Development of 24-hours Long Lasting Sustained-release Bilayered Matrix Tablets of Ondansetron Hydrochloride with the Synergistic Application of ANN and QbD

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***Abstract*—To address the limitations of short-acting ondansetron, this study developed a 24-hour bilayer (tab-in-tab) sustained-release tablet using Quality by Design (QbD) and Artificial Neural Networks (ANNs). The optimized Formulation (F4) combined an 8 mg sustained-release core with a 4 mg immediate-release layer. Results showed 96.88% of drug release over 24 h, following zero-order kinetics via diffusion and erosion. This computational framework significantly reduced trial-and-error costs while ensuring consistent therapeutic plasma levels, potentially improving patient adherence in chemotherapy-induced emesis.**

***Keywords*—ondansetron hydrochloride, bilayered matrix tablet, Quality by Design (QbD), Artificial Neural Networks (ANN), zero-order kinetics**

I. Introduction

Chemo-Induced Nausea and Vomiting (CINV) remain one of the prominent complications for cancer patients, often hindering adherence to treatment or leading to its discontinuation [1, 2]. Ondansetron hydrochloride is a potent 5-hydroxytryptamine receptor 3 (5-HT3) receptor antagonist. It has long been used as a standard treatment for nausea and vomiting [3]. It has a shorter intracellular half-life of only 3–4 h, which limits its clinical utility. Due to these pharmacological limitations, ondansetron needs to be administered multiple times in a day, which results in undesirable fluctuations in plasma drug concentrations and makes it difficult for immunocompromised patients as it may increase undesirable therapeutic burden [4–6].

To overcome these limitations, the pharmaceutical industry is turning to bilayer matrix systems that enable controlled drug release [7–9]. Many standard bilayer tablets have a "delayed-action" problem because the extended-release core is not available right away after the first dose [10, 11]. A tab-in-tab (sandwich) structure for this investigation was designed, consisting of an Immediate-Release (IR) layer for fast disintegration and the Extended-Release (ER) core which maintains a steady concentration throughout 24 h [12].

A profound comprehension of the nonlinear interactions among the formulation variables is highly necessary for framing up this kind of intricate pharmaceutical formulations. Traditional trial-and-error methods are time-consuming and unable to accurately explore the entire design space. Consequently, for formulation optimization, Quality by Design (QbD) principles have been unified with Artificial Neural Networks (ANNs) [13–16]. QbD provides a structured statistical framework through Response Surface Methodology (RSM), and ANNs demonstrate superior predictive capabilities by learning from complex data models, ensuring that the final product meets the predetermined Target Quality Profile (TQP) [16–22].

This study intended to frame a long-acting (24-hour) ondansetron bilayer formulation using this synergistic computational method and to verify its efficacy. By optimizing the concentrations of Polyvinylpyrrolidone (PVP) K30 (conjugate) and Hydroxypropylmethylcellulose (HPMC) K100M (delayed-release agent), a nearly perfect zero-order release profile was obtained. This study not only presents a formulation effective in improving adherence to drug therapy but also demonstrates how laboratory-based computational modeling can be effective in reducing experimental costs and time in modern drug development [23–25].

II. Materials and Methods

A sophisticated integration of pharmaceutical engineering and computational modeling has been followed in the development of the Ondansetron HCl bilayered matrix tablets. This methodology focused on achieving a biphasic release profile to improve patient adherence to chemotherapy-induced vomiting [3, 11].

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A. Materials

Ondansetron hydrochloride was supplied by a large pharmaceutical company in Bangladesh. The Sustained-Release (SR) matrix was made using HPMC K100M and ethylcellulose as rate-controlling polymers [6, 26]. For the Immediate-Release (IR) layer, PVP K30 was used as the binder and crospovidone (PVPP) and sodium starch glycolate (Na-SG) as superdisintegrants [11, 27]. Other excipients included Avicel PH-102, magnesium stearate, and talc, all analytical grade [27].

