Research Article

Extended-Release Divalproex Sodium Tablets: Formulation Strategies and *In-Vitro* Evaluation

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ABSTRACT

Background: Divalproex Sodium, an antiepileptic drug, is widely used for epilepsy, migraine prophylaxis, and bipolar disorder. However, its clinical utility is limited by a narrow therapeutic index, dose-dependent hepatotoxicity, short half-life, and poor bioavailability. Developing an extended-release (ER) formulation can enhance therapeutic efficacy by ensuring sustained drug release and improving patient compliance.

Objective: This study aims to formulate, optimize, and evaluate ER tablets of Divalproex Sodium to overcome the limitations of conventional dosage forms while achieving controlled drug release.

Methods: Matrix-based ER tablets were prepared using hydrophilic and hydrophobic polymers, with Hydroxypropyl Methylcellulose (HPMC) as the primary release-modifying agent. Pre-formulation studies confirmed excellent flow properties and good compressibility. Response Surface Methodology (RSM) optimized the drug-to-polymer ratio. Formulations were assessed for weight variation, hardness (13–14 kg/cm²), friability (<1%), drug content (97.43%–99.61%), dissolution, and stability at 40°C/75% RH for one month. The dissolution behavior of the optimized formulation (F8) was compared with Depakote ER.

Results: The optimized formulation (F8) exhibited a dissolution profile (99.84%) bioequivalent to the reference product (98%). Drug release followed Higuchi's model (R^2 = 0.974–0.994), with Korsmeyer-Peppas slope values (0.414–0.443) indicating Fickian release. ANOVA results ($F = 17.16$, $p < 0.005$) confirmed model significance (89.72% variability). Stability studies showed no significant changes in parameters.

Conclusion: The optimized ER formulation provides sustained drug release, improved efficacy, and better patient compliance, demonstrating the potential of extended-release technology in overcoming conventional formulation challenges.

Keywords: Divalproex Sodium, Extended-Release Tablets, Hydrophilic Polymers, Response Surface Methodology, Drug Release Optimization, Matrix Tablets, Depakote ER.

INTRODUCTION

Oral drug delivery remains the most preferred and widely accepted route of administration due to its ease of use, accurate dosing, and patient compliance[1,2]. However, conventional oral drug formulations often face challenges such as inconsistent drug release, fluctuating plasma concentrations, and variable bioavailability, which can affect therapeutic efficacy[3]. These limitations are particularly concerning in the management of chronic conditions like epilepsy, where maintaining stable plasma drug levels is crucial for effective seizure control and symptom management[4]. Divalproex Sodium, a well-established antiepileptic drug, is extensively used for treating epilepsy, migraine prophylaxis, and bipolar disorder. Despite its proven efficacy, its clinical application is hindered by a narrow therapeutic index, dose-dependent hepatotoxicity, a short biological half-life, and poor bioavailability [5,6]. Frequent dosing of conventional formulations can lead to patient non-compliance and undesirable fluctuations in drug concentration, increasing the risk of breakthrough seizures and adverse effects. To address these challenges, developing extended-release (ER) formulations offers a promising solution by providing a sustained and controlled drug release profile. ER formulations help maintain consistent therapeutic drug levels, reduce dosing frequency, minimize side effects, and improve patient adherence[7]. Matrix-based ER drug delivery systems, utilizing hydrophilic and hydrophobic polymers such as Hydroxypropyl Methylcellulose (HPMC), are widely employed to achieve controlled drug release. These polymers form gel-like barriers or inert matrices that regulate the diffusion of the drug, ensuring a prolonged therapeutic effect [8,9].

MATERIALS AND METHODS

MATERIALS

The materials used in the formulation of extended-release (ER) tablets include Divalproex Sodium procured from Harmaan API, Gujarat, and various grades of Hydroxypropyl Methylcellulose (HPMC) such as HPMC K15M, HPMC K4M,

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and HPMC K100M**,** sourced from Nova Excipients, Mumbai. Lactose**,** Microcrystalline Cellulose**,** and Magnesium Stearate were obtained from S.D. Fine Chem. Ltd., Mumbai.

METHODS

Preformulation Studies

Organoleptic Properties:

The organoleptic properties of Divalproex Sodium were assessed based on appearance, color, odor, taste, and texture. Visual inspection determined appearance and color, while odor was evaluated by gentle inhalation. A minute quantity was used for taste assessment, ensuring safety precautions. Texture was examined by rubbing the sample between the fingers. Findings were documented systematically [10].

