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Mathematical Model Application for In Vitro Release Kinetics of Ranolazine Extended-Release Tablets

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ABSTRACT

Introduction: Mathematical models are vital tools in understanding drug release mechanisms and release kinetics of different dosage forms, which can be achieved by assessing dissolution release profiles. This study aimed to determine and compare the mechanism of drug release using in vitro data for ranolazine extended-release tablets. **Methods:** Seven formulations of ranolazine extended-release tablets (500 mg) were prepared using a wet granulation technique with matrix-forming polymers. Dissolution tests were conducted in 0.1 N hydrochloric acid using United States Pharmacopeia (USP) apparatus 2 operating at 50 rpm for 24 h. Drug release data were compared using different mathematical models (zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell) in DDsolver. **Results:** Formulation batch F5 and the reference product best fit the Korsmeyer–Peppas model, with a coefficient exponent value of 0.5, indicating Fickian drug release, and Higuchi square root diffusion-controlled mechanisms were noted for both of these formulations, where the fraction of drug released is proportional to the square root of time. **Conclusion:** Having a similar dissolution profile and diffusion-controlled drug release mechanism, formulation F5 tablets are considered interchangeable with the reference product.

KEYWORDS: drug release, mathematical models, dissolution

INTRODUCTION

Dissolution involves the solubilization of a solid substance in a specific solvent, resulting in mass transfer from solid to liquid phase (*1*). Drug release occurs when a drug is converted into the required product formulation and undergoes pharmacokinetic processes, including absorption, metabolism, distribution, and excretion, after appropriate administration via a suitable route, making it available to exhibit its therapeutic action.

IImmediate-release products allow the drug to disintegrate and dissolve without delay; modified-release products are designed to provide prolonged availability of the drug after administration (e.g., delayed and extended release). In the development of new formulations, in vitro dissolution studies are used to depict the drug release profile from pharmaceutical dosage forms (*2, 3*). Quantitative analytical evaluation of drug release from any dosage form is facilitated by applying appropriate mathematical formulas. Kinetic models consider the quantity of dissolved drug (C) from the dosage form over time (t), represented as $C = f(t)$ (*4*).

Ranolazine is used for the treatment of angina, and unlike other anginal drugs such as beta-blockers and nitrates, ranolazine alone does not significantly affect blood pressure or heart rate. Therefore, ranolazine is beneficial for patients with angina who do not achieve the desired response with maximum tolerated doses of other anti-anginal drugs (*5*). Extended-release formulations are used to release ranolazine continuously over a prolonged period, maintaining a therapeutic concentration range in plasma.

Mathematical models assist in evaluating drug release rates and diffusion behavior after administration, reducing the need for extensive experimentation to design effective treatment plans and refine dosing regimens (*6, 7*). These models provide a logical foundation by relating to the mechanism of mass transport associated with controlled drug release, thereby facilitating the rationalization of existing dosage forms and the development of novel forms. Successful drug delivery systems are known for their constituents, alignment, and geometrics. Some models consider the

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combined effects of drug diffusion, dissolution, and drug adsorption onto tablet components, leading to fragmentation into multiple dimensions. Drug release mechanisms are governed by various models, including zero-order, first-order, and Higuchi release by diffusion, Korsmeyer–Peppas release by semi-empirical diffusion, and Hixson–Crowell (cube root) release by erosion (*4, 8*). Statistical analyses are often used to determine the best-fitting mathematical model. Calculating the coefficient of determination (R^2) is a common method to evaluate the suitability of model equations. The model with the highest adjusted R^2 (R^2_adj) considered the best fit and is selected for further study. Other statistical-based methods, such as multivariate analysis of variance, one-way analysis of variance (ANOVA), and calculating the correlation coefficient may also be used for comparing and selecting models (*6, 9*).

In this study, ranolazine extended-release tablets were designed using various polymers in different ratios to achieve 85% release within 20 h with a once-daily dosage. In vitro dissolution behavior and mechanisms of release for the optimized formulations were assessed and compared with a reference product according to the Hixson–Crowell, Korsmeyer–Peppas, Higuchi square root, first-order, and zero-order release models.