B. Physicochemical and Pre-compression Characterization

To confirm the formulation stability, Fourier Transform Infrared Spectroscopy (FTIR) was conducted in the 4000–400 cm^{-1} range using the KBr pellet method to screen for drug-excipient interactions [27]. Before compression, the rheological properties of the powder blends were rigorously evaluated [28]. Key parameters included:

- Bulk and Tapped Density: Calculated by dividing the powder mass by its volume, before and after mechanical tapping, respectively. Bulk Density uses the initial volume, while Tapped Density uses the final volume after the powder stops settling, measured in g/cm^3.
- Hausner Ratio and Carr's Index: Hausner Ratio was calculated by dividing tapped density by bulk density and Carr's Index was calculated by dividing the difference of the densities by tapped density.
- Angle of Repose (AoR): Determined via the fixed-height hopper method to ensure suitability for high-speed rotary tableting [29–31].

C. Preparation of Bilayered Matrix Tablets

A Tab-in-Tab (Sandwich) design was implemented to eliminate the "time lag" typical of multi-layered systems [8, 24].

1) Sustained-Release (SR) matrix core

The 8 mg SR core was manufactured via direct compression to preserve the polymer's structural integrity [6, 28]. Ondansetron HCl was geometrically diluted with a hydrophobic-hydrophilic matrix of HPMC K100M and Ethylcellulose [26]. Dicalcium phosphate and Avicel PH-102 were added as insoluble fillers. The mixture was sieved (40-mesh), lubricated with Magnesium Stearate and Talc, and compressed into the core (Table I).

2) Immediate-Release (IR) layer

To prevent premature super disintegrant activation, a non-aqueous wet granulation technique was employed [11]. 4 mg of Active Pharmaceutical Ingredient (API) was blended with PVPP, Na-SG, and Lactose Monohydrate. PVP K30 (5% w/v in Isopropyl Alcohol) acted as the granulating agent [27, 32]. The granules were dried at 45°C, screened (30-mesh), and lubricated before final compression (Table II).

TABLE I. COMPOSITION OF THE SUSTAINED RELEASE CORE TABLET (MG)

Formulation	API	HPMC K100M	Ethyl Cellulose	Di Basic Calcium	Avicel PH 102	Mg-Stearate	Talc
F1	8	12	5	45	2	0.1	0.1
F2	8	16	5	41.2	2	0.1	0.1
F3	8	20	5	37.2	2	0.1	0.1
F4	8	24	5	33.2	2	0.1	0.1
F5	8	28	5	29.2	2	0.1	0.1
F6	8	32	5	25.2	2	0.1	0.1

TABLE II. COMPOSITION OF THE IMMEDIATE-RELEASE (IR) LAYER (MG)

Form.	API	Mannitol	Na Starch Glycolate	PVP	Saccharine	Talc	Mg-Stearate
F1	4	36.5	1.5	0.6	1	0.8	0.4
F2	4	35	3	0.6	1	0.8	0.4
F3	4	33.5	4.5	0.6	1	0.8	0.4
F4	4	32	6	0.6	1	0.8	0.4
F5	4	30.5	7.5	0.6	1	0.8	0.4
F6	4	29	9	0.6	1	0.8	0.4

3) Final compression

The tablets were produced using a 10-position rotary tableting machine (ZP-10) with a compression force of 5–7 kg/cm^2, ensuring interfacial stability between the IR and SR components [23, 33].

D. Experimental Design (QbD) and Optimization

A QbD approach was executed using Stat-Ease Design-Expert software [12, 13]. A Response Surface Methodology (RSM) involving 13 trials assessed the concentrations of PVP K30 (X1) and HPMC K100M (X2) as independent variables [14, 15]. The Critical Quality Characteristics (CQCs) monitored were 24-hour drug release (R1) and tablet hardness (R2) [23, 34].