Solubility:

The solubility of Divalproex Sodium was determined in various solvents, including distilled water, methanol, ethanol, acetone, chloroform, and pH 6.8 phosphate buffer, using the shake flask method. The solutions were agitated for 48 hours at 25 ± 1°C, filtered, and analysed for drug content using a UV-Visible spectrophotometer[10].

Determination of λ max:

The maximum absorbance (λ max) of Divalproex Sodium was determined by scanning its methanolic solution between 190–380 nm using a UV spectrophotometer (Shimadzu 1800) [11].

Melting Point:

The melting point of Divalproex Sodium was determined using the capillary method in triplicate[11].

Standard Curve:

A standard solution of Divalproex Sodium was prepared in methanol, and aliquots (5–30 µg/ml) were analyzed at 210 nm using a UV spectrophotometer. Absorbance values were used to construct a standard curve.

Compatibility Studies:

Drug-excipient compatibility was assessed using FT-IR spectroscopy and DSC analysis

FT-IR Spectroscopy:

FT-IR spectroscopy (Shimadzu IRAffinity-1S FT-IR Spectrophotometer) assessed drug-excipient compatibility by analyzing Divalproex Sodium and its physical mixtures (1:1) for peak shifts. Samples were blended with KBr (1:100), compressed into pellets, and scanned within 4000–400cm^{-1} using an FT-IR spectrophotometer[11].

DSC Analysis: Thermal properties of the drug and its mixtures were analyzed using a Differential Scanning Calorimeter (Shimadzu DSC-60). Samples were heated from 25 to 350°C at 10°C/min under nitrogen [12].

Experimental Design (DOE)

Response Surface Methodology is used to design and develop Divalproex Sodium extended-release tablets. Computational design strategy by Box-Behnken design using Design Expert Software is performed with three factors, HPMC E-15, Maltodextrin, and glycerine. The effect of independent variables on the response, Thickness, Disintegration Time, and Drug Release was studied to select the optimal formulation as shown in Tables 1 & 2 [13,14].

Table 1: Design Table for factors and their levels

FACTORS (Independent Variables)	Units	-1	1	Response (Dependent variables)
X1 HPMC k100M	G	50	190	Y1 Dissolution (%)
X2 HPMC k15M	G	40	185	
X3 HPMC k4M	G	75	115	

Table 2: Formulation of Divalproex sodium Extended-release tablets

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Divalproex sodium (mg)	500	500	500	500	500	500	500	500
2	Lactose (mg)	220	93	212	97	35	120	145	260
3	HPMC K4M (mg)	95	50	25	120	200	170	120	50
4	HPMC K100M (mg)	120	185	113	115	120	40	115	60
5	HPMC K15M (mg)	10	115	95	113	90	115	65	75
6	Microcrystalline cellulose (mg)	50	50	50	50	50	50	50	50
7	Magnesium stearate (mg)	4	4	4	4	4	4	4	4
8	Aerosil (mg)	1	1	1	1	1	1	1	1
9	Total (mg)	1000	1000	1000	1000	1000	1000	1000	1000

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Preparation of extended-release Divalproex sodium tablet:

Accurately weighed Divalproex sodium and polymer and other ingredients were taken and dry mixed in RMG for 5 minutes. The Binding liquid used isopropanol and water mixture (5:1 ratio). The powder was mixed with a sufficient quantity of isopropanol and water solution mixture until a wet mass formed. The cohesive mass obtained was dried in a hot air oven at 55 °C for 1 h. The dried granules again passed through sieve # 20 to break the large lumps. Then granules were mixed with talc and magnesium stearate and compressed into 1000 mg tablets by adjusting hardness [15,16]. The formulations were shown on Table no 2.

Evaluation of Pre-Compression Parameters[17,18]

Angle of Repose: The angle of repose was determined using the funnel method. Granules were weighed, poured through a funnel adjusted to touch the heap's apex, and allowed to flow freely. The heap's diameter was measured, and the angle of repose was calculated.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where θ = the angle of repose, h = height of the heap of the powder, r = radius of the heap of the powder

Determination of bulk density and tapped density: Two grams of powder (W) were placed in a 25 ml cylinder. The initial volume was noted, and the cylinder was tapped from a 2.5 cm height at 2-second intervals until volume stabilization. Bulk and tapped densities were then calculated.

