 0A using an auto Coater (JFC-1500; JEOL) and examined under SEM.

Accelerated Stability Study

The stability study of optimized formulation was carried out at accelerated conditions (40°C± 2°C and 75 ± 5% RH) for 6 months as per ICH guidelines.[32] The formulation was analyzed for physical characteristics, assay, and release profile at different time intervals. Similarity factors and difference factors were determined for comparison of the drug release profiles obtained at different time intervals during the stability study. Shelf life was determined by using Minitab Software version 19.

Results and Discussion

Experimental Design for Metoclopramide Osmotic Tablets

The univariate, trial and error-based approach had largely been replaced by QbD approach for the development of quality pharmaceutical products. DoE is a powerful statistical tool, and has been adopted by the pharmaceutical sector for discovery, development, and manufacturing process of the drug products because of high yield, reduce the experimental runs, and low development and manufacturing cost.[33]

QbD approach was successfully applied to control the release of MCP at zero order rate for 12 hours, from osmotic

Table 3 Evaluation of Core and Coated Tablets

Formulation	Core Tablet Weight (mg (n=20)	Coated Tab Weight (n=20)	Core Tab Thickness mm (n=20)	Coated Tab Thickness mm (n=20)	Core Tab Diameter mm (n=20)	Coated Diameter mm (n=20)	Core Tab Hardness kg/cm^2 (n=20)	Coated Tablet Hardness kg/cm^2 (n=20)	Friability (% n=20)	Drug Content % (n=20)
F-1	201.15±9.33	222.9±3.79	3.23 ±0.127	4.67 ±0.39	8.66 ± 0.455	9.64± 0.28	7.59±0.496	10.16±0.48	0.183 ± 0.12	97.07±0.962
F-2	199.2 ± 9.73	205.1 ±4.55	3.22 ±0.134	4.37±0.21	8.71 ± 0.203	9.62 ± 0.28	8.01±0.516	10.14±0.39	0.221 ±0.13	100.06± 1.4
F-3	206.55 ± 7.27	209.7±7.84	3.25 ±0.146	4.40±0.29	8.69 ± 0.193	9.65±0.15	7.58±0.373	10.26 ± 0.44	0.177 ±0.12	99.82±1.13
F-4	200.85 ± 9.81	208.3±7.47	3.28 ±0.158	4.51±0.25	8.76 ± 0.145	9.77±0.14	7.73±0.506	9.97 ± 0.43	0.193 ± 0.14	100.531±0.2
F-5	201.5 ± 8.90	219.3±5.11	3.23 ±0.131	4.57±0.33	8.79 ± 0.30	9.80±0.06	7.54±0.382	10.34 ± 0.28	0.186 ± 0.11	97.37±1.67
F-6	201.1 ± 8.91	212.15±4.00	3.22 ±0.129	4.55±0.32	8.77 ±0.039	9.76±0.173	7.63±0.319	10.26 ± 0.44	0.226 ± 0.11	97.06±0.74
F-7	205.3 ± 9.52	208.15±5.21	3.24 ±0.127	3.37±0.42	8.69 ± 0.181	9.67±0.21	7.63±0.488	10.19 ± 0.5	0.193 ± 0.14	100.14±1.24
F-8	197.9 ± 8.36	222.7±7.022	3.30 ±0.162	4.54±0.34	8.76 ± 0.084	9.75± 0.17	7.82±0.551	10.0 ± 0.41	0.203 ± 0.11	99.84±1.45
F-9	199.5 ± 9.37	220.8±5.65	3.33 ±0.229	4.43±0.26	8.71 ± 0.175	9.68± 0.26	8.05±0.589	10.12 ± 0.52	0.239 ± 0.16	99.07±1.45
F-10	200.35 ± 9.74	213.8±7.06	3.28 ±0.152	4.58±0.301	8.76 ± 0.065	9.77± 0.07	7.68±0.574	10.06 ± 0.39	0.241 ±0.10	100.32±0.88
F-11	200.75 ± 8.48	200.5±5.97	3.20 ±0.229	4.39±0.27	8.76 ± 0.04	9.59± 0.31	7.73±0.444	10.09 ± 0.46	0.176 ± 0.12	98.94±1.62
F-12	204.6 ± 6.75	211.2±5.42	3.28 ±0.184	4.44±0.21	8.68 ±0.219	9.67± 0.23	8.11±0.461	9.99± 0.45	0.2 ± 0.12	99.49±1.07
F-13	201.75 ± 6.28	204.5±4.77	3.24 ±0.122	4.39±0.22	8.60 ± 0.129	9.67± 0.15	7.33±0.493	9.74 ± 0.49	0.17 ± 0.9	98.80±1.67
F-14	205 ± 7.36	218.65±5.96	3.24 ± 0.12	4.42±0.27	8.74 ± 0.080	9.76± 0.11	7.32±0.488	9.98 ± 0.42	0.192 ± 0.13	97.92±0.84
F-15	204.75 ± 7.98	223.35±6.01	3.30 ±0.179	4.44±0.27	8.73 ± 0.141	9.75± 0.11	7.56±0.430	9.85 ± 0.46	0.184 ± 0.12	98.076±0.97
F-16	202.6 ± 8.65	214.75±5.26	3.36 ±0.245	4.39±0.17	8.76 ± 0.128	9.64± 0.19	7.40±0.474	9.86 ± 0.5	0.209 ± 0.15	100.29±0.61
F-17	203.05 ± 8.45	213.95±4.37	3.26 ± 0.176	4.51±0.26	8.80 ± 0.049	9.71± 0.12	7.78±0.550	10.03 ± 0.48	0.178 ± 0.11	100.2±0.73
F-18	203.3 ± 5.23	213.95±5.70	3.34 ± 0.233	4.42±0.24	8.74 ± 0.079	9.69± 0.19	7.03±0.492	9.97 ± 0.46	0.19 ± 0.14	100.13±1.13
F-19	198.55 ± 8.03	212.2±5.75	3.26 ± 0.151	4.57±0.23	8.64 ± 0.182	9.68± 0.17	7.12±0.654	10.12 ±0.51	0.225 ± 0.11	99.69±1.08
F-20	200.45 ± 8.73	204.75±5.09	3.21 ± 0.176	4.50±0.27	8.70 ± 0.247	9.54± 0.22	7.58±0.437	10.05 ± 0.42	0.211 ± 0.13	100.48±0.22