METHODS

Materials

Ranolazine was provided as a gift by Natco Pharma Ltd (India). Other excipients used were received as gifts from Aurobindo Pharma Ltd (India), including microcrystalline cellulose (Avicel PH 101 and PH 200; FMC Biopolymer, NY, USA), lactose monohydrate (Granulac 200; Meggle USA, Inc, USA), hydroxypropyl methylcellulose (Methocel K15M and K100 CR; DOW Chemical Pacific Ltd, Singapore), carnauba wax (SP 63 XFP; Strahl & Pitsch LLC), and magnesium stearate (Peter Greven, China). All other ingredients and chemicals used were of analytical grade.

Formulation of Ranolazine Extended-Release Tablets

Formulation of ranolazine extended-release tablets was conducted using a wet granulation technique. Accurately weighed active ingredient and other excipients were mixed geometrically, sifted, and resifted using an ASTM 30 mesh sieve. Purified water was used as the granulation fluid. The wet mass was sifted using ASTM 10 mesh and then dried in a fluid bed processor at 50–55 °C to achieve a loss on drying (LOD) under 2% w/w. The dried granules were sifted using ASTM 20 mesh. The sifted and dried granules were further lubricated and compressed into oval-shaped tablets (16.50 × 6.50 mm) using a 20-station rotary compression machine (EP-400, Elizabeth, India). The compression force was adjusted to achieve tablet hardness between 140 and 180 N (14.276–18.355 kp).

Composition of the ranolazine extended-release tablets is detailed in Table 1. Physical properties of tablets, such as tablet average weight, dimensions (length and width), thickness, hardness, and friability, and chemical properties, such as assay, dissolution, and content uniformity, were evaluated.

Among the various trials of ranolazine extended-release tablets, seven optimized formulation batches were selected for further study based on the extent of release for a once daily dosing regimen using dissolution testing, including solid-state characterization, similarity index (f_2), and mathematical models of drug release mechanisms.

Table 1. Formulation Details of Ranolazine Extended-Release Tablets (500 mg)

Composition (mg)	Formulation Batch Numbers						
	F1	F2	F3	F4	F5	F6	F7
Ranolazine	500.000	500.000	500.000	500.000	500.000	500.000	500.000
Microcrystalline cellulose (PH 101)	37.500	37.500	18.750	37.500	31.250	21.875	12.500
Lactose monohydrate	9.375	9.375	9.375	9.375	9.375	9.375	9.375
Hypromellose (methocel K15M CR)	56.250	-	37.500	34.375	34.375	34.375	34.375
Hypromellose (methocel K100 CR)	-	56.250	37.500	21.875	21.875	21.875	21.875
Carnauba wax	-	-	-	-	6.250	15.625	25.000
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Microcrystalline cellulose (PH 200)	15.625	15.625	15.625	15.625	15.625	15.625	15.625
Magnesium stearate	6.250	6.250	6.250	6.250	6.250	6.250	6.250
Total	625.00	625.00	625.00	625.00	625.00	625.00	625.00

PH: pharmaceutical grade; CR: controlled release; dash (-) indicates not applicable.

Solid State Characterization

The drug substance, along with controlled tablet samples and accelerated stability study samples taken at 6 months (i.e., 40 ± 2 °C/75 ± 5% RH), were analyzed using x-ray powder diffraction (D8 Discover, Bruker, Germany).

Dissolution Method

The dissolution profile of ranolazine extended-release tablets was studied in 900 mL of 0.1 N hydrochloric acid. The dissolution test was conducted at 37 ± 0.5 °C using a United States Pharmacopeia (USP) type 2 (paddle) apparatus (TrustE-14, Electrolab India) operated at 50 rpm. Dissolution samples (5 mL) were collected at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h and filtered with a 0.45-µm membrane filter. To maintain sink conditions, the same volume of fresh dissolution solution was substituted for the collected samples. The samples were analyzed using a UV-visible spectrophotometer (2377, Electronics India) to measure the absorbance at 272 nm, the wavelength of maximum absorption (λmax).