Db= Mass of powder/bulk volume of the powder

Dt = mass of powder/ tapped volume of powder

Carr's index: It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by

Carr's Index % = tapped density-bulk density/tapped density × 100

Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow. Hausner's ratio was measured by the ratio of tapped density to bulk density.

Hausner's ratio = tapped density/bulk density

Evaluation of Post-Compression Parameters[19,20]

Weight Variation Test: To study weight variation, 20 tablets of each formulation were weighed using electronic balance, and the test was performed according to the official method.

Hardness: Tablet hardness, critical for resistance to breakage during storage and handling, was tested using a Monsanto hardness tester. The average hardness of 5 randomly selected tablets, measured in kg/cm², was recorded.

Friability: Friability, indicating tablet cohesion, was tested using a Roche friabilator at 25 rpm for 100 revolutions. Weight loss of 10 tablets before and after rotation was recorded, and percentage friability was calculated.

% Friability = weight initial – weight final/weight initial × 100

Tablet Thickness: Tablet thickness, crucial for uniform size, was measured using Vernier caliper on ten tablets per formulation. Measurements combined readings from the metric and imperial scales for accuracy. Adjust readings by summing metric scale with imperial scale division (multiplied by 0.02).

Drug Content for ER tablet: For drug content analysis, ten tablets were weighed, and the average weight was calculated. The tablets were crushed, and powder equivalent to 100 mg of the drug was dissolved in pH 6.8 phosphate buffer, with the volume made up to 100 ml. The solution was sonicated for 1 hour. From the stock solution, 1 ml was transferred to a 10 ml volumetric flask, and the volume was adjusted with pH 6.8 phosphate buffer. The solution was filtered, and absorbance was measured spectrophotometrically at 210 nm against the buffer as a blank. The drug content in one tablet was then calculated.

***In vitro* dissolution studies of Extended release tablets:** The in vitro release of Extended release tablet was carried out for 18 hours using USP type-II apparatus (DT-1200) at 100 rpm in phosphate buffer medium pH 6.8 in 900 ml A 5 ml was withdrawn at different time intervals and replaced with an equal volume of fresh medium. The samples were suitably diluted with blank dissolution medium, filtered, and analyzed on a UV spectrophotometer at 210 nm [20,21].

Stability studies: The optimised formulations were subjected to stability studies for a period of one month in accelerated storage conditions (40℃ / 75% RH). The selected formulations were packed in aluminum foils, which were in wide mouth bottles closed tightly [22].

Mathematical modeling of drug release profile: The cumulative amount of Divalproex sodium release from the formulated tablets at different time intervals were fitted to Zero order kinetics, first order kinetics, higuchi model and korsmeyer-peppas model to characterize mechanism of drug release [23,24].

Zero order kinetic: It describes the system in which the release rate is independent of its concentration. $Q_t = Q_0 + K_0 t$

Q_t = amount of drug dissolved in time t Q_0 = initial amount of drug in the solution K_0 = zero order release constant

If the zero order drug release kinetic is obeyed, a plot of Q_t versus t will give straight line with a slope of K_0 and an intercept at Q_0.

First Order Kinetic: It describes the drug release from the system in which the release rate is concentration dependent.

$\log Q_t = \log Q_0 + K_1 t/2.303$

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Q_t = amount of drug dissolved in time; Q_0 = initial amount of drug in the solution

K_1 = first order release constant

If the release pattern of drug follows first order kinetics, then a plot of log ($Q_0 - Q_t$) versus t will be straight line with a slope of K_1 /2.303 and an intercept at t= 0 of logQ_0.

Higuchi's Model: It describes the fraction of drug release from a matrix is proportional to square root of time. $M_t / M_\infty = K_H t^{1/2}$

Where, M_t and M_∞ are cumulative amount of drug release at time t and infinite time, and

K_H = Higuchi dissolution constant reflection formulation characteristics.

If the Higuchi model of drug release is obeyed, then a plot of M_t / M_∞ versus $t^{1/2}$ will bestraight line with slope of K_H.