tablets. It may help in reducing the frequency of drug administration, maintaining the therapeutic drug plasma concentration for an extended period, and improving patient compliance for MCP, which has a short biological half-life (3–5 hrs) and requires drug administration 3–4 times a day.[7]

Formulation and process variables were selected based on the literature review.[3,34,35] Different researchers have reported various osmogens like mannitol, potassium chloride, fructose, sucrose, and sodium chloride. In current work, sodium chloride was selected as an osmogen because of its high potential of generating osmotic pressure in core tablets at comparatively lower concentrations.[5]

Preparation of the Core and Coated Tablets

Different formulations, each containing 30 mg of MCP were prepared, at the compression force of 10,000 N; as shown in Table 1, the yield value was calculated to be 91 MPa (see supplementary Table S1 and supplementary Figure S1). Opadry® CA dispersion has also been used by different formulation scientists to create semipermeable membrane over the core tablets.[36] Figure 2A shows an image of an osmotically controlled MCP tablet with a clear surface orifice. The SEM images of Figure 2B and C exhibit the uniform formation of the semipermeable membrane by Opadry® CA.[36]

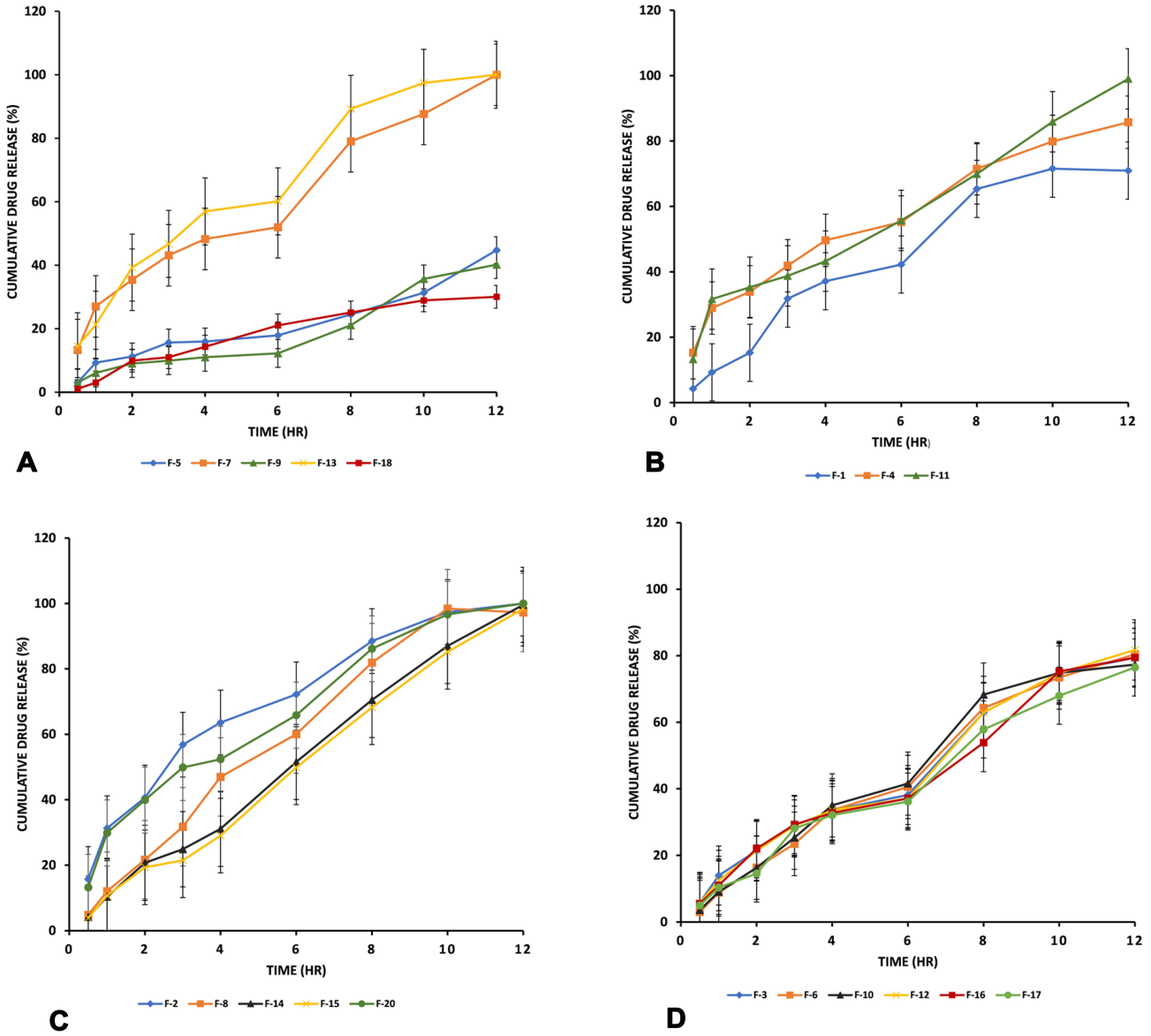


Figure 3 (**A**) Drug release profile of F-5, F-7, F-9,F-13, and F-18 batches, (**B**) drug release profile of F-1, F-4, and F-11 batches (**C**) drug release profile of F-2, F-8, F-14, F-15, and F-20 batches (**D**) drug release profile of F-3, F-4, F-20, F-12, F-16, and F-17 batches.