E. In Vitro Dissolution and Kinetic Modeling

Dissolution was performed using a USP Type II (Paddle) apparatus at 50 rpm and 37 ± 0.5°C [35, 36]. To simulate gastrointestinal transit, a sequential pH change (pH 1.2 for 2 h followed by pH 6.8) was applied [26, 37]. Drug concentrations were measured via UV Spectrophotometry at 248 nm [4]. Data were fitted to mathematical models including Zero-Order, First-Order, and Higuchi to determine the release mechanism [35, 38]. The Korsmeyer-Peppas equation was used to distinguish between Fickian diffusion ($n \leq 0.45$) and Non-Fickian/Anomalous transport ($0.45 < n < 0.89$) [39–41].

The mathematical models employed are summarized in Table III.

TABLE III. MATHEMATICAL MODELS FOR DRUG RELEASE ANALYSIS

Model	Application	Equation
Zero-Order	Constant release independent of concentration	$Q_t = Q_0 + K_0 t$
First-Order	Concentration-dependent release	$\frac{dC}{dt} = -KC$
Higuchi	Diffusion-based release from insoluble matrix	$Q = K_H \sqrt{t}$
Korsmeyer-Peppas	Mechanism identification via diffusion exponent (n)	$\frac{Mt}{M\infty} = Kt^n$

F. Artificial Neural Network (ANN) Integration

A Multilayer Perceptron (MLP) ANN was designed to optimize the formulation [16, 18]. The architecture utilized a sigmoid transfer function in the hidden layer to analyze non-linear interactions [17, 20]. Training was performed using the Levenberg-Marquardt backpropagation algorithm [42]. The ANN-QbD framework defined the ideal design space to ensure high predictive performance [19, 25]. Statistical significance was assessed via one-way ANOVA ($p < 0.05$) [15, 23].

III. RESULTS AND DISCUSSION

A. Physicochemical Compatibility (FTIR)

The chemical integrity of Ondansetron HCl within the matrix was confirmed via IR spectroscopy, where comparative analysis of the pure drug, individual excipients, and the final formulation revealed no harmful chemical interactions. Key peaks were consistently observed, including the N-H stretching at 3402 cm^{-1}, the carbonyl group (C=O) at 1637 cm^{-1}, and the aromatic group (C=C) at 1458 cm^{-1}. While a broad hydroxyl (−OH) band from the cellulose polymers (3400–3500 cm^{-1}) overlapped with the amine signal, the absence of new peaks or significant shifts confirmed the chemical inertness of the system, indicating that the drug remains stable within the developed bilayer matrix (Fig. 1).

B. Micromeritic and Physical Characterization

The powder blends for both the IR and SR layers demonstrated excellent flow properties, which are essential for successful direct compression. Specifically, the flowability parameters, including an angle of repose ranging from 29.3° to 38.2° and Hausner ratios between 1.12 and 1.19, strictly met USP criteria for pharmaceutical powders. Regarding tablet integrity, the measured hardness of 5.12–5.43 kg/cm² combined with low friability (0.38–0.47%) indicated high mechanical elasticity and durability of the bilayer structure. Furthermore, the content uniformity analysis showed a drug content of 89.30–96.88%, ensuring precise therapeutic dosing across all production batches (Table IV).