Mathematical Modeling of Drug Release

Various mathematical models were used to characterize the drug release mechanism using in vitro dissolution data and DDSolver (Microsoft Excel add-in, version 1), as described below (*10*). The model with the highest R^2, lowest Akaike information criterion (AIC), and highest model selection criterion (MSC) is considered to be the best fit.

Zero-order model

According to pharmacokinetic principles, the release of a drug from any dosage form can be described by the equation: $Ct = C_0 + K_0 t$, where Ct is drug quantity released at time t, C_0 is drug quantity released at time $t = 0$, and K_0 is the rate constant. The zero-order equation suggests that the drug delivery system releases drug continuously following zero-order kinetics, resulting in a constant drug level in the blood throughout delivery. To determine if the drug release mechanism follows zero-order kinetics, data obtained from in vitro dissolution testing were plotted as cumulative drug release (% w/w) versus time (h).

First-order model

First-order kinetics can be described by the equation: $dC/dt = -K_1 C$, where K_1 represents the rate constant of the first order, expressed per hour. First-order kinetics implies that the reaction rate is directly proportional to the quantity of the drug, resulting in linear release. Rearranging and integrating the equation yields $\log C = \log C_0 - K_1 t/2.303$, where C_0 is initial drug concentration, and C is the percentage of drug residue at time t. To determine if the drug release mechanism follows first-order kinetics, data from in vitro dissolution testing were plotted as the log % of drug residue against time.

Higuchi square root model

In this era of advanced modified-release concepts, the Higuchi square root model has emerged as the most effective (*11*). The Higuchi model is based on the following assumptions: (i) the initial quantity of drug in the drug product is greater than the solubility of the matrix; (ii) perfect sink conditions are maintained; (iii) the diffusivity of the drug remains constant; and (iv) swelling of the polymer is negligible. The Higuchi square root equation is: $Q = A\sqrt{D(2C_0 - C_s)\,C_s\,t}$, where Q is the cumulative quantity of drug release at time t per unit area (A), C_0 is initial drug concentration, C_s is drug solubility in the matrix, and D is the diffusion coefficient of the drug.

This equation effectively describes the relationship in the dosage form until the drug is depleted, and it evaluates dissolution in a general mixed matrix dosage form, where the quantity of drug in the matrix is less than its solubility, and release occurs through a permeable structure. Thus, the equation can be expressed as: $Q = \sqrt{(D\delta/\tau)\,(2C_0 - \delta C_s)\,t}$, where δ represents the matrix porosity, D is the diffusion coefficient of the drug in the solvent, and τ represents the matrix tortuosity. Q, A, C_s, and t have the same significance as mentioned previously. Tortuosity is a measure of the radius in the matrix obtained by dividing the pores and channels. By simplifying the above equation, it can be presented as $Q = K_H \times t^{1/2}$, where K_H is the Higuchi constant of dissolution.

To determine if the drug release mechanism follows Higuchi kinetics, the obtained data were plotted as the percentage of cumulative drug release (Q) against the square root of time, where the slope represents the K_H constant.

Korsmeyer–Peppas model

When the drug release mechanism primarily follows the diffusion approach according to the Higuchi square root model, it is necessary to determine the type of diffusion exhibited by the drug release. The drug release data can be analyzed using the Korsmeyer–Peppas empirical equation: $M_t/M_\infty = Kkp.t^n$, where M_t/M_∞ represents the fraction of drug released at time t. By logarithmic conversion, it becomes $\log(M_t/M_\infty) = \log Kkp + n \log t$. In this equation, M_t denotes the quantity of drug released at time t, M_∞ denotes the quantity of drug released after

infinite time, n represents the exponent of diffusion, and Kkp represents the Korsmeyer drug release constant.

