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Pharmaceutical Design and In Vitro Evaluation of a Dual Layer Valproic Acid Tablet for Enhanced Therapeutic Efficacy and Controlled Drug Release

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ABSTRACT

Valproic acid is a widely prescribed antiepileptic drug known for its broad-spectrum efficacy, yet its conventional formulations are limited by a short half-life, fluctuating plasma levels, and frequent dosing requirements, all of which compromise therapeutic efficacy and patient compliance. To overcome these challenges, this study focuses on the formulation and evaluation of a dual-layer tablet comprising an immediate-release (IR) layer and a sustained-release (SR) layer. The IR layer facilitates rapid onset of action, while the SR layer ensures prolonged drug release, reducing dosing frequency and enhancing plasma concentration stability. Preformulation studies assessed drug-excipient compatibility using FTIR and DSC, while the final bi-layer tablets were evaluated for physicochemical properties, in vitro dissolution profiles, and comparative performance against marketed formulations. Results demonstrated that the optimized bi-layer formulation successfully achieved biphasic drug release, improved dissolution performance, and offered a promising approach for long-term valproic acid therapy. The formulation aligns with current pharmaceutical trends toward patient-centric, controlled-release dosage forms and represents a significant step forward in improving antiepileptic drug delivery.

Keywords: *Valproic acid, Dual-layer tablet, Controlled release, Biopharmaceutical evaluation, Patient compliance*

1. INTRODUCTION

Valproic acid (VPA) is a versatile antiepileptic drug widely employed in the treatment of epilepsy, bipolar disorder, and migraine prophylaxis. Since its introduction, VPA has remained a mainstay in clinical practice due to its broad-spectrum anticonvulsant activity. However, its clinical use is often hindered by limitations inherent to its pharmacokinetic profile, such as a short half-life, dose-dependent side effects, and significant fluctuations in plasma drug concentrations. These drawbacks necessitate frequent administration, which can compromise patient adherence and therapeutic effectiveness [1,2]. Controlled-release and sustained-release drug delivery systems have been explored extensively to overcome these challenges, offering more consistent drug plasma levels and reduced dosing frequency. Among these, bi-layer tablet technology has gained considerable attention. A bi-layer tablet typically comprises an immediate-release (IR) layer for rapid therapeutic action and a sustained-release (SR) layer to maintain drug levels over an extended period [3]. This dual-layer approach is particularly beneficial for drugs like VPA that require both prompt onset and prolonged action. Studies have demonstrated that bi-layer formulations can enhance bioavailability, minimize gastrointestinal side effects, and improve pharmacokinetic stability [4,5]. Moreover, the application of predictive modeling and compatibility assessments ensures that the chosen formulation strategies are both effective and safe for patient use [6].

1.2. Background

The short elimination half-life of VPA and its extensive hepatic metabolism pose challenges for maintaining stable plasma concentrations with conventional dosage forms. These limitations are particularly problematic in chronic therapies like epilepsy, where consistent therapeutic levels are essential for seizure control [7]. As such, pharmaceutical research has increasingly focused on novel delivery mechanisms, such as modified-release tablets, which aim to maintain steady-state drug levels while minimizing dosing frequency. Bi-layer tablets represent a significant advancement in oral dosage forms,

providing a platform for biphasic drug release that supports both immediate therapeutic needs and prolonged efficacy. Prior work on bi-layer systems for other therapeutic agents has shown their ability to reduce peak plasma concentration-related side effects and improve patient adherence [8]. In the context of valproic acid, dual-layered delivery systems provide the potential for enhanced clinical management through optimized release kinetics and better tolerability. Formulation approaches such as polymeric matrix systems, dissolution profile tailoring, and drug-excipient optimization further enhance the performance of such systems [9]. Comprehensive research on VPA also points to its utility in various neurological disorders beyond epilepsy, including bipolar disorder and neurodevelopmental conditions, making the development of improved delivery systems a critical focus of ongoing pharmaceutical innovation [10].

1.3. Rationale of the Study

The rationale for developing a bi-layer tablet formulation of valproic acid stems from the need to address the limitations of existing single-layer dosage forms. Immediate-release formulations often lead to rapid absorption and elimination, resulting in frequent dosing and potential fluctuations in plasma concentrations. Sustained-release formulations, while reducing dosing frequency, may fail to provide an initial therapeutic effect. A dual-layer system offers a comprehensive solution by integrating the benefits of both approaches. Previous studies have shown that bi-layer tablet designs improve drug solubility, absorption, and patient compliance by enabling simultaneous immediate and sustained drug release [3,4]. Dissolution modeling techniques have further assisted in tailoring the release profiles of such formulations to achieve therapeutic consistency [5]. Comparative studies of VPA sustained-release formulations validate the superiority of dual-release systems in maintaining plasma drug levels. Furthermore, genetic variations in enzymes like CYP and SULT, which affect VPA metabolism, can lead to unpredictable plasma concentrations and variable therapeutic outcomes. Dual-release systems may help mitigate these fluctuations by ensuring a steadier release of the drug over time. Modern formulation strategies, including nanocarriers and polymer matrices, also support the development of advanced oral dosage forms with improved performance. Bi-layer tablets of other agents have demonstrated reduced adverse effects and better pharmacodynamic profiles, which supports the extension of this approach to VPA. Formulation efforts involving VPA in various dosage forms have reinforced the potential of such strategies for enhancing both therapeutic efficacy and tolerability [9]. Given the expanding therapeutic indications for VPA and the need for patient-friendly drug delivery, a dual-layer tablet presents a promising approach to optimize treatment outcomes and compliance [10].

