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Comparative Analysis of Statistical Methods for Modelling the Dissolution Profile of a Bentonite-Based Suppository

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ABSTRACT

Introduction: The advancement of modified-release pharmaceutical forms, such as bentonite-based suppositories, requires accurate modeling of the active ingredient's release kinetics. This study aimed to evaluate the capacity of four canonical release-kinetics models (Weibull, Higuchi, first-order, and Korsmeyer–Peppas) to define and describe the release profile of tramadol from bentonite-based suppository mixtures. **Methods**: Seventeen bentonite-based tramadol suppository mixtures were prepared according to a design comprising polyethylene glycol (PEG) and bentonite. All dissolution profiles were acquired using a USP basket apparatus. The release-kinetics models were fitted within both frequentist and Bayesian hierarchical frameworks. The frequentist analysis employed Akaike information criterion (AIC)-based selection to rank model performance, and the Bayesian approach incorporated informative priors and a hierarchical structure to capture intermixture variability. The comparison of the models employed leave-one-out cross-validation (LOO) and the widely applicable information criterion (WAIC). **Results**: The frequentist and Bayesian approaches both identified the Weibull model as the most suitable descriptor of the release behavior for tramadol. The Weibull model showed better performance in describing tramadol release. The hierarchical Bayesian method proposes many advantages in terms of uncertainty quantification and robustness. The complementary use of frequentist and Bayesian techniques offers a rigorous paradigm for sustained-release mixture development. **Conclusion**: Our study affirms the applicability of bentonite as a biocompatible, functional excipient for modifying drug release behavior of suppositories.

KEYWORDS: Bentonite, tramadol, suppository, dissolution profile, Bayesian statistics

INTRODUCTION

Tramadol is an analgesic drug indicated for moderate to severe pain (*1*, *2*). This synthetic opioid drug discovered in 1962 and marketed as Tramal in 1977 by Grünenthal GmbH (*3*). In the United States, the total number of tramadol prescriptions exceeded 30 million in 2021, making it one of the most prescribed opioids in the country (*4*–*7*). The need for therapeutically effective drug delivery systems has led researchers to develop new strategies (*8*). Rectal drug delivery uses pharmaceutical technology to control the release and delivery of active pharmaceutical ingredients (APIs) in the rectal ampoule (*9*–*11*). Suppositories remain among the most commonly used dosage forms. Many

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studies have focused on accelerating or slowing API release from suppositories by using coatings, emulsions, hydrogels, layering, nanoparticles, osmotic systems, thermoreversible matrices, and gelling agents (*10, 12*). These sustained-release mixtures are especially valuable for patients who cannot tolerate oral dosage forms or require long-acting preparations (*13*).

Bentonite is a natural clay composed mainly of montmorillonite (*14, 15*). It serves as a nontoxic, nonirritating matrix in topical gels and, on occasion, oral suspensions. Previous work has shown that alginic-acid-incorporated bentonite matrices can sustain morphine release in rabbits to manage nocturnal pain (*16*). A bentonite-based tramadol suppository could similarly provide prolonged analgesia compared to commercially available mixtures (*16*).

The study of active molecule dissolution kinetics and their optimization is traditionally based on frequentist statistics to select the best model. Special cubic polynomial fitting and Akaike information criterion (AIC)-driven model selection via DDSolver produce point estimates and rank candidate models by fit quality. Although these frequentist methods are well established, they yield limited insight into parameter uncertainty and batch variability (*17*).

Bayesian hierarchical modeling overcomes these limitations by treating kinetic parameters as random variables with prior distributions and by explicitly modeling variability at multiple levels (*18, 19*). Informative priors leverage existing knowledge of release-rate constants, while Markov Chain Monte Carlo sampling yields full posterior distributions that capture uncertainty (*20, 21*). Model comparison via leave-one-out (LOO) and WAIC balances fit and complexity, enabling rigorous ranking (*18*).