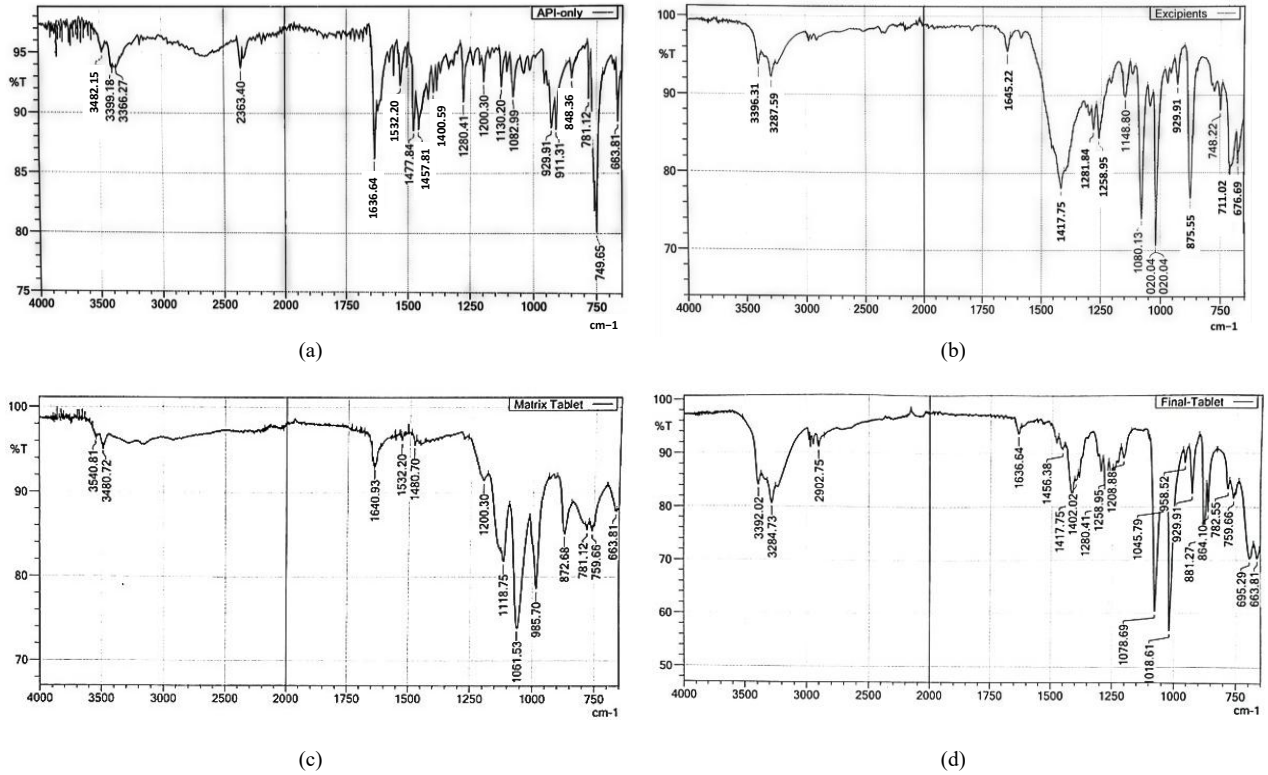


Fig. 1. FTIR spectrum of the final bilayer tablet formulation: (a) API-only; (b) Excipients; (c) Matrix tablet; (d) Final tablet.

TABLE IV. POST-COMPRESSION PHYSICAL CHARACTERIZATION

Form.	Wt. var. (g)	Thick. (mm)	Hardness (kg/cm²)	Friab. (%)	Drug content (%)	Wet. time (min)	Water abs. (%)	Disp. time (min)
F1	0.469±0.009	1.42±0.083	5.21±0.24	0.38±0.21	99.33±1.34	44±1.35	0.51±0.45	51±0.23
F2	0.472±0.008	1.44±0.134	5.42±0.22	0.46±0.25	99.32±1.45	45±1.42	0.56±0.46	49±0.65
F3	0.478±0.001	1.40±0.141	5.12±0.26	0.45±0.18	98.47±1.35	49±1.49	0.65±1.21	55±0.36
F4	0.474±0.001	1.42±0.083	5.43±0.38	0.47±0.29	99.23±0.92	51±1.55	0.55±0.36	48±0.63
F5	0.478±0.001	1.40±0.141	5.12±0.26	0.45±0.18	98.47±1.35	49±1.49	0.65±1.21	55±0.36
F6	0.474±0.001	1.42±0.083	5.43±0.38	0.47±0.29	99.23±0.92	51±1.55	0.55±0.36	48±0.63

C. *In-Vitro Biphasic Release Profile*

The "Tab-in-Tab" design successfully achieved a dual-action profile, where the IR layer released approximately 35% (4 mg) of the drug within the first 2 h at pH 1.2 to provide a rapid onset of action, while the SR core managed the remaining 8 mg over 22 hours at pH 6.8. Batches F1, F2, and F3 (containing 12–20 mg of HPMC) failed to maintain their structural integrity, leading to premature drug release within 12–16 h. The "Hero" formulation, F4 (containing 24 mg HPMC), achieved a 96.88% cumulative release over the full 24-hour period while successfully maintaining matrix stability throughout the dissolution study (Fig. 2).