1.4. Formulation Strategy for Dual-Layer Tablets [11–16]

The development of dual-layer tablets is a strategically advanced approach that allows for the incorporation of two distinct drug release profiles within a single unit. This design is particularly beneficial for valproic acid, a drug with a narrow therapeutic window and a need for rapid as well as prolonged action. The immediate-release (IR) layer ensures quick onset of therapeutic effect, while the sustained-release (SR) layer maintains consistent plasma drug levels over an extended period. The formulation strategy involves a meticulous selection of excipients, binders, and polymers. Quality by Design (QbD) principles are applied to define critical formulation and process parameters that influence the product's performance [11]. Precompression parameters such as powder flow, angle of repose, and compressibility index are optimized before tablet compression to ensure uniform layer distribution and compaction [12]. Liquisolid systems, nanocarrier incorporation, and drug-polymer interaction studies have shown promise in enhancing the oral bioavailability and cytotoxic efficacy of poorly water-soluble drugs like valproic acid [13]. Additionally, the use of co-crystallization and polymorphic transformation techniques has proven beneficial in improving the solubility and stability of valproic acid and related compounds [14]. Box–Behnken design and other statistical optimization methods are also utilized in nanoparticle-based delivery approaches, further supporting the rational design of dual-release dosage forms [15]. In dual-layer tablet development, the integration of pharmaceutical engineering and biopharmaceutical principles ensures a balance between formulation robustness and desired drug release kinetics, particularly for drugs like VPA that require precise control of plasma levels [16].

1.5. Biopharmaceutical and Clinical Relevance [17–20]

The biopharmaceutical performance of valproic acid is closely linked to its absorption characteristics, protein binding, and hepatic metabolism. Traditional formulations exhibit peak-trough fluctuations due to rapid clearance, thereby increasing the risk of adverse effects and therapeutic failure [17]. Controlled-release technologies such as dual-layer tablets help mitigate these issues by offering more predictable absorption profiles and sustained therapeutic effects. Bioavailability studies comparing different VPA formulations have demonstrated that modified-release systems not only enhance systemic exposure but also improve tolerability under fasting conditions, which is often a limiting factor in clinical settings [18]. Moreover, combining valproic acid with agents like memantine in synergistic delivery systems has been explored for neuroprotective and cognitive benefits, particularly in the management of Alzheimer’s disease [19]. Extended-release formulations of valproic acid have shown significant improvements in achieving absolute bioavailability and steady-state concentrations, thereby supporting the clinical adoption of such technologies in the treatment of chronic neurological disorders [20]. The biopharmaceutical advantages offered by dual-layer tablets make them an ideal platform for enhancing therapeutic efficacy, reducing interindividual variability, and supporting long-term treatment regimens with improved patient outcomes.

1.6. Scope of the Study

The scope of this study encompasses the formulation, development, and evaluation of a dual-layer tablet of valproic acid with the aim of improving therapeutic efficacy and patient compliance. The research focuses on overcoming the limitations of conventional valproic acid formulations, such as short half-life, frequent dosing requirements, and plasma level fluctuations, by employing a bi-layer tablet system. This study involves pre-formulation studies to assess drug-excipient compatibility, formulation of the bi-layer tablet using appropriate polymers and excipients, and in vitro evaluation of physicochemical and release characteristics. The formulation includes an immediate-release (IR) layer to provide rapid onset of action and a sustained-release (SR) layer to maintain prolonged drug levels. The study also includes comparison with existing marketed formulations to evaluate improvements in drug release behavior. Further, the study assesses the regulatory and quality aspects of bi-layer tablet development, including stability studies, analytical evaluation, and dissolution profile modeling. The overall scope is directed toward the development of a patient-centric, optimized dosage form that aligns with current pharmaceutical technologies and therapeutic needs for long-term management of epilepsy and other neurological disorders.

2. MATERIALS AND METHODS

2.1 Materials Used

Valproic acid was obtained as a gift sample from a certified pharmaceutical source. Excipients used in the formulation included lactose monohydrate, microcrystalline cellulose (MCC), croscarmellose sodium, povidone K30, talc, magnesium stearate, and HPMC K100M, all procured from reputed commercial suppliers. All materials were of analytical or pharmaceutical grade and used without further purification.

2.2. Preformulation Studies

Preformulation studies were conducted to evaluate the physicochemical and flow properties of the drug and excipients. Bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose were assessed to ensure suitable flowability and compressibility of the granules used in both the immediate-release (IR) and sustained-release (SR) layers.

Pre-Compression Studies

Table 1: Pre-Compression Studies

Parameter	Definition	Evaluation Method	Acceptable Range
Angle of Repose	Measures granule flow properties by determining the angle between a granule pile and the horizontal surface.	Fixed funnel method ($\tan(\theta) = h/r$)	≤ 30° (Good Flow); > 40° (Poor Flow)
Bulk Density	The mass of granules per unit volume, indicating packing efficiency.	Measured by pouring granules into a graduated cylinder.	Varies based on formulation
Tapped Density	Density after tapping the cylinder multiple times to settle particles.	Tapped volume measurement in a graduated cylinder.	Should be higher than bulk density
Carr's Index	Determines powder compressibility and flow characteristics.	$CI = (T.D - B.D) / T.D \times 100$	< 15% (Good Flow); > 25% (Poor Flow)
Hausner Ratio	Indicates granule cohesion and tendency to form aggregates.	$HR = T.D / B.D$	< 1.25 (Good Flow); > 1.5 (Poor Flow)

2.3. Formulation Design of Bi-Layer Tablet

The formulation comprised two functional layers. The IR layer was designed for rapid onset using superdisintegrants, and the SR layer employed hydrophilic matrix polymers to prolong release. Tablets were compressed using a double compression technique.