This study will analyze dissolution data for 17 tramadol suppository mixtures, varying in PEG molecular weights and bentonite content, using both frequentist and Bayesian hierarchical approaches. Four competing kinetic models will be implemented within each framework and compared for their performance.

METHODS

Materials and Reagents

All chemicals used in this study were of analytical grade and suitable for pharmaceutical research applications. The details of each material, including manufacturer, catalog reference, and reagent grade, are summarized in Table 1.

Table 1. Chemicals Used in the Study

Chemical	Manufacturer	Reagent grade
Tramadol hydrochloride	Merck, Germany	Pharmaceutical grade
PEG 1540, 4000, and 6000	Hoechst Chemikalien (Werk Gendorf), Germany	Analytical / pharmaceutical grade
Bentonite	Sigma-Aldrich, England	Analytical grade
Ethanol 96%	Sigma-Aldrich, England	HPLC grade
Mono-sodium phosphate	Sigma-Aldrich, England	Analytical grade
Di-sodium phosphate	Sigma-Aldrich, England	Analytical grade

PEG: polyethylene glycol

Preparation of Suppositories

The tramadol suppositories were prepared following a systematic mixture design aimed at assessing how variations in matrix composition influence drug release behavior. Seventeen formulations were developed by adjusting the ratios of polyethylene glycol (PEG 6000, 4000, and 1540) and bentonite, while maintaining a constant amount of tramadol to assess matrix composition effects on drug release. The formulations covered a wide range of PEG and bentonite proportions, including matrices without bentonite and balanced compositions combining equal PEG ratios. A detailed description of all formulations and their respective component ratios is presented in Table 2.

Table 2. Composition of Tramadol Suppository Formulations

Formulation	PEG 6000 (g)	PEG 4000 (g)	PEG 1540 (g)	Bentonite (g)
1	1.33	1.47	0.00	0.20
2	1.00	1.47	0.33	0.20
3	0.67	1.47	0.67	0.20
4	0.33	1.47	1.00	0.20
5	1.33	1.50	0.00	0.17
6	1.00	1.50	0.33	0.17
7	0.67	1.50	0.67	0.17
8	0.33	1.50	1.00	0.17
9	1.33	1.58	0.00	0.08
10	1.00	1.58	0.33	0.08
11	0.67	1.58	0.67	0.08
12	0.33	1.58	1.00	0.08
13	1.00	1.50	0.50	0.00
14	0.50	1.50	1.00	0.00
15	1.00	0.83	1.00	0.17
16	0.50	0.83	1.50	0.17
17	0.99	0.99	0.99	0.03

PEG: polyethylene glycol

The tramadol suppositories were produced using the conventional fusion molding technique under controlled temperature and stirring conditions to ensure homogeneity and stability. The detailed preparation steps are illustrated schematically in Figure 1.

The preparations were analyzed for appearance and hardness according to the *European Pharmacopoeia* guidelines. Appearance was evaluated visually for color, shape, and surface uniformity. Hardness was measured using a tablet hardness tester (Erweka, Germany), and all formulations met the acceptable limit of ≥ 1800 g.

In Vitro Dissolution Testing

The USP basket apparatus for tablets was used for dissolution testing. Three suppositories were tested for each formulation. Dissolution method parameters were presented in Table 3.

Table 3. Dissolution Method Parameters

Apparatus	USP Type 1- Basket
Brand	PHARMA TEST Apparatebau GmbH (Hainburg, Germany)
Medium volume	500 mL
Rotation speed	50 rpm
Medium	Phosphate buffer pH 7.2
Temperature	37 ± 0.5 °C
Sampling times	5, 20, 30, 50, and 60 min

Samples (5 mL) were collected at 5, 10, 20, 30, 50, and 60 mins during dissolution and replaced with fresh medium at 37 ± 0.5 °C to maintain sink conditions (*22*). The samples analyzed without dilution by UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan), and the concentration was determined at 270 nm according to the tramadol calibration range. The calibration range of tramadol (20–150 µg/mL) covered the concentration range of the tramadol product, which is 100 µg/mL (100 ppm) (Fig. 2).