Korsmeyer-Peppas Model: The power law describes the fractional drug release as exponentially related to the release time and adequately describes the release of drug from slabs, cylinders, and spheres, as expressed in the following equation

$M_t / M_\infty = K t^n$

$\log (M_t / M_\infty) = \log K + n \log t$

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic properties

The sample was analysed for its organoleptic properties. It is white in color, odorless, and has a bitter taste. The appearance is that of a crystalline powder. These observations provide a comprehensive overview of the organoleptic characteristics of the sample.

Drug solubility studies

The solubility of Divalproex sodium in different solvents was as follows: 7.35 mg/ml in distilled water, 48.45 mg/ml in methanol, 55.24 mg/ml in chloroform, and 29.73 mg/ml in phosphate buffer pH 6.8. Divalproex sodium showed limited solubility in water, good solubility in methanol and chloroform, and moderate solubility in phosphate buffer at physiological pH. These results suggest that Divalproex sodium is suitable for oral extended-release formulations, with potential for use in both aqueous and organic systems

Melting point:

The melting point of an organic solid can be determined by introducing a tiny amount into a small capillary tube, attaching this to the stem of a thermometer centred in a heating bath, heating the bath slowly, and observing the temperatures at which melting begins and is complete. The result was found to be 219-239 ℃.

FT-IR spectrum Analysis:

The FT-IR spectra of pure Divalproex sodium and its combination with polymers (Figure 1) showed all characteristic peaks, confirming drug-polymer compatibility. The data is presented in Table 6. The FT-IR spectra of pure Divalproex sodium and its combinations with HPMC K4M, HPMC K100M, and HPMC K15M exhibited all characteristic functional group peaks (Table 6) within the expected wave number range. The retention of key peaks, including aliphatic C-H stretch, C-H bend, C-H stretch, carboxylic acid, and O-H bend, confirms drug-polymer compatibility with no significant interactions or chemical modifications. Minor variations in wave numbers are attributed to polymer incorporation, ensuring the stability of Divalproex sodium in HPMC-based formulations

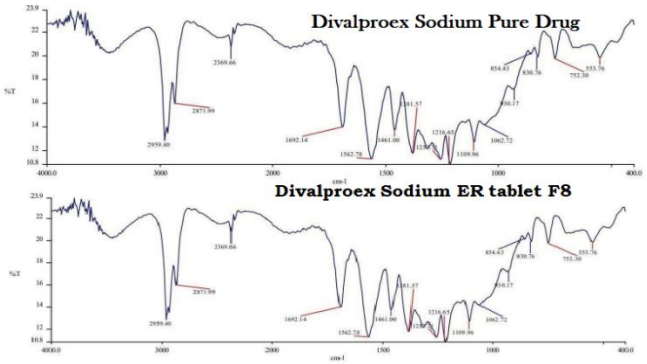

Figure 1: FTIR Chromatogram for Divalproex Sodium Pure Drug and Optimized Divalproex Sodium ER tablet F8

DSC Study Analysis:

The DSC thermogram of Divalproex sodium exhibited a sharp endothermic peak at 97.8°C, confirming its pure form. Formulations containing HPMC K15M, HPMC K4M, and HPMC K100M displayed a broader melting range (90–99°C), indicating that the drug remained unreacted. The prolonged melting process, influenced by excipients, suggests no adverse impact on formulation stability, thereby confirming drug-excipient compatibility, as shown in Figure No 2.

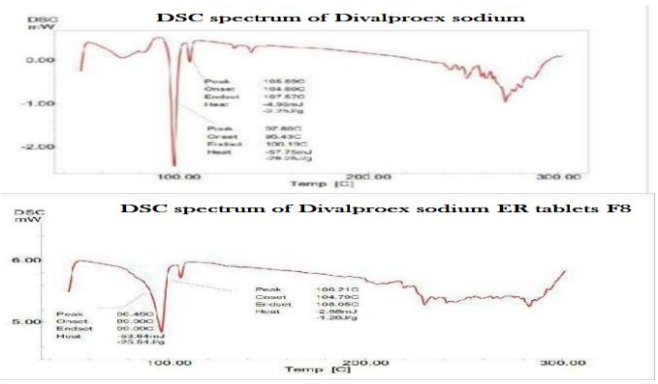

Figure 2: DSC spectrum of Divalproex sodium and optimized Divalproex sodium ER tablet F8

EVALUATION OF PRE-COMPRESSION PARAMETERS

Pre-formulation studies were carried out for all the formulations. Powder properties such as angle of repose, Carr's index, Hausner's ratio, bulk density, and tapped

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density were determined, which are shown in Table 3. Pre-formulation studies for the formulations depicted bulk density 0.512 to 0.66 g/cm^{3,} which indicated packing characteristics in dies. The Carr's compressibility index was found to be below 18%, which suggested good compressibility of the blend. The values of the Hausner ratio and angle of repose were found in the range of 1.13 to 1.25 and 16.59 to 22.54, respectively, suggesting excellent flow properties of the powder blend.