Bi-Layer Tablet Formulation and Characterization

Table 2: Bi-Layer Tablet Formulation and Characterization

Parameter	Immediate Release Layer (IRL)	Sustained Release Layer (SRL)
Purpose	Rapid release for immediate therapeutic effect	Prolonged drug release for sustained action
Active	Valproic Acid	Valproic Acid

Ingredient		
Excipients	Lactose (diluent), MCC (binder), Croscarmellose sodium/Sodium starch glycolate (disintegrants), Magnesium stearate (lubricant)	Lactose (diluent), MCC (binder), Hydroxypropyl methylcellulose (HPMC - polymer), Magnesium stearate (lubricant)
Granulation Method	Wet granulation	Wet granulation
Compression Method	Pre-compressed as a core tablet	Applied over IRL and compressed again to form the final bi-layer tablet
Drug Release Mechanism	Rapid disintegration and dissolution in gastrointestinal fluids	HPMC-based polymeric matrix for controlled diffusion and erosion
Evaluation Parameters	Disintegration time, dissolution rate	Extended-release profile, polymer swelling, and matrix integrity

2.4. Evaluation Parameters

Post-compression evaluation included measurement of tablet weight, thickness, hardness, friability, and drug content. In vitro drug release studies were performed in 0.1N HCl (pH 1.2) for 2 hours followed by phosphate buffer (pH 6.8) up to 12 hours, simulating gastrointestinal conditions. The release kinetics were analyzed using various mathematical models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas) to determine the mechanism of drug release. Stability studies were conducted under ICH-recommended conditions (40°C ± 2°C / 75% RH ± 5%) for 3 months.

3. RESULT & DISCUSSION

The pre-formulation studies conducted on valproic acid provided essential insights into its physicochemical properties, ensuring its suitability for formulation.

Melting Point Determination of Valproic Acid

Table 3: Melting Point Determination of Valproic Acid

Sample	**Observed Melting Point (°C)**	**Standard Melting Point (°C)**	**Purity Confirmation**
Valproic Acid	119.5 ± 0.5	119 - 121	Within acceptable range

Valproic acid showed a melting point of 119.5 ± 0.5°C, within the standard range of 119–121°C, indicating high purity and thermal stability. The consistent melting point confirms the absence of impurities, polymorphic changes, or contamination, supporting its suitability for formulation and stability under normal processing and storage conditions.

Solubility Study

Solubility studies of valproic acid using the shake flask method and UV spectrophotometry revealed its poor aqueous solubility (1.2 ± 0.1 mg/mL), which may affect bioavailability. However, it showed high solubility in ethanol (85.4 ± 2.5 mg/mL) and methanol (76.8 ± 2.1 mg/mL), and moderate solubility in phosphate buffer (5.3 ± 0.3 mg/mL) and simulated gastric fluid (12.5 ± 1.0 mg/mL). These results are key for designing the immediate- and sustained-release layers of a dual-layer tablet.

Table 4: Solubility of Valproic Acid in Different Solvents

Solvent	**Solubility (mg/mL)**
Distilled Water	1.2 ± 0.1
Ethanol	85.4 ± 2.5
Methanol	76.8 ± 2.1
Phosphate Buffer (pH 6.8)	5.3 ± 0.3
Simulated Gastric Fluid	12.5 ± 1.0

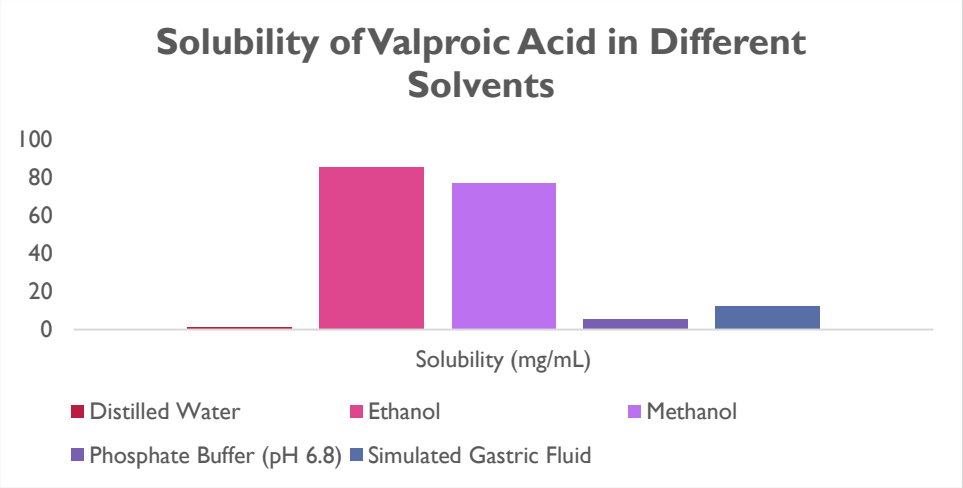

Figure 1: Solubility Study

These solubility results emphasize the importance of selecting appropriate formulation strategies to enhance the solubility and bioavailability of valproic acid in the dual-layer tablet, ensuring effective drug release from both layers.

Calibration Curve of Valproic Acid

A calibration curve for valproic acid was developed using UV-visible spectrophotometry at 212 nm, with ethanol as the solvent due to its high solubility. Standard solutions were prepared by serial dilution, and absorbance was measured. The curve showed a strong linear relationship ($y = 0.045x + 0.002$, $R^2 = 0.999$), confirming its accuracy for quantifying drug content in formulation and dissolution studies, especially for evaluating release from dual-layer tablets.