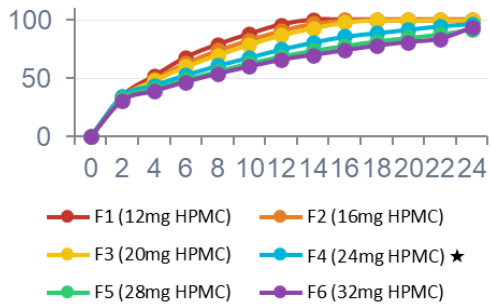


Fig. 2. In-vitro biphasic dissolution profile of all formulations (F1–F6) over 24 h.

D. *Release Kinetics and Mechanism*

The optimized formulation (F4) followed Zero-Order kinetics (R^2 = 0.999), indicating a constant drug release rate. The Korsmeyer-Peppas dispersion index (n = 0.68) suggests Anomalous (Non-Fickian) transport, where release is governed by a dual mechanism of drug diffusion through the HPMC gel layer and gradual polymer erosion. Kinetic modeling data for the optimized formulation are summarized in Table V.

TABLE V. KINETIC MODELING DATA FOR OPTIMIZED FORMULATION (F4)

Model	Equation Used	R^2 Value	Release Mechanism
Zero-Order	$Q_t = Q_0 + K_0 t$	0.999	Constant release
Higuchi	$Q = K_H \sqrt{t}$	0.962	Diffusion-controlled
Korsmeyer-Peppas	$\frac{Mt}{M\infty} = Kt^n$	0.985	Anomalous transport (n = 0.68)
Hixson-Crowell	$W_0^{1/3} - W_t^{1/3} = K_s t$	0.982	Erosion-controlled

E. *Computational Optimization and AI Topology*

A three-layer Artificial Neural Network (ANN) using the Levenberg-Marquardt algorithm was employed to map the complex nonlinear interactions between PVP K30 (A) and HPMC K100M (B), resulting in the regression equation $R1 = 95.25 - 1.72A - 7.61B - 3.25B^2$. A key finding from this model was the high negative coefficient for HPMC (−7.61), which confirms it as the primary regulator of release kinetics; as the HPMC concentration increases, it forms a thicker, more viscous gel layer that slows drug diffusion.

F. *Model Validation and Predictive Accuracy*

The MLP-ANN model demonstrated high robustness (R^2 = 0.9378). Validation of the optimized batch (F4) showed a minimal Relative Prediction Error (RPE) of 1.04% for drug release and 0.37% for hardness. A non-significant p-value (0.0802) for "Lack of Fit" confirmed the model's accuracy without overfitting. Validation results are presented in Table VI.

TABLE VI. VALIDATION DATA FOR THE OPTIMIZED FORMULATION F4 (PREDICTED VS. EXPERIMENTAL)

Response	Predicted Value	Experimental Value	Error (%)	95% CI Range
Drug Release (R1)	95.88%	96.88%	1.04%	94.45–99.31%
Hardness (R2)	5.41 kg/cm²	5.43 kg/cm²	0.37%	5.30–5.56