POST-COMPRESSION EVALUATION PARAMETERS:

Though the batch size of formulations were limited to 50-80, weight variation was reasonably satisfy the IP Limits and the drug content uniformity of all formulations was found to be 97.43-99.61 which indicated uniform distribution of drug in all batches of the formulations. Further hardness and friability were also between 13-14 kg/cm2 and less 1% respectively indicating stability of tablets against physical shock as shown in Table 4.

Table 3: Pre-compression parameters for Divalproex sodium ER tablets

Formulation	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Car's Index Mean ± SD	Haunsers Index Mean ± SD	Angle of Repose Mean ± SD
F1	0.584±0.009	0.694±0.003	13.780±0.208	1.154±0.009	19.607±0.279
F2	0.585±0.009	0.699±0.002	14.494±0.328	1.167±0.017	18.480±0.063
F3	0.601±0.004	0.688±0.004	11.225±0.186	1.132±0.009	18.203±0.088
F4	0.623±0.005	0.701±0.002	11.531±0.127	1.135±0.010	22.548±0.280
F5	0.621±0.004	0.695±0.003	14.560±0.202	1.154±0.009	19.777±0.293
F6	0.565±0.009	0.703±0.002	14.501±0.328	1.167±0.017	18.580±0.065
F7	0.594±0.009	0.700±0.002	11.255±0.188	1.132±0.009	18.203±0.088
F8	0.623±0.005	0.678±0.004	11.231±0.129	1.135±0.010	22.548±0.283

n=±6

Table 4: Post-compression parameters for Divalproex sodium ER tablets

Batch code	Weight variation Mean ± SD	Hardness (kg/cm^2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD
F1	1.01±0.012	13.06±2.09	0.32±0.06	6.89±0.019	99.38±1.19
F2	1.02±0.015	13.12±1.64	0.35±0.02	6.88±0.017	98.61±1.03
F3	1.03±0.017	14.69±0.91	0.43±0.03	6.87±0.022	97.43±1.28
F4	1.04±0.017	14.36±1.20	0.36±0.02	6.85±0.044	98.57±0.85
F5	1.07±0.014	13.86±1.09	0.33±0.06	6.91±0.017	99.38±1.19
F6	1.02±0.015	13.12±1.64	0.39±0.02	6.82±0.017	98.71±1.03
F7	1.08±0.011	14.70±0.95	0.45±0.03	6.84±0.022	99.83±1.28
F8	1.06±0.013	14.46±0.85	0.36±0.02	6.83±0.044	98.97±0.85

n=±6

***In vitro* dissolution study of Divalproex sodium ER tablets:**

The drug release from the marketed formulation followed a controlled and sustained profile, reaching 98% at 18 hours, as presented in Table 5 and depicted in Figure 3**.** Among the formulated batches, F1, F3, and F7 steadily increased drug release, with F3 reaching 72.22% at 18 hours**,** indicating a controlled but sustained release. In contrast**,** F5 exhibited the slowest release (30.12% at 18 hours), likely due to differences in polymer composition or matrix integrity**.** Higher polymer concentrations, as seen in F4 and F5**,** resulted in slower drug release (47.81% and 30.12%, respectively**),** suggesting enhanced matrix integrity delaying drug diffusion. Conversely, formulations F8, F1, and F3**,** with optimized polymer ratios, facilitated sustained drug release, with F8 achieving 99.84% at 18 hours**,** closely matching the marketed formulation. The drug release followed a biphasic pattern, an initial burst release followed by sustained diffusion**,** attributed to matrix surface erosion and polymer network diffusion.