Diffusion Model Fitting

Adsorption kinetics were evaluated using the dissolution profile (*16*). This study focused on diffusion by evaluating four mathematical models most commonly used in biopharmaceutics (first-order, Higuchi, Korsmeyer-Peppas, and Weibull) (*23*), independent of physicochemical properties such as the ratio of polymer components and molecular weight of the polymer.

The first-order model refers to a system where the release rate of the API is only a function of the remaining concentration of the API ($F = 100 \times (1 - e^{-k1 \times t})$). The Higuchi model suggests that the amount of API released from the dosage form is a function of the square root of time ($F = k_H \times t^{0.5}$). Korsmeyer-Peppas is another comprehensive semi-empirical model, which can, in general, define separate release phenomena involving either diffusion or swelling ($F = k_{HP} \times t^{0.5}$).

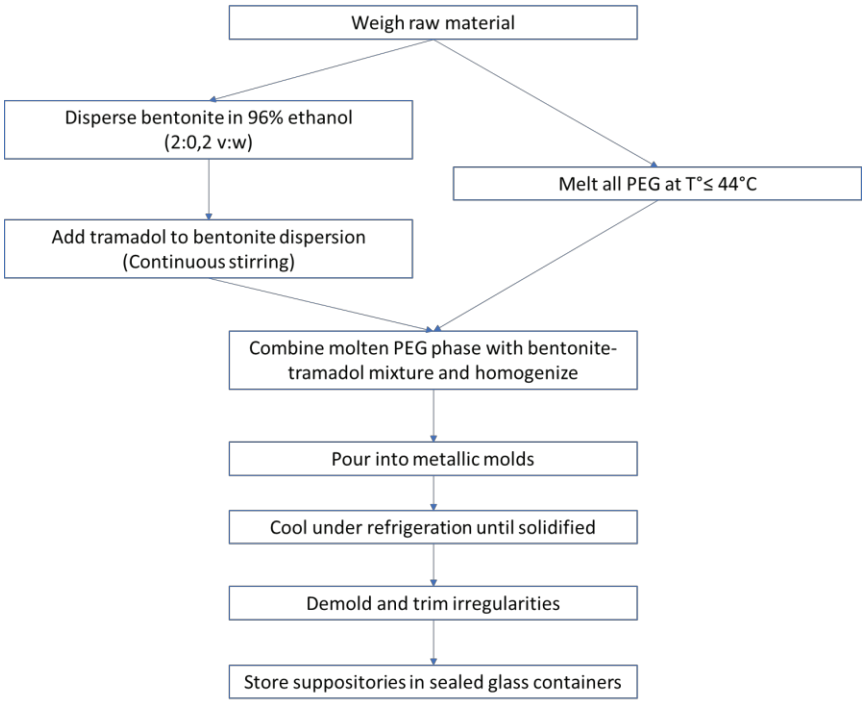

Figure 1. Flowchart for suppositories preparation. PEG: polyethylene glycol.

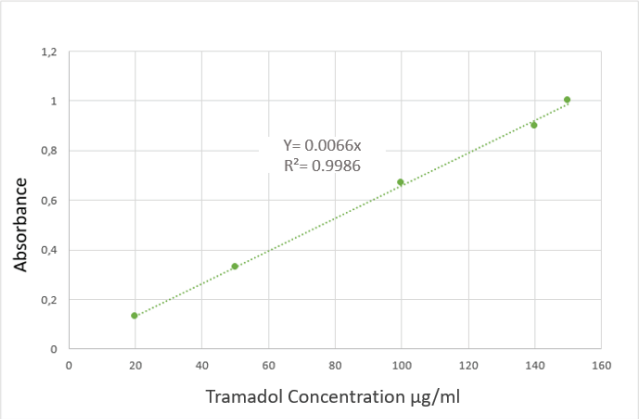

Figure 2. Calibration range of tramadol assay.