Pharmaceutical Quality Evaluation of Metoclopramide Osmotic Tablet

The hardness of all the core tablet batches was in the range of 7.03 ± 0.492 to 8.11 ± 0.461 kg/cm^2. The maximum friability recorded was 0.239± 0.16%. The thickness of the tablets was found, varying from 3.20 ± 0.229 to 3.36 ± 0.245 mm. The diameter of core tablets was 8.6± 0.129 to 8.8± 0.049 mm. The maximum and minimum average weight of all the tablets formulations were 197.9± 8.36 and 206.55± 7.27 mg, respectively. Tablet weights were found in the desired range of ±7.5% (USP). Drug content (%) was in the range of 97.06±0.74% to 100.531±0.2%, as shown in Table 3.

The hardness of coated batched was 9.74 ± 0.49–10.34 ± 0.28kg/cm^2; the thickness was 3.37 ±0.42 to 4.67 ±0.39mm and diameter in the range of 9.54 ± 0.22 to 9.8 ±0.06mm. The maximum and minimum average weight of all the coated tablet formulations were found in the range of 200.5±5.97 and 223.35±6.01 mg, respectively (Table 3).

In vitro Drug Release Study

The results of % CDR at 1, 6, and 12 hrs are given in Table 1. For a better understanding of the influence of input variables X_1, X_2, and X_3, on drug release, the total number of trial batches was grouped based on sodium chloride concentration, as shown in Figure 3A-D. Thakkar et al also grouped dissolution data of trial formulations based on different osmogen levels.[37]

Burst release was observed from the comparison of drug release profile of low level (−1) group F-7, and F-13, whereas F-5, F-9, and F-18, failed to meet the recommended criteria of osmotic tablets %CDR 6 and 12 hours (Figure 3A). Burst effect was also observed for the medium-level group F-4 and F-11 (Figure 3B) and high-level group F-2 and F-20 (Figure 3C). When the release profiles of formulation from the low-level group (−1) F-5 and F-9, and that of the high-level group (+1) F-14 and F-15, were compared, a positive effect of orifice size on MCP release was found as also reported in other studies.[38] The cumulative drug release of center point formulations F-3. F-6, F-10. F-12. F-16 and F-17 are given in Figure 3D. The axial point formulation without orifice, F-19 exhibited zero percent drug release, as given in Table 1. In medium level group (0) F-4 and F-11 showed burst release due to large orifice size and minimal weight gain after coating, respectively. F-1 bearing orifice of 0.5mm also failed to meet the criteria of controlled release tablet for % CDR 6 and 12 hrs (Table 1). Table 4 presents the CCD generated polynomial equation, the positive values of the coefficients against the individual terms, indicate the additive effect of X_1 and X_2 on drug release.

The response surface curves in Figure 4A-D presents the significant effect of input variables (Sodium Chloride concentration, orifice size, and tablet weight gain after coating) on response variables. The best fit for each of the responses Y_1 (% CDR at 1hr.), Y_2 (% CDR at 6 hrs.) and Y_3 (% CDR at 12 hrs.) and Y_4 (RSQ zero) were found for linear model or quadratic models on the basis of p-value less than 0.05% (Table 4). Polynomial equations were generated to measure the effect of the independent variables on the response variables. Mathematical relationships in the form of a polynomial equation for all the time constraints are shown in Table 4. The concentration of sodium chloride was found to be positively influencing the drug release rate, as also expressed by the design generated polynomial equation. It was also observed that the release rate of all trial batches (F1-F20) was initially increased with an increment in osmogen amount and then decreased with further increase in

Table 4 Probability Value of Selected Responses and Regression Coefficient of Applied Constraints

Response	***p*-value**
Y_1	0.0010
Y_2	0.0004
Y_3	0.0094
Y_4	0.0398
The regression coefficient of applied constraints	
Y_1=20.3379 + 0.493808 * X1 + 11.4995 * X2 + −2.02491 * X3	
Y_2=25.1651 + 2.38424 * X1 + 28.0141 * X2 + −2.58589 * X3	
Y_3=49.6625 + 3.3092 * X1 + 36.606 * X2 + −3.00681 * X3	
Y_4=0.493169 + −0.0388303 * X1 + 2.33354 * X2 + −0.0129157 * X3 + −0.00824167 * X1 * X2 + 0.00276812 * X1 * X3 + 0.0155729 * X2 * X3 + 0.000998447 * X1^2 + −2.1592X2^2+ −0.000213218 * X3^2	

concentration. The common ion effect may be the plausible reason for this trend.[39] In a similar study by Dev et al, the release of Triprolidine hydrochloride was modulated by the osmotic pressure generated by osmogene at zero-order rate. The common ion effect was the reported rate-controlling reason.[40] Figure 3A-D shows the drug release profiles of all the groups of NaCl concentrations. Upon the comparison of dissolution profiles of F-5, F-9, and F-14, F-15, respectively, a positive effect of NaCl concentration was found on drug release. The difference in the osmotic pressure in the core tablet and its exterior (due to changing the concentration of NaCl in dissolution media), is the driving force for drug release, so the lesser the difference lesser will be the drug release.