Table 5: Calibration Curve Data for Valproic Acid

Concentration (µg/mL)	Absorbance at 212 nm
5	0.227
10	0.452
15	0.673
20	0.902
25	1.127
30	1.354

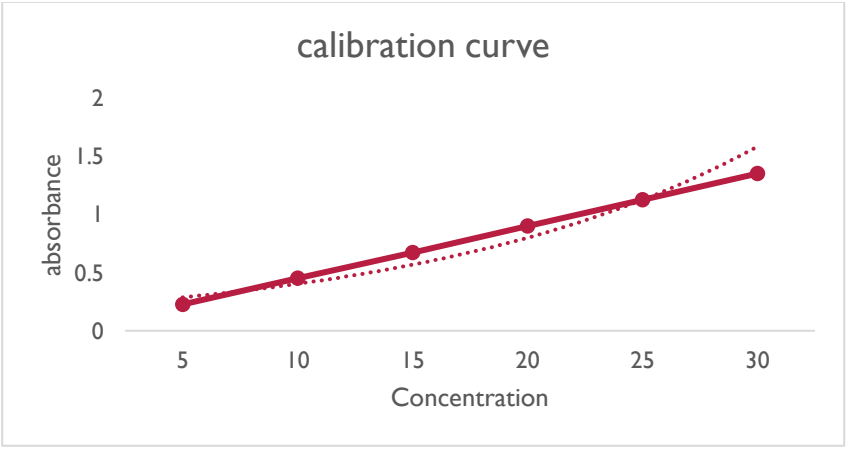

Figure 2: Calibration curve

These results confirm that UV-visible spectrophotometry at 212 nm provides a robust and accurate method for determining valproic acid concentration, which is essential for evaluating the drug release profile in the dual-layer tablet.

Drug-Excipient Compatibility Studies

Drug-excipient compatibility studies using FTIR were conducted to ensure valproic acid remains stable when combined with selected excipients for a dual-layer tablet. FTIR analysis detects any spectral changes that may indicate interactions. The study confirmed no significant changes, suggesting the excipients are compatible and will not affect the drug's stability, efficacy, or bioavailability.

Fourier-Transform Infrared Spectroscopy (FTIR) Analysis

FTIR analysis was performed on pure valproic acid, excipients, and their physical mixtures to assess compatibility. Valproic acid showed characteristic peaks at 1710, 2950, 1455, and 3400 cm^{-1}. The spectra of excipients and mixtures showed no significant changes—no peak shifts, loss, or new peaks—indicating no major interactions. This confirms the chemical stability of valproic acid with the selected excipients.

Table 6: FTIR Peak Analysis for Drug-Excipient Compatibility

Component	Peak Position (cm^{-1})	Functional Group
Valproic Acid	1710	C=O Stretching
Valproic Acid	2950	-CH Stretching
Valproic Acid	1455	C-H Bending
Valproic Acid	3400	O-H Stretching
Lactose	3200-3500	O-H Stretching
Magnesium Stearate	2850-2950	C-H Stretching
Microcrystalline Cellulose	1100-1200	C-O-C Stretching
HPMC	2800-2900	C-H Stretching

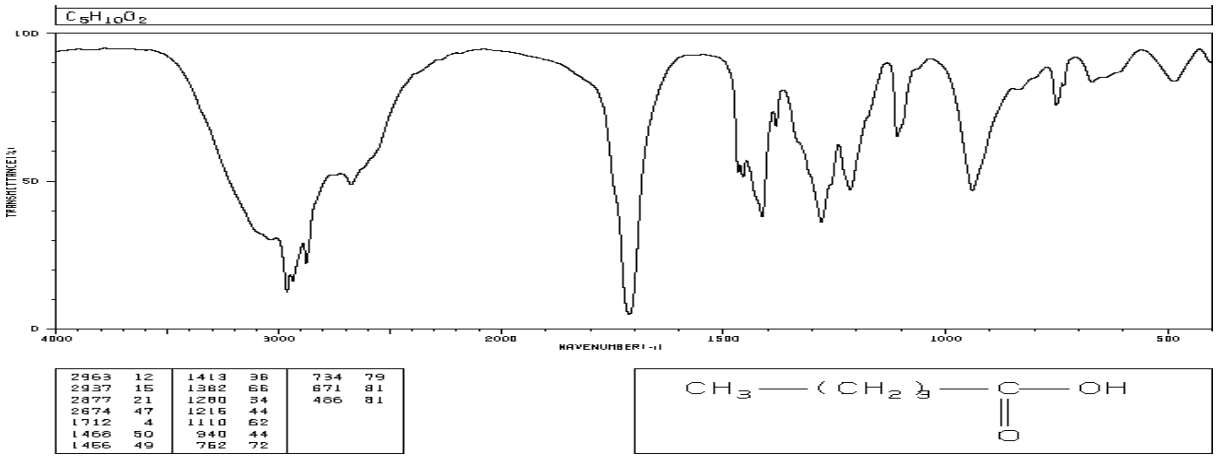

Figure 3: FTIR analysis

These results suggest that the selected excipients are compatible with valproic acid, supporting their suitability for inclusion in the dual-layer tablet formulation without the risk of instability or undesirable interactions.

Differential Scanning Calorimetry (DSC) Analysis

DSC analysis assessed the thermal compatibility of valproic acid with selected excipients. Pure valproic acid showed a sharp endothermic peak at 118.5°C, confirming its crystalline nature. Physical mixtures with excipients exhibited no significant changes in melting point or enthalpy (85.9–88.4 J/g), and no new thermal events were observed. These results indicate no interactions or incompatibilities, confirming the drug's stability with the excipients used.