According to Weibull model, the logarithm of released ingredient and the logarithm of time have a linear relationship (*24*). It is initiated on a function originally proposed by Weilbull in 1951, and Langenbucher in 1972 adapted the function permitting to describe drug release curves (*25*). The equation can be expressed as a function (F) of the fraction of drug accumulated in the solution at time (t):

$$F = 100 \times (1 - e^{-(\frac{t-Ti}{\alpha})^{\beta}})$$

α (the scale parameter) describes the time scale of the process, however, Ti (the localization parameter) defines the latency time of the release process, i.e., how many times being zero (*24*). β (the exponent of time of Weibull function) is, according to the cited equation, linearly related to the exponent (n) of the power law derived from the analysis of the first 60% of the release curves. The value of β is considered as an indicator that describes the mechanism of transport of a drug through the matrix. β ≤ 0.75 generally indicates Fickian diffusion in either fractal or Euclidian spaces, whereas a combined mechanism is associated with β values in the range of 0.75–1. When the β value is > 1, we estimate that drug transport corresponds to a complex release mechanism.

Statistical Analysis

DDSolver (add-in tool for Microsoft Excel) was used to determine the best fitting model based on the dissolution profile (based on $R_{sq\ (Adjust)}$ and AIC) and the API release mechanism from the matrix (*26, 27*).

In addition to DDSolver, a Bayesian hierarchical modeling approach was used to compare the fit of four models to the release kinetics of all the formulations. PyMC and ArviZ, Python libraries specialized in Bayesian modeling and analysis, were used for model specification, sampling, and evaluation (*28*).

For the four candidate models (Weibull, Higuchi, first order, and Korsmeyer–Peppas), each model defined a likelihood function based on the respective kinetic equation and incorporated informative prior distributions for the parameters. A hierarchical structure was implemented to account for potential run-to-run variability.

Markov Chain Monte Carlo (MCMC) methods were used to draw samples from the posterior distributions of the model parameters. Convergence of the chains was assessed visually and statistically. Model fit was evaluated by using the LOO cross-validation in addition to WAIC metrics, allowing for objective comparison and selection of the best-fitting model (*29*). MCMC convergence was assessed using trace plots and the Gelman-Rubin statistic.

RESULTS AND DISCUSSION

The appearance of the suppositories varied between a whitish and yellowish coloration depending on whether they contained only PEGs or the PEGs-Bentonite mixture. For the hardness, all preparations met the requirement of 1800 g according to the *European Pharmacopoeia*.

Dissolution Testing

Table 4 summarizes the dissolution data for the 17 preparations used in the experiments. After 5 minutes of dissolution, the mean percentage of drug release varied from 7.54% to 34.48%, then was 12.58–46.55% at 10 mins, 20.45–68.71% at 20 mins, 27.58–88.14% at 30 mins, 38.03–99.17% at 50 mins, and 41.82–100.89% at 60 mins.

Adsorption Diffusion Models

Table 5 provides a summary of the results of fitting the four models to the dissolution data obtained. Of the 17 formulations, 10 fit the Weibull model, five fit the Korsmeyer-Pappas model, and two fit the linear and Higuchi model.

The Weibull model is an empirical model that explains both delayed and immediate releases of various drug delivery systems. The AIC, which is now considered as a standard measure of model and data fit based on maximum likelihood, displays the best-fitting model when comparing a group of models, and the model with the lowest AIC is the best fit (*30*). As shown by the the lowest AIC values, the Weibull model best defines the release behavior of active pharmaceutical ingredients from bentonite-based matrix. Nonetheless, slight deviations suggest that the Weibull model may not always be the right model for tramadol release. All parameters affecting the API release should be defined and controlled.