The tablet weight gain after coating (%) produced a profound effect on the dissolution profile and was observed

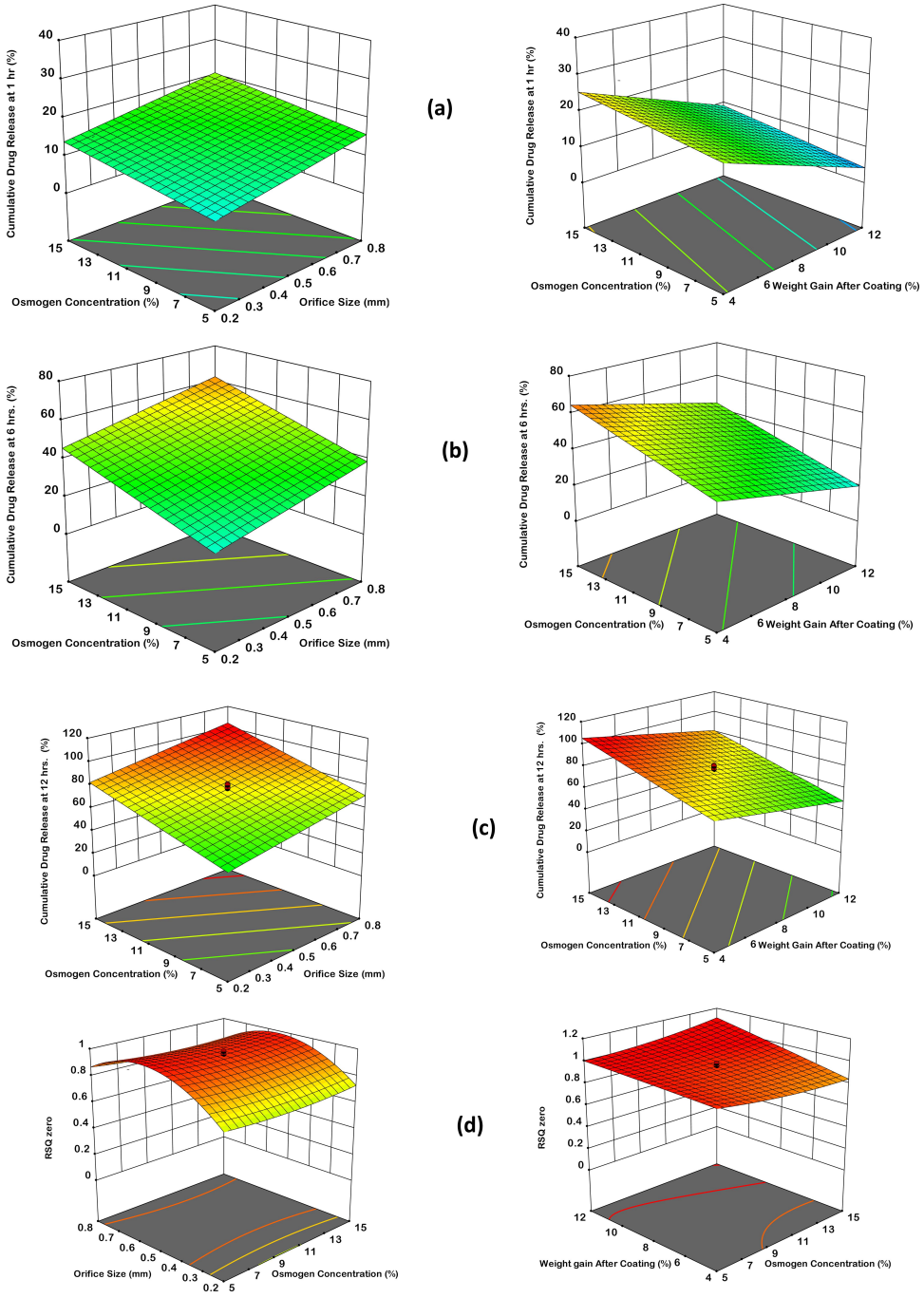


Figure 4 Response surface plots (3D) showing effect of osmogen concentration (X_1), orifice size (X_2) and weight gain after coating (X_3) on release of MCP osmotic tablet (a) at 1hr (b) at 6 hrs. (c) at 12 hrs. (d) on regression coefficient of release data fitted to zero-order (r^2).

Table 5 Release Kinetics Data of Batches F-1–F-20

Formulation	Zero Order		First Order		Higuchi		Hixon Crowell		Korsmeyer Peppas		
Code	r^2	K_o (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	K_{HC}($h^{-1/3}$)	r^2	K_{KP} (h^n)	n
F-1	0.9150	7.024	0.9732	0.113	0.8920	19.858	0.9712	0.033	9619	12.215	0.745
F-2	0.5946	10.315	0.9755	0.269	0.9852	19.858	0.9582	0.072	0.9853	30.54	0.495
F-3	0.9498	7.250	0.9594	0.116	0.8910	20.359	0.9696	0.033	0.9770	11.41	0.791
F-4	0.6422	8.442	0.9255	0.168	0.9874	24.655	0.8807	0.046	0.9875	24.255	0.508
F-5	0.9009	3.469	0.9030	0.042	0.8421	9.758	0.9035	0.013	0.9217	5.355	0.800
F-6	0.9813	8.442	0.9647	0.113	0.8595	20.082	0.9818	0.033	0.9874	9.150	0.892
F-7	0.8191	9.212	0.9233	0.186	0.9511	26.500	0.9236	0.051	0.9704	21.454	0.608
F-8	0.9778	9.373	0.9426	0.177	0.8834	26.277	0.9740	0.050	0.9804	14.158	0.811
F-9	0.9238	3.155	0.9391	0.037	0.7427	8.645	0.9080	0.012	0.9301	2.260	1.151
F-10	0.9594	7.299	0.9650	0.116	0.8655	20.389	0.9779	0.034	0.9739	10.291	0.842
F-11	0.8072	8.922	0.9010	0.174	0.9445	25.666	0.8992	0.048	0.9616	21.018	0.602
F-12	0.9582	7.304	0.9537	0.116	0.8803	20.480	0.9672	0.034	0.9770	10.811	0.820
F-13	0.7949	9.952	0.9534	0.224	0.9608	28.735	0.9592	0.061	0.9759	24.039	0.591
F-14	0.9955	8.528	0.9120	0.142	0.8387	23.523	0.9550	0.041	0.9959	9.064	0.972
F-15	0.9944	8.309	0.9120	0.135	0.8222	22.828	0.9474	0.039	0.9945	8.015	1.016
F-16	0.9542	7.044	0.9504	0.110	0.8783	19.757	0.9617	0.032	0.9732	10.471	0.818
F-17	0.9702	6.764	0.9683	0.103	0.8760	18.909	0.9789	0.030	0.9838	9.491	0.845
F-18	0.9249	2.916	0.9610	0.034	0.9115	8.256	0.9509	0.011	0.9780	5.196	0.734
F-19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
F-20	0.7417	9.957	0.9547	0.230	0.9788	28.900	0.9509	0.062	0.9848	26.011	0.554