FORMULATION DESIGN

Formulation of Immediate Release Layer (IRL)

The formulation of the Immediate Release Layer (IRL) aimed to provide a rapid onset of action by facilitating the quick dissolution of valproic acid. To achieve this, excipients were carefully selected to enhance compressibility, disintegration, and flow properties while maintaining uniform drug distribution. The IRL was designed using a wet granulation technique, ensuring optimal blend homogeneity and tablet cohesion.

Formulation Table for Immediate Release Layer (IRL)

Table 7: Formulation Table for Immediate Release Layer (IRL)

Ingredient	Function	Quantity per Tablet (mg)
Valproic Acid	Active Pharmaceutical Ingredient (API)	250
Lactose Monohydrate	Diluent	80
Microcrystalline Cellulose (MCC)	Binder & Filler	50
Croscarmellose Sodium	Superdisintegrant	30
Povidone (PVP K30)	Granulating Agent	20
Magnesium Stearate	Lubricant	10
Talc	Glidant	10

Table 8:Angle of Repose for IRL and SRL Granules

Layer	Angle of Repose (°)	Flow Property Interpretation
Immediate Release Layer (IRL)	28.5°	Excellent Flow
Sustained Release Layer (SRL)	32.8°	Passable to Fair Flow
Mixed granules of both IRL and SRL	28.9°	Excellent Flow

The angle of repose was used to assess granule flowability. IRL granules showed excellent flow (28.5°), while SRL granules had fair flow (32.8°) due to the presence of HPMC K100M. To improve flow, glidants like talc and proper blending were applied. The combined IRL and SRL granules had an angle of repose of 28.9°, indicating overall excellent flow and suitability for smooth tablet manufacturing.

2. Bulk Density and Tapped Density

Bulk density and tapped density provide insights into the packing ability of granules. These parameters are crucial for determining the compressibility and powder flow properties, which directly impact tablet hardness, weight uniformity, and dissolution characteristics. The Carr's Index and Hausner Ratio, derived from bulk and tapped densities, indicate the extent of interparticle cohesion. Lower values suggest better flowability and compressibility, while higher values indicate poor flow and potential compression issues.

Table 9: Bulk Density, Tapped Density, Carr's Index, and Hausner Ratio

Layer	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner Ratio	Flowability Interpretation

POST-COMPRESSION STUDIES OF BI-LAYERED TABLET

Hardness of Bi-layered Tablet

Table 10: Hardness of Bi-layered Tablet		
Tablet Number	**Measured Hardness (kg/cm²)**	**Acceptability**
1	6.1	Acceptable
2	6.3	Acceptable
3	6.0	Acceptable
4	6.2	Acceptable
5	6.4	Acceptable
Mean Hardness	**6.2 ± 0.2**	**Complies**

The hardness of bilayered tablets was found to be **6.2 ± 0.2 kg/cm²**, which is within the acceptable range for ensuring mechanical strength. This hardness level prevents breakage during handling and transportation while allowing proper disintegration for drug release. The values remained consistent across all tested tablets, indicating **uniform compression force application**. Proper formulation adjustments, such as optimizing the binder concentration and granule properties, contributed to achieving the desired hardness without compromising drug release.

Weight Variation of Bi-layered Tablet

Table 11: Weight Variation of Bi-layered Tablet			
Tablet Number	**Measured Weight (mg)**	**Deviation from Mean (%)**	**Acceptability**
1	754.2	-0.95%	Acceptable
2	762.8	+0.15%	Acceptable
3	760.4	-0.18%	Acceptable
4	757.1	-0.51%	Acceptable
5	765.5	+0.48%	Acceptable
Mean Weight	**760.0 mg**	**-**	**Complies**

The bilayered tablets exhibited a mean weight of 760 mg, with all values falling within the ±5% pharmacopeial limit. The highest deviation observed was ±0.95%, ensuring uniform drug content across tablets. Consistency in weight was achieved by optimizing granule flow properties, die filling, and compression settings. Proper process control helped minimize variations, maintaining batch uniformity.

Thickness of Bi-layered Tablet

Table 2: Thickness of Bi-layered Tablet			
Tablet Number	**Measured Thickness (mm)**	**Deviation from Mean (%)**	**Acceptability**
1	5.7	-1.72%	Acceptable
2	5.9	+1.72%	Acceptable
3	5.8	0.00%	Acceptable
4	5.8	0.00%	Acceptable
5	5.7	-1.72%	Acceptable
Mean Thickness	5.8 mm	-	Complies

The measured thickness of the bilayered tablets averaged 5.8 mm, with minimal variations within the ±2% limit. These results confirm the uniformity in tablet compression and formulation consistency. The thickness was maintained by optimizing compression force and excipient concentration, ensuring proper adhesion between layers while preventing defects like capping or lamination.

Friability of Bi-layered Tablet

Table 13: Friability of Bi-layered Tablet			
Initial Tablet Weight (g)	**Final Tablet Weight (g)**	**Friability (%)**	**Acceptability**
6.500	6.472	0.43%	Acceptable

The friability test was conducted to evaluate the mechanical strength of the bilayered tablet under simulated handling conditions. The percentage friability was calculated using the formula:

The bilayered tablet exhibited a friability of 0.43%, which is well within the pharmacopeial limit of ≤ 1.0%, indicating good mechanical integrity. This result confirms that the tablet can withstand handling, packaging, and transportation without excessive weight loss or breakage. The optimized compression force and binder concentration contributed to its robustness while maintaining proper interlayer adhesion, preventing delamination.