Table 4. Mean Percentage Dissolved of the Experimental Formulations

Formulation	5 min	10 min	20 min	30 min	50min	60 min
	T1 %	T2 %	T3 %	T4 %	T5 %	T6 %
1	7.54	15.76	20.45	40.00	44.24	62.27
2	6.62	12.58	20.61	27.58	42.73	59.55
3	13.18	22.12	42.88	46.82	58.33	69.55
4	29.64	33.91	44.26	64.77	67.24	74.30
5	29.64	33.91	44.26	64.77	67.24	74.30
6	23.76	30.11	39.55	51.64	55.06	67.14
7	29.12	36.50	51.47	62.83	73.70	78.20
8	34.48	49.20	68.71	84.03	84.29	89.36
9	30.68	46.55	55.76	69.85	89.76	92.76
10	28.11	39.68	60.94	70.85	92.56	94.47
11	34.70	42.61	62.98	76.26	92.24	93.26
12	32.97	45.42	60.11	76.05	96.58	97.56
13	24.18	35.64	60.45	80.38	96.52	100.89
14	25.73	41.71	68.89	88.14	99.17	98.83
15	6.82	14.39	18.33	28.79	38.03	41.82
16	23.79	34.55	55.15	66.52	69.39	72.27
17	24.55	36.36	55.61	68.94	70.30	71.06

T: Content of dissolved tramadol

Table 5. Release Kinetics of 17 Formulations of Tramadol Using Different Mathematical Models Obtained by DDSolver

PARAMETERS		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FIRST ORDER MODEL	R^2 Adj	0.94	0.96	0.94	0.92	0.63	0.80	0.89	0.92	0.97	0.94	0.95	0.95	0.98	0.98	0.94	0.75	0.70
	K1	0.014	0.013	0.021	0.015	0.022	0.033	0.061	0.047	0.005	0.053	0.054	0.054	0.051	0.06	0.01	0.032	0.033
	AIC	30.75	28.06	31.77	30.87	39.08	37.75	35.55	34.84	28.39	32.30	32.65	32.65	28.83	25.67	25.24	39.24	40.22
HIGUCHI MODEL	R^2 Adj	0.87	0.83	0.95	95.02	0.90	0.93	0.95	0.77	0.97	0.98	0.95	0.98	0.97	0.93	0.94	0.87	0.82
	KH	6.67	6.06	8.56	7.01	10.55	8.67	10.75	13.07	12.57	12.75	13.06	13.37	13.37	13.98	5.104	10.42	10.53
	AIC	36.29	36.68	29.41	28.38	33.23	28.53	29.01	39.93	27.98	24.29	31.54	27.27	31.62	36.23	25.93	35.24	36.92
KORSMEYER-PEPPAS	R^2 Adj	0.79	0.97	0.96	0.96	0.93	0.96	0.99	0.90	0.98	0.98	0.98	0.98	0.97	0.92	0.98	0.90	0.87
	K	2.77	1.21	6.52	4.80	14.73	11.90	15.19	23.46	15.93	13.81	17.84	16.30	11.50	15.59	2.77	15.38	16.66
	N	0.79	0.93	0.57	0.60	0.39	0.42	0.40	0.33	0.43	0.47	0.41	0.44	0.54	0.47	0.66	0.39	0.37
	AIC	32.36	26.37	29.53	27.32	31.44	26.00	19.68	35.39	24.00	25.48	26.98	24.55	32.68	37.92	19.41	34.27	35.56
WEIBULL MODEL	β	1.14	2.80	0.68	0.596	0.59	0.56	0.63	0.69	0.79	0.88	0.79	0.85	2.31	1.93	0.76	0.48	0.44
	R^2 Adj	0.90	0.97	0.96	0.96	0.93	0.95	0.99	0.96	0.95	0.98	0.97	0.95	0.99	0.99	0.98	0.97	0.93
	AIC	34.60	27.00	28.96	26.31	31.41	27.31	18.51	28.65	32.88	27.59	27.86	32.44	28.48	9.52	20.75	30.31	25.73

Adj: adjusted; AIC: Akaike Information Criterion; β, Weibull shape parameter; K1, first-order rate constant; KH, Higuchi rate constant; K, Korsmeyer-Peppas rate constant; N, Korsmeyer-Peppas release exponent.