to influence drug release negatively, as also expressed by the equation given in Table 4. At the same levels of X_1 and X_2 in F-1 and F-11, it was observed that the formulation (F-11) with 1.27% of tablet weight gain exhibited burst release after coating. In comparison, F-1, with the highest level of tablet weight gain 14.72%, the drug release rate decreased significantly. The results were mainly because of the barrier property of the membrane towards the dissolution medium, which increases with the rise in tablet weight again after coating that eventually reduces the drug release rate. A similar conclusion was also drawn by Liu et al.[41]

Drug Release Kinetics

The Dissolution profiles of all the trial batches (F1-F20) were fitted to different kinetic models to analyze the drug release kinetics and mechanism to provide the theoretical basis of the controlled release tablets.[42] The coefficient of correlation and release rate constant values were calculated using *DDSolver* are given in Table 5. First-order release kinetics were the best-fitted model to the low-level group (−1), ie, F-5 and F-9, that contains the low level of NaCl as osmogen. The high-level group (+1) with a high concentration of NaCl exhibited more compliance with the zero-order release kinetics. The formulations F-4 and F-11 from a medium level group (0) showed burst release, and F-1 followed First-order kinetics, the F-19 axial formulation without orifice, exhibited no drug release. It is evident that the formulation containing a higher concentration of osmogen followed Zero-order kinetics and showed better release control over the given time. The shift from First-order to Zero-order drug release was due to a change in drug solubility within the core of the pump. The possible reason for this decreased drug solubility is the common ion effect.[39,43]

Formulation Optimization

For optimizing the four responses with different target ranges, a multi-criteria decision approach was applied for the optimum settings of independent variables. Numerical optimization by the desirability function was used, the RSQ zero (Y_4) was maximized with different constraints of drug