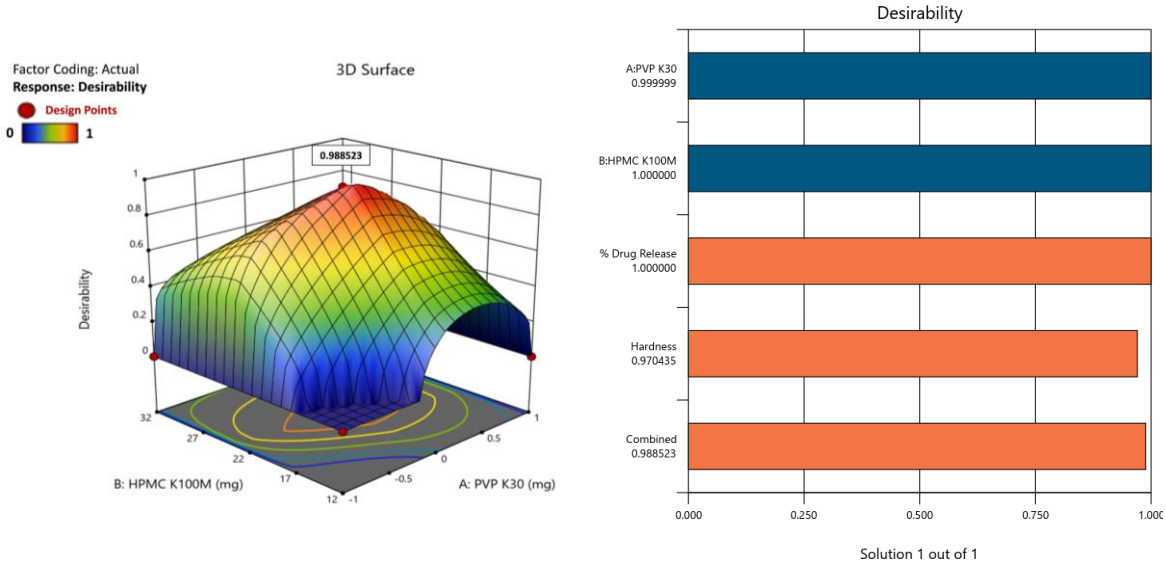
G. *Statistical Interpretation and Desirability Analysis*

The ANOVA results confirmed a highly significant correlation (F = 30.64, $p < 0.0001$) between the formulation variables and the drug release rate, validating the model's predictive power. Perturbation analysis further revealed that HPMC (Factor B) exerts a strong nonlinear effect on the release profile, whereas PVP K30 (Factor A) remains relatively stable, highlighting HPMC's critical role in controlling the matrix dynamics. Through multi-objective optimization within the design space, a high Desirability Score of 0.9885 was achieved, identifying the "ideal" parameters as 22.07 mg of HPMC K100M and 12.50 mg of PVP K30 to ensure both structural integrity and a precise 24-hour release (Fig. 3).