Among the models considered, Weibull is a favorable model that comprises parameters sensitive to all the ranges of the API release profile. In the Weibull equation, *Ti* is the localization parameter that defines the latency time of the release process, and the exponent β, a shape parameter, characterizes the shape of the API release curve and may be related to some physiological effects. For equations with β = 1, the curve has an exponential shape, β > 1 has a sigmoidal shape, and β < 1 is a parabolic curve. This suggests that the Weibull model is flexible with great potential to be applied to a variety of API release patterns.

The experimental response is explained by the Weibull model mathematical equation, where variations in tramadol release rates are described by the calculation

of its natural logarithm. In other words, although the Weibull model does not disregard the alteration of the API release rate between successive phases of the same release model, it deactivates the effect of these changes on the pattern by calculating their natural logarithm.. Otherwise, the exponent β could be employed to predict and optimize the release conditions of a drug delivery system in the development process and provide more necessary release profiles, though further in vivo studies would be required to confirm the clinical relevance of these findings.

Numerous APIs are adsorbed into bentonite by interacting with the surface of the clay sheets. These adsorptions vary depending on the type of the ingredient, nevertheless, the main mechanism is cation exchange. The surface of bentonite sheets is negatively charged ($Al_2H_2Na_2O_{13}Si_4$), which is why the surface charge is permanently balanced by cation exchange. Particularly, cationic API are adsorbed into the surface by these electrostatic interactions; this is the case of tramadol HCl. Thus, the release mechanism of tramadol from a bentonite-based suppository is by diffusion. Other factors including solvent pH, solvent temperature, ionic strength, and the initial concentration of active ingredient can also influence the results (*31*).

The dissolution profile of the optimal formulation after 24 h gave satisfactory results, which can only be explained by the Weibull model ($R_{sq\ (Adjust)}$ = 99% and AIC = 14.7861).

Bayesian Model Selection Approach

In evaluating the model comparisons based on the LOO and WAIC criteria, distinct trends emerge in the ranking and performance of the models. For the LOO comparison (Table 6), the Weibull model secures the top position (elpd_loo = –292.85), indicating its superior predictive ability compared to other models. Notably, the Korsmeyer-Peppas and Higuchi models follow closely, demonstrating competitive performance (–321.53 and –323.001, respectively). The first order model had the lowest value (–402.41) but showed a substantial difference in expected log predictive density (elpd_diff), suggesting a notable deviation in predictive accuracy. In the WAIC comparison (Table 7), a similar pattern emerges, with the Weibull model leading, closely pursued by the Korsmeyer-Peppas and Higuchi models. Interestingly, the first order model exhibits a pronounced elpd_diff, emphasizing its inferior performance.

The β parameter of the Weibull model followed a normal distribution in all cases, as indicated by Figure 3. Estimated β values were 0.56–1.16, with standard error values of 0.071–0.16. Standard error values were 5.11 for LOO and 4.82 for WAIC.

The pooled and hierarchical Bayesian models were compared using the Weibull model as a reference. The hierarchical model outperformed the pooled model in both LOO and WAIC comparisons (ranked first in both metrics [LOO rank: 0; WAIC rank: 0]). The hierarchical model boasts significantly lower values (elpd_loo: –292.77 vs. –404.01 and elpd_waic: –289.57 vs. –404.00), indicating superior predictive accuracy and model fit compared to the pooled counterpart, which received negligible weight in both comparisons. This reinforces the conclusion that the hierarchical Bayesian approach offers substantial advantages for Weibull model.

Table 6. Ranking of Hierarchical Models Based on LOO Metrics

Model	Rank	elpd_LOO	p_LOO	elpd_diff	weight	SE
Weibull	0	–292.9	29.45	0.00	1.00	5.11
Korsmeyer–Peppas	1	–321.54	19.94	28.68	0.00	6.46
Higuchi	2	–323.00	18.23	30.14	0.00	6.57
First order	3	–402.41	2.22	109.56	0.00	5.60

LOO: leave-one-out cross validation; diff: difference; elpd: expected log predictive density; p: p-value; SE: standard error.