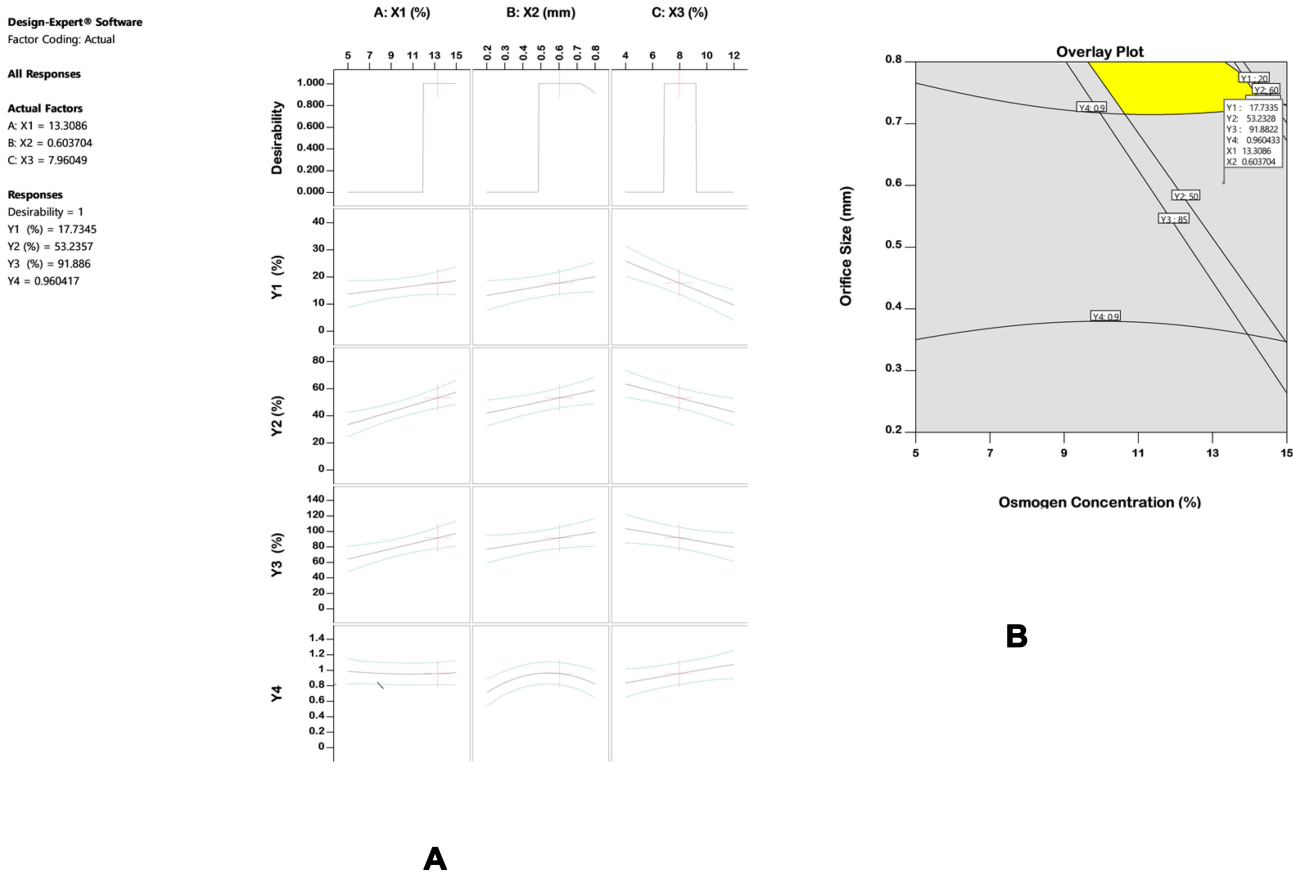


Figure 5 Desirability function and overlay plot. (**A**) graphical representation of numerical optimization results for achieving optimized MCP osmotic tablets. The optimum value of osmogen concentration (X_1), orifice size (X_2) tablet weight gain after coating (X_3) to achieve an overall desirability of 1.00 is depicted in desirability ramp. (**B**) overlay plot showing the recommended design space (yellow color) for selection of optimized MCP osmotic tablet.

Table 6 Composition of Optimized Formulation F-A and Random Formulation F-B and F-C, with Predicted and Experimental Values

Formulation	X_1	X_2	X_3	Responses	Predicted Values[a]	Experimental Values[b]	% Error
A	13.308	0.603	7.96	Y_1 Y_2 Y_3 Y_4	17.73 53.235 91.886 0.9604	18.014 52.87 95.18 0.9703	1.60 −0.68 −3.5 1.03
B	14.940	0.458	7.270	Y_1 Y_2 Y_3 Y_4	18.260 54.812 94.001 0.943	17.943 53.57 93.087 0.9648	−1.73 −2.26 −0.9 2.3
C	11.768	0.546	6.581	Y_1 Y_2 Y_3 Y_4	15.901 51.509 88.816 0.928	16.194 51.419 86.458 0.952	1.84 −0.17 −2.65 2.58

Notes: [a]Predicted value are calculated by the Design. Expert Ver 11.0. [b]Experimental values are the observed data.

release ($0 \leq Y_1 \leq 20$, $50 \leq Y_2 \leq 60$, $85 \leq Y_3 \leq 100$) Table 2. The desirability function response plot is shown in Figure 5A. Three optimum checkpoints F-A, F-B, and F-C (Table 6) were selected randomly to validate the experimental design and obtain the polynomial equations. The formulations corresponding to these checkpoints were prepared and evaluated for the selected response properties. Subsequently, the resultant experimental data of the responses (Y_1-Y_4) were quantitatively compared with that of their predicted values. Formulation A was chosen in the center of the select areas containing 13.3% of osmogene, percentage weight gain was 7.96, orifice size was 0.6 mm with the desirability of 1.00 (100%). Two additional random formulation F-B and F-C were also selected in the experimental matrix to confirm the model adequacy. Experimental values obtained were in high agreement with predicted values obtained by the DoE, so CCD can be considered as a useful tool in predicting the composition of formulation with targeted responses.

The results were further reinstated by graphical optimization, using the overlay plot in Figure 5B. The yellow region of the plot is the acceptance area, where the formulation A falls. F-A contains osmogen (13.3%), orifice size (0.6mm), and coating weight gain (7.96%) that is satisfying the desirable (targeted) characteristics needed for the optimized formulation (Table 6–7).[44,45]

Characterization of Optimized Formulation

The effect of pH 1.2, 4.5, and 6.8 (Figure 6A) on in vitro release of the optimized formulation F-A was evaluated, and similarity and difference factors were calculated. The value of similarity factor (*f2*) between pH 1.2 and 4.5, pH 4.5 and 6.8, and pH 1.2 and 6.8 were found to be (*f2*>50%) 80.42%, 84.77% and 71.93, whereas, the difference factor (*f1*) values were (*f1*<7) 4.30, 3.27 and 6.41, respectively.[46]

In vitro drug release study was carried out in 0.1 N HCl, 1 mol/lit NaCl and 2 mol/lit NaCl as dissolution media at pH 1.2 (Figure 6B), % CDR was found to be 97.52%, 80.12%, and 68.45%, respectively. Two different molar concentrations of NaCl were used to confirm that the osmotic pressure difference was the main driving force for drug release from the osmotic tablet.

In vitro release of optimized formulation was also observed at three different agitation speeds, ie, 50, 75, and 100 rpm of Dissolution USP Apparatus II. A non-significant difference of release profile (Figure 6C) at

Table 7 Composition of the Optimized Formulation (F-A)

Ingredients	Quantity (mg)
MCP	30
NaCl	26.6
Aerosil	3
Magnesium Stearate	4
Avicel pH 101	136.4
Tablet weight	203.3
Orifice Size	0.6mm
Tablet Coating Composition	
Opadry ® CA	
Tablet Weight gain	7.96% (Tablet weight 219.1 mg)