H. *Summary of Formulation Selection*

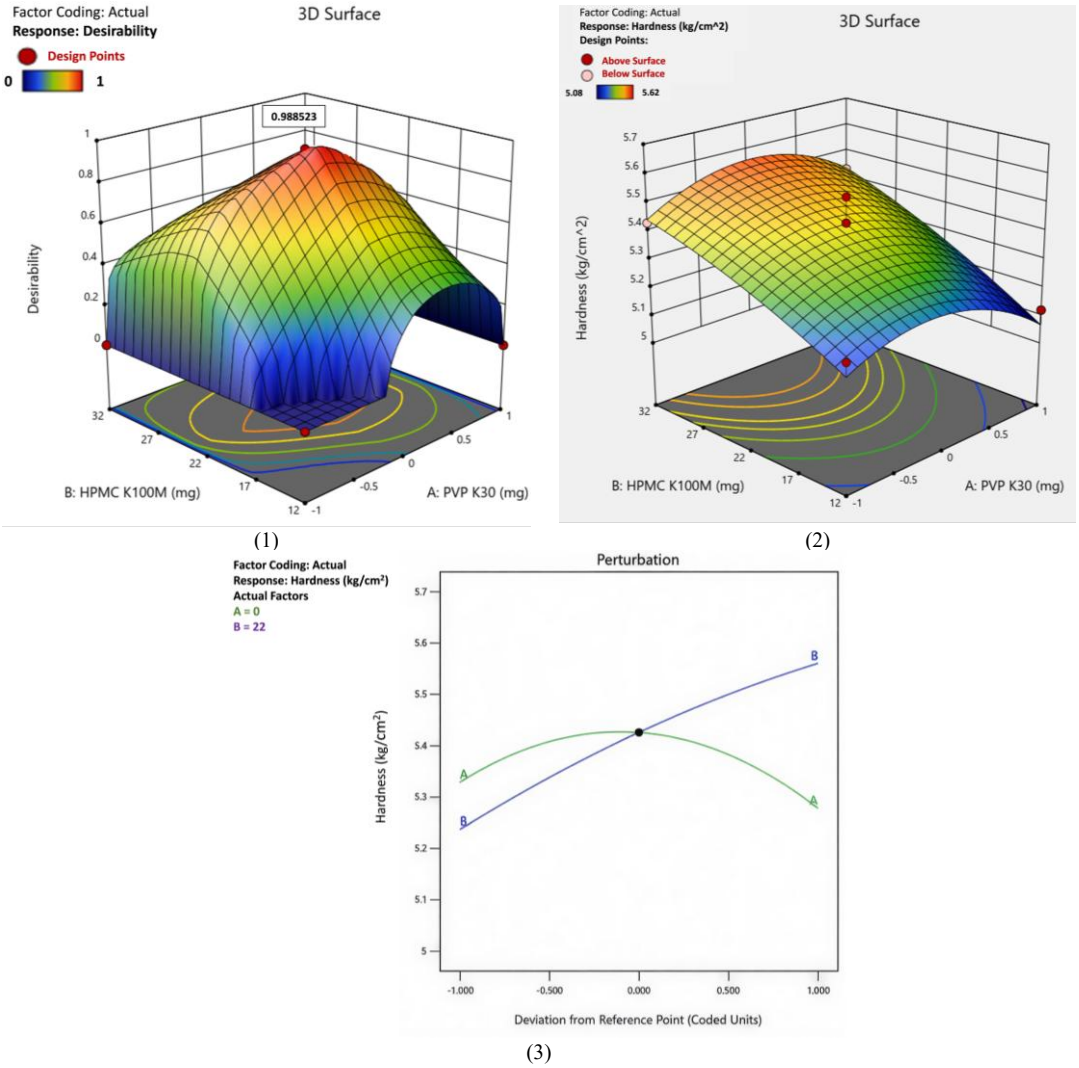
While all formulations targeted a 24-hour release, comparative analysis revealed that F1–F3 (12–20 mg HPMC) failed due to insufficient polymer density, causing rapid erosion and 100% dissolution within 12–16 h, while

F5–F6 (28–32 mg HPMC) were overly stable, delaying release and resulting in lower cumulative rates (92.3%–93.5%).



(1) (2)

Fig. 3. Multi-objective optimization design space (1) 3D desirability surface plot, (2) Numerical optimization bar chart (desirability).



(1) (2)

(3)

Fig. 4. 3D Response surface plots of % drug (a) release, (2) hardness, and (3) perturbation plot.

F4 (24 mg HPMC) was identified as the "Hero" formulation, maintaining structural integrity for 24 h with a superior bioavailability of 96.88%. A three-layer Multilayer Perceptron (MLP) ANN trained using the Levenberg-Marquardt algorithm achieved a negligible validation error of −1.04% for F4 and confirmed the accuracy of this "dry lab" approach (p = 0.1235). Statistical validation of the reduced quadratic model further supported these findings, yielding an R^2 of 0.9108 (F = 30.64, $p < 0.0001$) and an adjusted precision index of 17.0239, which demonstrates high signal-to-noise robustness (Fig. 4).

IV. Conclusion

This study successfully developed a 24-hour bilayer ondansetron tablet using a QbD-ANN hybrid approach. By optimizing the Tab-in-Tab (Sandwich) structure, the formulation achieved a 96.88% release rate and 5.43 kg/cm² hardness, following a stable diffusion-erosion mechanism. HPMC K100M was identified as the primary release regulator, while PVP K30 ensured structural stability. This "dry lab" computational strategy eliminates traditional trial-and-error costs, providing a precise, cost-effective solution for chemotherapy-induced vomiting. Ultimately, this high-tech optimization enhances patient adherence and safety, offering a robust framework for advanced pharmaceutical manufacturing and improved global healthcare outcomes.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Pavel Rahman Tonmoy: Research conceptualization, visualization, methodology, analysis, manuscript preparation and writing. Professor Nahid Sharmin: Validation of methodologies, review of writing and overall supervision. All authors approved the final version.

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