Table 7. Ranking of Hierarchical Models Based on WAIC Metrics

Model	Rank	elpd_WAIC	p_waic	elpd_diff	weight	SE
Weibull	0	–289.72	26.31	0.00	1.00	4.82
Korsmeyer–Peppas	1	–319.92	18.32	30.20	0.00	6.20
Higuchi	2	–321.69	16.92	31.97	0.00	6.33
First order	3	–402.41	2.21	112.69	0.00	5.60

WAIC: widely applicable information criterion; diff: difference; elpd: expected log predictive density; p: p-value; SE: standard error.

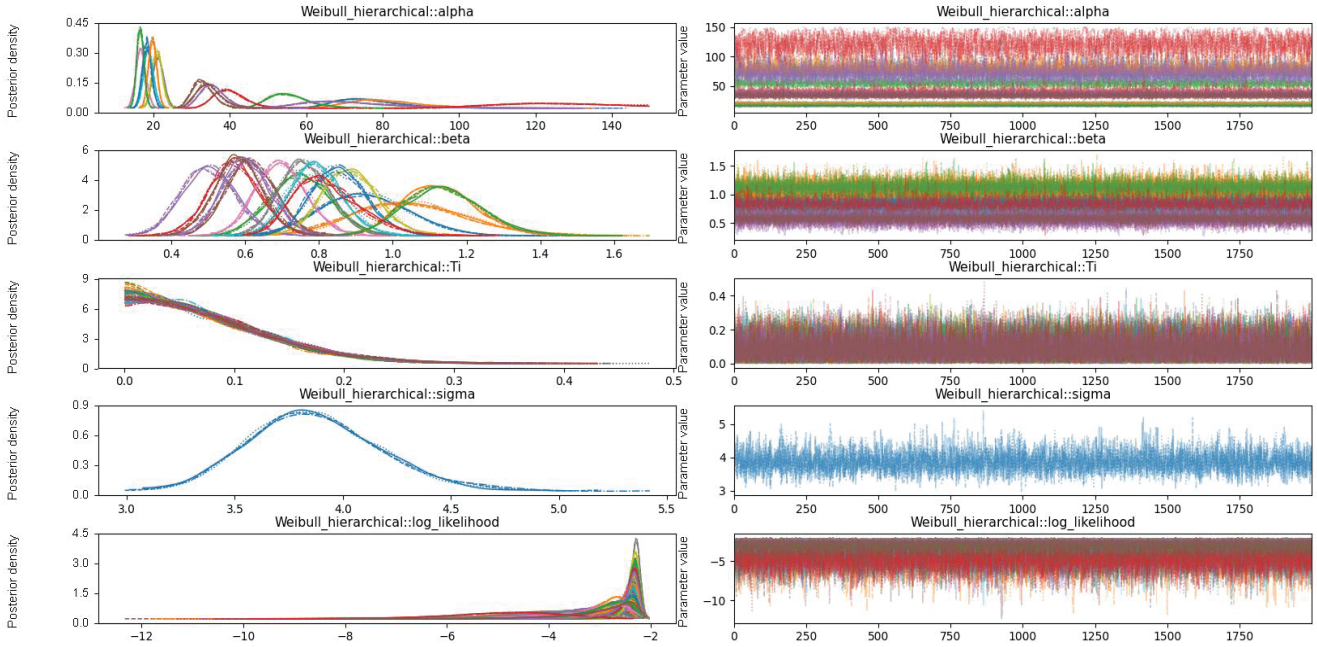

Figure 3. Trace plots and posterior distribution of the best model parameters and its standard deviation (sigma).

The hierarchical Bayesian method's strength lies in its consistent selection of a reliable model (Weibull) for the formulation series. The frequentist approach provides a range of possibilities, but the Bayesian method shines in its accurate representation of the observed data (Fig. 4).