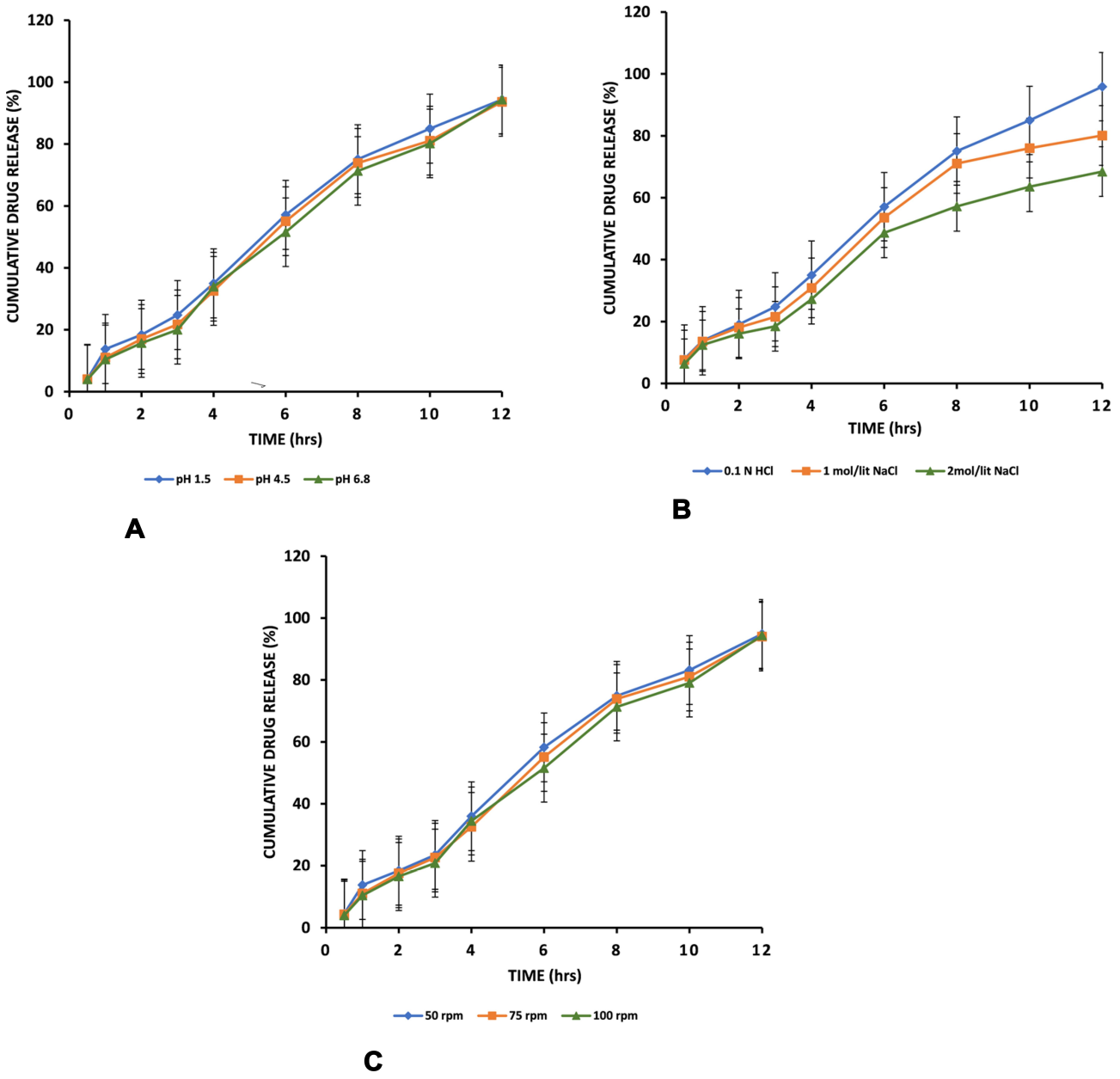


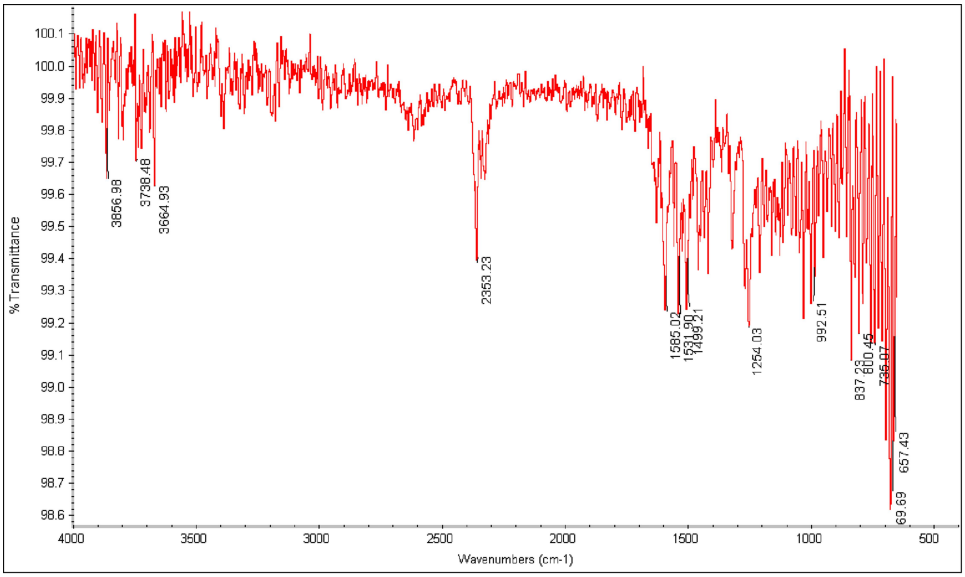
Figure 6 Characterization of optimized formulation (**A**) effect of pH on the release of MCP (**B**) effect of osmolarity of dissolution medium on the release of MCP (**C**) effect of agitation on the release of MCP.

varying rotational speed was confirmed by *f2* values, which were 82.39% (between 50 and 75 rpm), 72.96% (between 50 and100 rpm), and 83.44% (between 100 and 75 rpm).