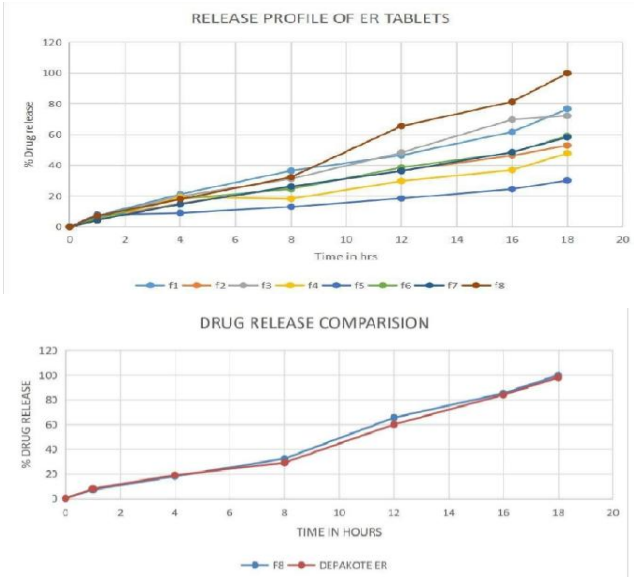

Figure 3: Cumulative drug release of Divalproex sodium ER tablet formulations (F1 to F8) and Comparison of optimized Divalproex sodium ER tablet with marketed Depakote ER

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Table 5: *In vitro* dissolution study of Divalproex sodium ER tablet formulations (F1 to F8) and Marketed Formulation

Time (Hrs)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	Marketed Formulation
0	0	0	0	0	0	0	0	0	0
1	7.22±0.105	5.558±1.591	6.51±1.281	3.99±0.024	7.905±1.234	5.458±1.691	4.33±0.014	7.12±0.105	8
4	21.22±0.331	15.527±1.114	19.91±1.532	13.469±1.22	8.995±0.134	18.231±1.281	14.75±0.064	18.01±0.101	19
8	36.41±0.073	25.742±1.427	31.12±1.321	18.231±1.28	13.006±1.994	24.502±1.083	26.22±0.427	32.25±0.331	29
12	46.51±0.046	36.518±0.831	48.27±0.826	29.735±0.94	18.521±1.421	38.852±1.521	36.31±0.074	65.51±0.466	60
16	61.71±0.078	46.331±0.891	69.76±0.906	36.936±1.25	24.502±1.083	48.234±0.826	48.51±0.046	81.24±0.094	84
18	76.620±1.64	52.852±0.792	72.22±2.001	47.81±0.539	30.12±1.503	59.12±1.193	58.22±0.444	99.84±0.675	98

The optimized extended-release formulations were evaluated for dissolution profile, content uniformity, friability, hardness, and other physicochemical parameters. In vitro dissolution studies confirmed that F8 exhibited a release profile comparable to marketed Depakote ER, demonstrating bioequivalence. Among all formulations, F8 showed the highest drug release (99.84% at 18 hours), surpassing the marketed formulation (98%), indicating its potential for enhanced therapeutic efficacy shown in Figure 3.

In Vitro Release Order Kinetics for Divalproex Sodium ER Tablets

The release kinetics of formulations (F1–F8) were analyzed using Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models shown in Table 6. All formulations predominantly followed Zero-order kinetics**,** with the highest R^2 values for F2 (0.9953) and F7 (0.9957)**,** confirming controlled, sustained drug release. Although the First-order model showed moderate correlation (F2 = 0.9943, F6 = 0.9777, F4 = 0.9743), its values were lower, indicating that drug release is independent of concentration. The Higuchi model regression values **(**0.9168–0.9601**)** suggest a diffusion-controlled release, with F2 (0.9601) and F8 (0.9573) showing the highest correlation. The Korsmeyer-Peppas model (n = 0.414–0.464) confirms a Fickian diffusion mechanism**,** meaning drug release occurs primarily through simple diffusion, as shown in Table 6. Overall, all formulations follow Zero-order kinetics with a diffusion-dominated release mechanism**,** and F2 and F8 emerge as the best candidates for sustained drug release**.**

Table 6: *In Vitro* Release Order Kinetics for Divalproex Sodium ER Tablets (F1-F8)