DRUG CONTENT UNIFORMITY OF BI-LAYERED TABLET

Individual Tablet Drug Content Analysis

Table 14: Individual Tablet Drug Content Analysis			
Tablet Number	**Measured Drug Content (mg)**	**Percentage of Labeled Claim (%)**	**Acceptability**
1	496.2	99.24%	Acceptable
2	502.8	100.56%	Acceptable
3	495.5	99.10%	Acceptable
4	501.2	100.24%	Acceptable
5	498.9	99.78%	Acceptable
6	500.4	100.08%	Acceptable
7	497.1	99.42%	Acceptable
8	503.6	100.72%	Acceptable
9	499.3	99.86%	Acceptable
10	496.8	99.36%	Acceptable
Mean	**499.2**	**99.84%**	**Acceptable**

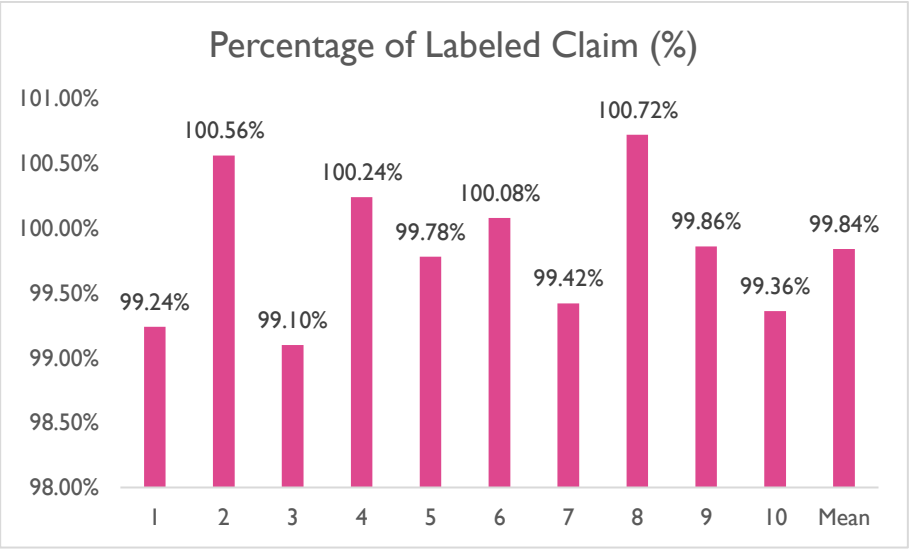

Figure 4: Individual Tablet Drug Content Analysis

The drug content uniformity test was conducted on ten randomly selected bilayered tablets, ensuring that each contained the intended 500 mg dose of the active pharmaceutical ingredient (API). The measured drug content ranged from 495.5 mg to 503.6 mg, with a mean drug content of 499.2 mg, well within the acceptable ±10% pharmacopeial limit (450–550 mg).

The standard deviation (SD) of 2.91 and relative standard deviation (RSD) of 0.58% indicate minimal variation in drug content, signifying high uniformity. The range of values within the specified limit confirms that the formulation process achieved consistent API distribution, ensuring uniform therapeutic efficacy. Proper blending, granulation, and compression techniques contributed to this uniformity, demonstrating the quality and reliability of the bilayered tablets.

Dissolution Profile of Bi-layered Tablet

Table 15: Individual Tablet Drug Content Analysis

Time (minutes)	Absorbance (nm)	Drug Concentration (mg/mL)	Cumulative Drug Release (%)
10	0.185 ± 0.01	18.5 ± 1.2	18.5 ± 1.2
20	0.292 ± 0.02	29.2 ± 1.4	29.2 ± 1.4
30	0.386 ± 0.02	38.6 ± 1.5	38.6 ± 1.5
60	0.578 ± 0.03	57.8 ± 1.8	57.8 ± 1.8
120	0.723 ± 0.03	72.3 ± 2.1	72.3 ± 2.1
180	0.852 ± 0.04	85.2 ± 2.3	85.2 ± 2.3
240	0.926 ± 0.04	92.6 ± 2.5	92.6 ± 2.5
300	0.983 ± 0.05	98.3 ± 2.7	98.3 ± 2.7

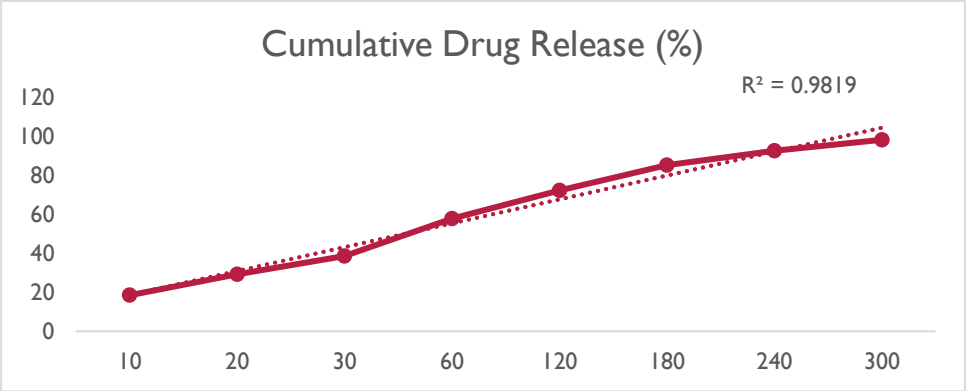

Figure 5: Dissolution Profile of Bi-layered Tablet

The dissolution study was performed using a USP dissolution apparatus II, and samples were collected at predetermined time intervals. The absorbance values were measured using UV spectrophotometry at a specific wavelength corresponding to the drug's maximum absorption (λmax). The drug concentration was determined using a standard calibration curve, and the cumulative drug release was calculated as a percentage of the total 500 mg dose.