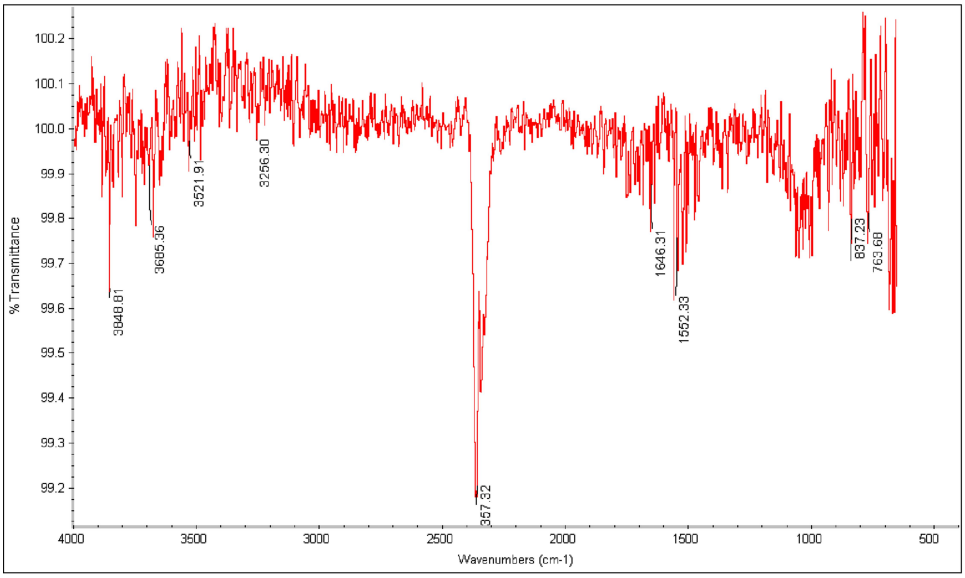
The findings reveal that the release of MCP is independent of pH and agitation speed, as shown in Figure 6A-C. The values of the difference factor and similarity factor indicated that there was no significant difference in drug

Table 8 Summary of Mathematical Modeling of Release Profile of an Optimized Batch (F-A)

Zero Order		First Order		Higuchi		Hixon Crowell		Korsmeyer Peppas	
r^2	Ko (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	K_{HC} ($h^{-1/3}$)	r^2 (h^n)	n
0.9703	8.423	0.9368	0.144	0.8757	23.55	0.9645	0.041	0.9838	0.847



(a)



(b)

Figure 7 Fourier transform spectroscopy of (a) metoclopramide HCl (b) an optimized formulation.

release profiles at different pH and agitation speed since osmotic systems, to a more considerable extent, are independent of the physiological variables of the GIT.[5]

On the bases of the goodness of fit of the optimized formulation dissolution data, the data was best fitted to the zero order kinetic model with the maximum value of the

Table 9 Stability Study Data of the Optimized Formulation

Time (Months)	Physical Appearance	Weight Variation (mg)	Hardness (kg/cm^2)	Drug Content %	Similarity Factor (f_2)[a]
0	White colored	203.75	9.46	99.56	–
3	White colored	203.01	9.39	98.75	84.44
6	White colored	202.7	9.01	98.16	73.24

Note: [a]The similarity factor was calculated by comparing the dissolution profiles of the optimized formulation (FA) at 3 and 6 months with the initial value at 0 month.

coefficient of correlation as compared to other tested models (Table 8). The slope of the release profile showing diffusion component 0.847 of the optimized formulation F-A that exhibits zero order anomalous release due to non-Fickian diffusion.[29]

Fourier Transform Infrared Spectroscopy Study

The results of the FTIR study are shown in Figure 7 the interaction between drug and excipients was determined by FTIR Spectroscopy. The results of pure drug FTIR as shown in Figure 7A indicate a sharp absorption band of the benzene derivative at 680cm−1, C-Cl at 850–550 cm −1,1050 cm−1 of (C-O-C), –N–H stretching vibration at 1,580 cm−1,C–N band at 1,020 cm−1and C-H bands at 1450 cm−1. The results of FTIR confirmed the compatibility MCP and other selected excipients (Figure 7B).

SEM Analysis

The physical characteristics of the optimized formulation were determined after the dissolution study. There was no significant change in the physical appearance of the tablet that was observed. The semipermeable membrane was found intact before and after dissolution, but pores were developed on the surface of the tablet after drug release., as shown in SEM images (Figure 2D and E).

Stability Study

The stability study of optimized formulation was carried out at accelerated conditions for 6 months as per ICH guidelines.[32] The stability samples of optimized formulation showed no significant changes in physical characteristics, drug content, and release profiles as compared to the initial sample (Table 9). The shelf life was found to be 2.8 years (Minitab software). The physical observation of the MCP osmotic tablet after completion of the drug release study showed no change and the presence of intact semipermeable membrane after drug release.

Conclusion

Osmotically controlled metoclopramide tablet formulation was optimized by central composite design - Numerical optimization methodology. The optimization procedure exhibited excellent predictability because the observed and predicted values were in close agreement for the optimum formulation. The drug release from the optimized formulation was complete at zero-order release rate till 12 hours. It is proved that central composite design with numerical optimization is a useful method for the model development and optimization of osmotic systems and for a better understanding of the influence of formulation and variables on drug release. This statistical approach for formulation optimization is a useful approach when the simultaneous evaluation of several variables is needed. The stability studies showed that the formulation remained stable for six months under accelerated conditions. This study provides an excellent preliminary data for future IVIVC (in vitro in vivo correlation) studies.

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Disclosure

The authors have no conflicts of interest.

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