Formulation Code	Kinetic Models				
	Zero order	First order	Higuchi	Korsmeyer	
	R^2	R^2	R^2	n	R^2
F1	0.9812	0.9364	0.9372	0.421	0.9158
F2	0.9953	0.9943	0.9601	0.414	0.9236
F3	0.9931	0.9628	0.9319	0.441	0.8906
F4	0.9893	0.9743	0.9226	0.464	0.7233
F5	0.9554	0.9538	0.9168	0.431	0.8143
F6	0.9877	0.9777	0.9406	0.414	0.9011
F7	0.9676	0.7784	0.9372	0.443	0.9677
F8	0.9957	0.9766	0.9573	0.447	0.9014

OPTIMIZATION OF DIVALPROEX SODIUM ER TABLETS:

The optimization of Divalproex Sodium Extended Release (ER) tablets was carried out using Response Surface Methodology (RSM) in Stat-Ease Design Expert software version 13, employing a Central Composite Design (CCD). The study investigated the influence of three independent variables—HPMC K100M, HPMC K15M, and HPMC K4 M—on the dissolution (Y1) of the formulation. A total of 10 formulations were developed in a 3-factor, 1-response setup, including one center point.

The dissolution data obtained from experimental runs demonstrated significant variability, confirming that the response was highly dependent on the selected formulation variables. The dissolution percentage ranged from 30.57% to 99.84%, with the highest dissolution observed in formulation run 2 (99.84%) and the lowest in formulation run 4 (30.57%). This variation highlights the critical role of polymer composition in modulating drug release.

The three-dimensional response surface and two-dimensional contour plots generated by the software provided insights into the interaction effects of independent

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variables on dissolution, as shown in Figure 4. The response surface plot showed that as the concentration of HPMC K100M and HPMC K15M increased, dissolution tended to decrease, indicating their role in sustaining drug release. On the other hand, a moderate concentration of HPMC K4M contributed to achieving a balanced dissolution profile. The statistical analysis using ANOVA confirmed the significant effect of these formulation factors on dissolution, further validating the model.

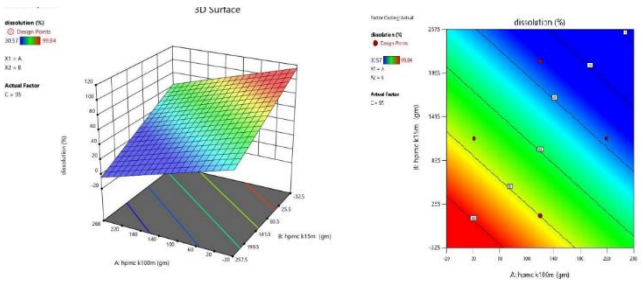

Figure 4: Effect of process variable on dissolution

ANOVA:

The responses were obtained and adjusted, and the predicted R^2 was determined based on Central composite Design, and ANOVA was calculated from the model. The P values, precision, % CV, adjusted and predicted R^2. The obtained R^2 value of the whole model was 0.8972, indicating the significance of the model. It means that the model could describe around 15.53% of the variability around the mean. ANOVA of the entire model as shown in Table 12. The model F value of 17.16 indicated that the proposed model was significant. The regression output demonstrated a p <0.005 value specifying the significance of the model.

Stability Studies:

The short-term stability study of F8 at 40°C / 75% RH for three month showed minimal changes in hardness (13.36 ± 1.20 to 13.21 ± 1.11 kg/cm²), friability (0.35 ± 0.02% to 0.36 ± 0.02%), drug content (99.23 ± 0.532% to 99.35 ± 0.751%), and drug release (99.823% to 98.421%). These results confirm that F8 remains stable, maintaining its extended-release performance and integrity.

CONCLUSION

This study successfully formulated and optimized extended-release matrix tablets of Divalproex Sodium using Hypromellose as a water-swellable polymer. By employing a one-level central composite design, the optimized formulation (F8) demonstrated desirable *in-vitro* release characteristics, aligning with in-house specification limits and exhibiting comparable performance to the reference product, Depakote ER. The developed formulation ensured a controlled and sustained drug release over 18 hours, following zero-order kinetics, thereby maintaining consistent therapeutic levels. Comprehensive physicochemical characterization, including assessments of thickness, diameter, weight uniformity, drug content, hardness, and friability, confirmed the robustness and uniformity of the tablets. Furthermore, stability studies validated the formulation's integrity under evaluated conditions. Overall, this research successfully achieved its objectives, presenting a well-optimized extended-release formulation with the potential to improve therapeutic efficacy and enhance patient adherence in epilepsy management.

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