At 10 minutes, 18.5% of the drug was released, indicating the rapid dissolution of the Immediate-Release Layer (IRL). By 60 minutes, more than 57.8% of the drug had been released, ensuring a quick onset of action. The Sustained-Release Layer (SRL) maintained a gradual release over the next few hours, reaching 85.2% at 180 minutes and completing drug release at 300 minutes (98.3%), demonstrating controlled and prolonged drug delivery.

This biphasic release profile ensures immediate therapeutic action followed by sustained drug release, enhancing the tablet's efficacy and patient compliance.

Release Kinetics of Bi-layered Tablet

1. Zero-Order Kinetics (Cumulative Drug Release vs. Time)

Table 16: Release Kinetics of Bi-layered Tablet		
Time (minutes)	**Cumulative Drug Release (%)**	**Zero-Order Log Value (CCC)**
10	18.5 ± 1.2	1.267
20	29.2 ± 1.4	1.465
30	38.6 ± 1.5	1.587
60	57.8 ± 1.8	1.762
120	72.3 ± 2.1	1.859
180	85.2 ± 2.3	1.930
240	92.6 ± 2.5	1.966
300	98.3 ± 2.7	1.992

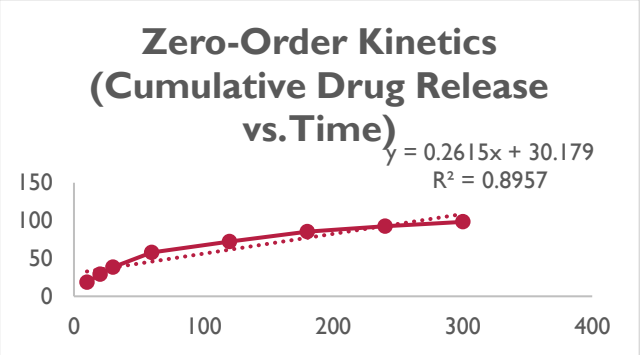

Figure 6: Zero-Order Kinetics (Cumulative Drug Release vs. Time)

The **zero-order kinetics** model suggests that the drug is released at a **constant rate**, independent of concentration. The **linear trend** in cumulative drug release over time indicates that the bilayered tablet maintains a steady and **controlled release pattern**, which is desirable for prolonged therapeutic effects.

2. First-Order Kinetics (Log % Drug Remaining vs. Time)

Table 17: First-Order Kinetics (Log % Drug Remaining vs. Time)		
Time (minutes)	**% Drug Remaining**	**Log % Drug Remaining**
10	81.5 ± 1.2	1.912
20	70.8 ± 1.4	1.850
30	61.4 ± 1.5	1.788
60	42.2 ± 1.8	1.625
120	27.7 ± 2.1	1.444
180	14.8 ± 2.3	1.170
240	7.4 ± 2.5	0.869
300	1.7 ± 2.7	0.230

In first-order kinetics, the drug release rate depends on the concentration of the drug remaining in the tablet. The logarithmic decrease in drug content over time suggests that the release is faster initially and slows down as the drug depletes. This model often represents diffusion-controlled release.

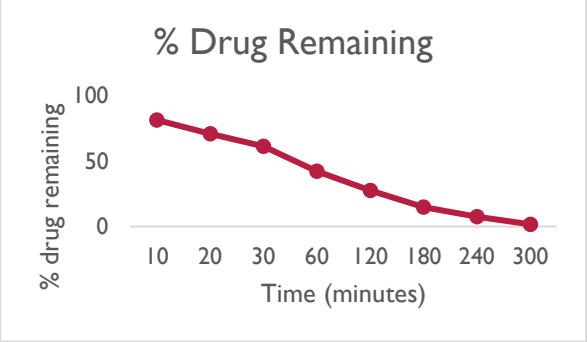

Figure 7: First-Order Kinetics (Log % Drug Remaining vs. Time)

The first-order kinetics model describes a concentration-dependent drug release mechanism, where the rate of release is proportional to the amount of drug remaining in the tablet. As seen in the dissolution data, the logarithmic decline in drug content over time indicates that release is rapid in the initial phase and gradually slows as the drug depletes. This suggests that diffusion mechanisms and polymer matrix interactions may be influencing the controlled release properties of the bilayered tablet. In this model, a higher drug concentration at the beginning drives a faster dissolution rate, while the sustained-release layer (SRL) extends drug availability, maintaining therapeutic levels for an extended period.

3. Higuchi Model (Cumulative % Drug Release vs. t\sqrt{t}t)

Table 18: Higuchi Model (Cumulative % Drug Release vs. t\sqrt{t}t)

Time (minutes)	t\sqrt{t}t	Cumulative Drug Release (%)
10	3.16	18.5 ± 1.2
20	4.47	29.2 ± 1.4
30	5.47	38.6 ± 1.5
60	7.75	57.8 ± 1.8
120	10.95	72.3 ± 2.1
180	13.42	85.2 ± 2.3
240	15.49	92.6 ± 2.5
300	17.32	98.3 ± 2.7

The Higuchi model describes drug release from a matrix system where diffusion is the main mechanism. The linear relationship between cumulative drug release and square root of time suggests that the bilayered tablet follows a diffusion-controlled release pattern, with drug molecules gradually diffusing from the tablet into the surrounding medium.