Hixson–Crowell model

The Hixson–Crowell model describes the release of a drug from delivery systems when there is variation in the surface area and the thickness of the particles (tablets) (*2*, *12–14*). According to this relationship, particle size is proportional to the cube root of particle volume. Based on this relation, the Hixson–Crowell equation for drug release from delivery systems is: $K_{HC}t = (W_0)^{1/3} - (W_t)^{1/3}$ where W_0 represents initial drug quantity (t = 0), W_t represents residual drug quantity at time t, and K_{HC} is the constant for Hixson–Crowell that defines the relationship between volume and surface area.

RESULTS AND DISCUSSION

Physical Properties

The physical properties of 500-mg ranolazine extended-release tablets are presented in Table 2. All tablets passed the weight variation test as per *British Pharmacopeia* (BP) criteria for tablets that are batch-formulated (*15*). For tablet weights of 250 mg or higher, no two tablets should deviate by 5% and no single tablet should deviate by 10%. Tablet weight for formulated tablets ranged from 625.3 (624.3–627.8) to 628.1 (622.7–628.9) mg. As per BP, for thickness and diameter (or length × width) values, an acceptable deviation from mean values is 0.02 and 0.06, respectively, and should not deviate by more than 5%. No significant deviation was observed for thickness and diameter within and across trial formulation batches. In addition, all batches were within acceptable limits for friability (< 1% weight loss) and hardness (140–180 N).

Solid State Characterization

The drug substance, along with controlled samples of tablets and accelerated stability study samples taken at 6 months (i.e., 40 ± 2 °C/75 ± 5% RH), were analyzed using the X-RD method. The details of the analysis are ranolazine active ingredient (Drug substance/API- batch no.: 11102440) that exhibits crystalline polymorphic form-I. All tested samples of ranolazine (Control sample tablets, batch no.: T501500; Accelerated stability condition (i.e., 40 ± 2 °C/75 ± 5% RH) and 6-month sample tablets, batch no.: T501500) consistently displayed crystalline polymorphic form-I only, indicating no polymorphic changes during formulation development and accelerated stability study. This minimizes the potential impact on the dissolution study of ranolazine extended-release tablets for further evaluation. The placebo batch no. P001 and Ranolazine standard batch no. WS1500012 were used for evaluation. The X-RD diffractogram for ranolazine is shown in Figure 1, the specific 2θ values obtained were as follows: 5.0747, 9.4872, 10.0242, 10.3704, 12.2540, 12.4977, 13.1542, 14.3537, 15.5913, 16.9239, 19.3507, 19.8194, 21.3927, 22.3922, 23.4267, 24.6624, 25.4281, 26.4974, 27.9187, 30.1472, 31.8108, 32.2975, 33.6066, 34.5555, 35.8669, 37.4801, and 38.6075.

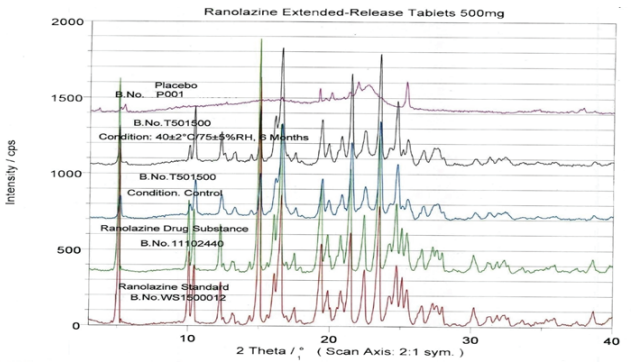

Figure 1. X-ray powder diffractogram shows stability of ranolazine extended-release tablets after 6 months of storage.

Dissolution Profiles

The dissolution profiles for formulation batches F1–F7 and the reference product are shown in Figure 2. The goal was to achieve 85% drug release within 20 h for a once-daily dosing regimen.