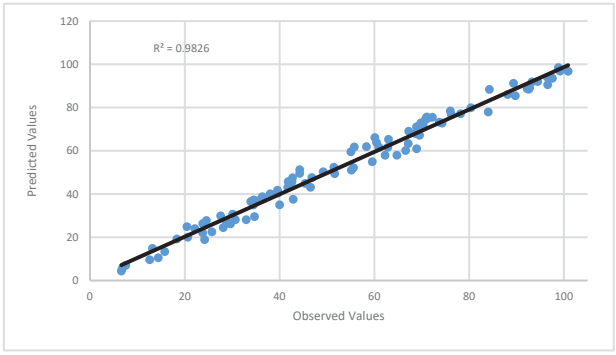

Figure 4. Observed versus predicted cumulative release mean values (%) by the hierarchical Bayesian method (Weibull model).

A posterior predictive plot was generated (Fig. 5) to delve deeper into the compatibility between our hierarchical model and the observed data. The model generally aligned well with the data, capturing the major features and distributions of the observed cumulative percentage of tramadol released at each time point across all formulations ("y_obs_hierarchical"). Although some minor deviations exist, these nuances do not detract from the overall positive assessment. The model provides a robust and reliable representation of the observed phenomena.

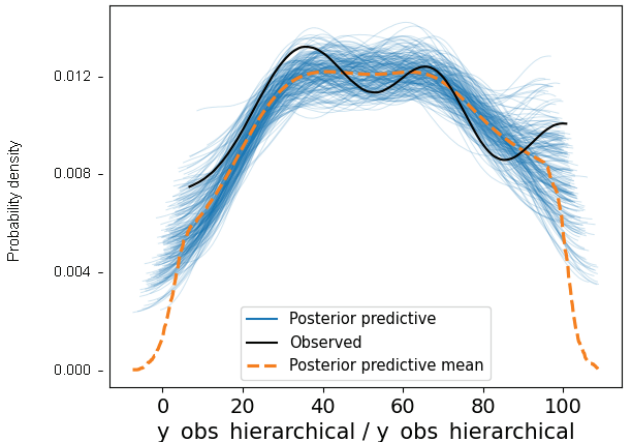

Figure 5. Plot of the posterior predictive checks for the best fit model. y obs hierarchical: observed cumulative release (%) used as the response variable in the hierarchial Bayesian model.

CONCLUSION

Our study effectively proved the potential of bentonite-based sustained-release tramadol suppositories formulated through systematic mixture design. The incorporation of bentonite as a matrix-forming agent, combined with varying PEG compositions, allowed modulation of the drug release profiles, highlighting the clay's functional role in controlled delivery systems.

A comprehensive modeling approach was undertaken to characterize the dissolution kinetics using both frequentist and Bayesian frameworks. The comparative analysis revealed that the Weibull model consistently provided the best fit for most formulations in both

frameworks, effectively capturing the complexity of the release behavior. While the frequentist approach (using AIC-based ranking) served as a reliable initial screening tool, the Bayesian hierarchical modeling approach offered superior advantages, including robust uncertainty quantification, explicit handling of inter-formulation variability, and rigorous model ranking through LOO and WAIC metrics. This comparison underscores that, for complex formulations with inherent batch-to-batch variability, hierarchical Bayesian methods provide a more informative and generalizable model selection strategy.

The estimated Weibull shape parameter (β) suggested that diffusion remains the predominant release mechanism for tramadol from these bentonite-based matrices, consistent with theoretical expectations for clay-polymer systems. The flexibility of the Weibull model, capable of describing both Fickian and anomalous release kinetics, underscores its suitability for evaluating complex drug delivery platforms.

Collectively, these findings advocate for the integration of Bayesian hierarchical modeling as a robust, informative tool in the development of sustained-release formulations. Moreover, the results affirm the applicability of bentonite as a biocompatible, functional excipient for modifying drug release behavior. Future investigations should incorporate compatibility studies, advanced physicochemical characterization, and in vivo validation to further substantiate these preliminary conclusions and optimize clinical translation.

DISCLOSURES

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