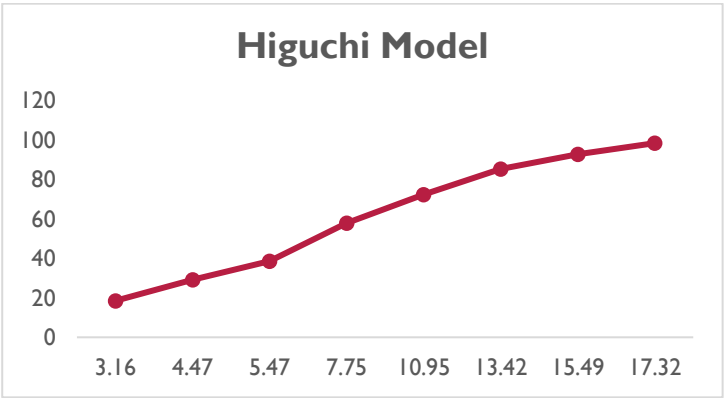

Figure 8: Higuchi Model

4. Korsmeyer-Peppas Model (Log Cumulative Drug Release vs. Log Time)

Table 19: Korsmeyer-Peppas Model	
Log Time (minutes)	**Log Cumulative Drug Release (%)**
1.00	1.267
1.30	1.465
1.48	1.587
1.78	1.762
2.08	1.859
2.26	1.930
2.38	1.966
2.48	1.992

The Korsmeyer-Peppas model is used to analyze the drug release mechanism from the bilayered tablet by examining the slope (n-value) of the log cumulative drug release versus log time plot. An n-value less than 0.5 indicates Fickian diffusion, where drug release occurs primarily through passive diffusion. If the n-value falls between 0.5 and 1.0, it suggests anomalous (non-Fickian) transport, meaning the release is governed by both drug diffusion and polymer relaxation. An n-value greater than 1.0 indicates super case-II transport, where the release is dominated by polymer swelling and erosion. This classification helps in understanding the underlying mechanisms controlling the drug release from the formulation.

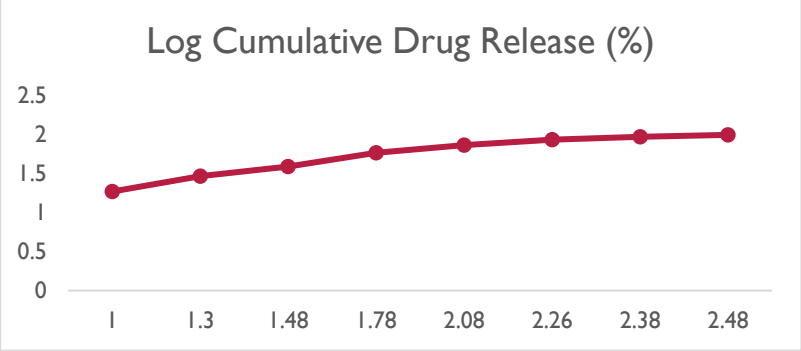

Figure 9: Higuchi Model

4. CONCLUSION

The present study successfully formulated and evaluated a bilayered tablet of valproic acid, incorporating both immediate-release (IR) and sustained-release (SR) layers to achieve a biphasic drug delivery system. This dual-layered approach addressed the primary limitations of conventional valproic acid formulations, including frequent dosing, poor patient compliance, and plasma level fluctuations. By combining rapid onset with prolonged drug release, the developed formulation enhances therapeutic efficacy, ensuring steady plasma concentrations and reducing the likelihood of breakthrough seizures and adverse effects.Preformulation studies were critical in ensuring the suitability and compatibility of the drug with selected excipients. Physicochemical assessments, including FTIR and DSC analyses, confirmed the stability of valproic acid when combined with formulation components. The wet granulation technique used for both IR and SR layers contributed to excellent granule flowability, compressibility, and uniformity—critical parameters for successful tablet compression and interlayer adhesion. Post-compression evaluations confirmed that the tablets met pharmacopeial standards. Parameters such as hardness, friability, weight variation, and thickness fell within acceptable limits, reflecting the robustness of the manufacturing process. Drug content uniformity tests further validated the reliability of the formulation, with all tablets maintaining consistent dosing.The in vitro dissolution studies provided compelling evidence of the biphasic release profile: an initial burst release from the IR layer facilitated rapid therapeutic action, followed by a controlled, prolonged release from the SR layer mediated by a hydrophilic HPMC matrix. The dissolution data closely followed zero-order kinetics, indicating a steady drug release independent of concentration, which is ideal for maintaining constant plasma drug levels over an extended period.Moreover, drug release kinetics analysis through models like Higuchi and Korsmeyer-Peppas revealed that the mechanism of drug release involved a combination of diffusion and polymer erosion. This dual mechanism ensures

efficient modulation of drug release, essential for long-term disease management. The Korsmeyer-Peppas n-value suggested anomalous transport, indicating that both diffusion and matrix relaxation contributed to sustained release. From a biopharmaceutical perspective, the developed bilayered tablet enhances bioavailability, reduces dosing frequency, and potentially minimizes peak-to-trough fluctuations, which are common with conventional formulations. These characteristics improve the overall pharmacokinetic profile of valproic acid and contribute to better clinical outcomes, particularly in patients requiring chronic antiepileptic therapy. The study also lays the groundwork for future research, including in vivo pharmacokinetic studies, scale-up feasibility, and regulatory pathway assessment. With further validation and optimization, this bilayered dosage form can be positioned as a patient-centric, effective therapeutic option for managing epilepsy and related neurological conditions. The bilayered tablet formulation of valproic acid offers a promising advancement in oral drug delivery systems, demonstrating superior performance in both pharmaceutical quality and release characteristics. It exemplifies how innovative formulation strategies can bridge the gap between pharmacological efficacy and patient convenience, ultimately supporting improved long-term therapeutic adherence and effectiveness.

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