Table 2. Physical Properties of Ranolazine Extended-Release Tablets (500 mg)

Tablet Parameters	Formulation Batch Numbers						
	F1	F2	F3	F4	F5	F6	F7
Mean weight, mg (range)	627.4 (623.2– 628.9)	625.3 (624.3– 627.8)	627.6 (623.0– 627.9)	628.1 (622.7– 628.9)	627.2 (623.0–628.3)	626.7 (622.5–628.7)	627.4 (622.5–628.3)
Thickness, mm	4.90–5.16	4.87–5.11	4.85–5.17	4.91–5.14	4.80–5.05	4.91–5.14	4.95–5.28
Length, mm	16.51 ± 0.01	16.52 ± 0.01	16.50 ± 0.01	16.50 ± 0.01	16.50 ± 0.01	16.50 ± 0.01	16.50 ± 0.01
Width, mm	6.52 ± 0.01	6.52 ± 0.01	6.50 ± 0.01	6.51 ± 0.01	6.51 ± 0.01	6.50 ± 0.01	6.51 ± 0.01
Hardness, N	145–180	140–175	140–175	145–170	140–175	140–175	140–160
Friability, %	0.28	0.39	0.24	0.37	0.21	0.17	0.19

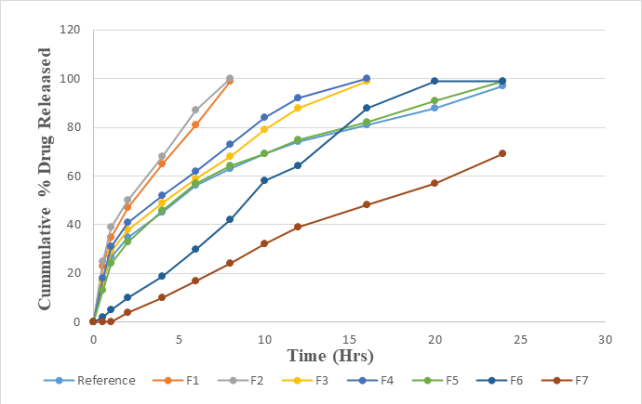

Figure 2. Comparison of in vitro dissolution profiles for the reference product and various formulations of ranolazine extended-release tablets (500 mg).

Ranolazine extended-release tablet batches F1 and F2 were formulated with a single rate-controlling polymer, i.e., hypromellose (Methocel K15M or K100 CR), which exhibited complete release within 8 h, which was not desirable. Batches F3 and F4 were formulated with a 1:1 (F3) and 3:2 (F4) combination of rate-controlling polymers, which exhibited complete release within 16 h.

Batches F5, F6, and F7 were formulated with Methocel K15M CR and K100 CR in a 3:2 ratio and carnauba wax added at 1% (F5), 2.5 % (F6), and 4% (F7). These batches exhibited controlled drug release; however, F7 showed poor release and F6 exhibited very controlled release, but F5 exhibited the required controlled release for 24 h.

In vitro dissolution profiles for batches F5 and F6 were further compared with reference product using the similarity factor index. The calculated similarity factors were 81.95 and 37.33, respectively. Thus, the dissolution profiles for batch F6 and the reference product are not considered to be similar.

Drug Release Mechanism

The suitability of batches F5 and F6 and the reference were checked with various mathematical dependent models (zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell).

As per summary data reflected in Table 3, F5 and the reference product did not fit well with the zero-order model (cumulative drug release vs. time), having a low R^2_adj value F6 had high R^2_adj (0.960), MSC (3.037), and AIC (71.412) values. The first-order model (log cumulative drug remaining vs. time) did not fit well either, having low R^2_adj, low MSC, and high AIC values.

F6 was compatible with the Hixson–Crowell cube root model (cube root of drug remaining vs. time), with high R^2_adj (0.966) and MSC (3.200) values but AIC was not low (69.620). F6 exhibited a small drug release by erosion-controlled drug release as signified by the high R^2. F5 and RP had high R^2_adj (0.983 and 0.971) and MSC (3.918 and 3.342) values but AIC values were not low (55.371 and 60.109).

Table 3. Statistical Evaluation of Goodness of Fit for Various Kinetic Release Models.

Product	Parameter	Zero-order	First-order	Higuchi	Korsmeyer–Peppas	Hixson–Crowell (cube root)
F5	K	5.154	0.134	21.164	24.674	0.036
	R^2_adj	0.475	0.949	0.983	0.993	0.905
	AIC	93.386	67.666	55.371	46.743	74.607
	MSC	0.462	2.8	3.918	4.703	2.169
	n	-	-	-	0.44	-
F6	K	4.84	0.089	18.702	7.608	0.025
	R^2_adj	0.96	0.934	0.872	0.972	0.966
	AIC	71.412	76.884	84.192	68.375	69.62
	MSC	3.037	2.54	1.875	3.313	3.2
	n	-	-	-	0.84	-
Reference	K	5.063	0.132	20.881	26.267	0.035
	R^2_adj	0.345	0.909	0.971	0.997	0.847
	AIC	94.217	72.539	60.109	37.493	78.232
	MSC	0.241	2.212	3.342	5.398	1.695
	n	-	-	-	0.41	-

K: rate constant; R^2_adj: coefficient of determination adjusted; AIC: Akaike information criterion; MSC: model selection criterion; n: exponential coefficient; dash (-) indicates not applicable.

The Korsmeyer–Peppas model (log cumulative % drug released vs. log time) had high R^2_adj values of 0.9943, 0.975, and 0.997 for F5, F6, and the reference, respectively, and high MSC values of 4.703, 3.313, and 5.398, respectively. The model had low AIC values of 46.743 and 37.493 for F5 and the reference, respectively, but F6 had a high AIC value of 68.375.

Aside from the Korsmeyer–Peppas model, the Higuchi square root model had the best fit for F5 and the reference, indicating that drug release was mostly via diffusion (Table 3).

The Korsmeyer–Peppas model exponent coefficient (n) describes the drug release as Fickian and non-Fickian. According to Lokhandwala et al., Fickian (case I) is diffusion-controlled drug release with an n of 0.45, whereas non-Fickian (anomalous) is n greater than 0.45 but less than 0.89; non-Fickian diffusion (case II transport) is n = 0.89, and non-Fickian (super case II transport) is n > 0.89. Drug release may be polymer relaxation/swelling-controlled, whereas anomalous drug release may follow both diffusion and erosion-controlled mechanisms (*9*). In the current study, n values for F5 and the reference were < 0.45, exhibiting Fickian diffusion, whereas F6 had n = 0.84, exhibiting non-Fickian (anomalous) diffusion.

Polymer-developed tablet formulations follow either drug release by diffusion or erosion of the matrix by filling its pores with water (*16, 17*). Hydrophilic polymers like hypromellose, where the matrix is initially penetrated by dissolution media, result in polymer swelling, causing disintegration of polymer linkages, leading to erosion.

Based on mathematical models, F5 and the reference fit the Higuchi square root and Korsmeyer–Peppas models, reflecting Fickian drug release governed by both diffusion (following Fick's law of diffusion proportional to the square root of time) and through a swollen matrix with water-filled pores. F6 fit the zero-order, Hixson–Crowell cube root, and Korsmeyer–Peppas models, showing non-Fickian (case II) drug release and polymer relaxation/swelling-controlled drug release. Anomalous drug release followed both diffusion and erosion-controlled mechanisms.

CONCLUSION

Matrix tablets containing 500 mg of ranolazine were formulated using polymers such as carnauba wax and hypromellose to achieve prolonged or extended-release profiles. The polymorphic form of ranolazine remained consistent throughout the development process, and stability testing indicated minimal influence on dissolution performance. Formulation batch F5 and the reference best fit the Korsmeyer–Peppas model, with a coefficient exponent value (n = 0.45) indicating Fickian drug release, and Higuchi square root diffusion-controlled mechanisms. Thus, Batch F5 and the reference product are considered to be interchangeable.

DISCLOSURES

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