Original Research Article

THE DESIGN AND OPTIMIZATION OF FAST-DISSOLVING ORAL DRUG DELIVERY SYSTEM (ODDS) OF VALPROIC ACID (VLA) AN ANTI-EPILEPTIC CATEGORY DRUG

Abstract:

Objective: Develop and optimize a fast-dissolving oral drug delivery system (ODDS) for Valproic acid (VLA), an anti-epileptic drug, using Design of Experiments (DoE).

Methodology: DoE, a powerful tool for optimizing formulations, was employed to investigate the impact of various factors on the dissolution rate of VLA ODDS. Key factors studied includedsuperdisintegrants (sodium starch glycolate, crospovidone), diluents (lactose, microcrystalline cellulose), and lubricants (magnesium stearate). A Box-Behnken design was used to create experimental runs, and the dissolution rate at 30 minutes was chosen as the response variable.

Results: The DoE analysis revealed significant interactions between factors affecting the dissolution rate. The formulation containing sodium starch glycolate, lactose, and low magnesium stearate concentration exhibited the fastest dissolution rate (Q30 > 85% in 10 minutes).

Conclusion: This study successfully designed and optimized a fast-dissolving ODDS for VLAusing DoE. The optimized formulation offered rapid drug release, potentially improving patient compliance and therapeutic efficacy. This approach demonstrates the effectiveness of DoE in optimizing pharmaceutical formulations for enhanced performance.The findings indicated that the RSM was effectively utilized in developing valproic acid fast dispersible tablets, thus representing a significant progress in the treatment of epileptic seizures.

Keywords:design of experiments; optimization; epileptic; response surface methodology; development; disintegration; computational approach; formulations; dissolving tablet.

1. INTRODUCTION

In recent years, the development of innovative pharmaceutical formulations has become imperative to enhance drug delivery efficiency and patient compliance. The focus has shifted towards optimizing oral drug delivery systems to overcome challenges associated with conventional dosage forms. This research endeavors to address these challenges through the design and optimization of a Fast Dissolving Oral Drug Delivery System (ODDS) specifically tailored for Valproic Acid, a potent Anti-Epileptic Category Drug [1].

Epilepsy, a neurological disorder characterized by recurrent seizures, remains a significant global health concern affecting millions of individuals. VLAhas emerged as a cornerstone in the management of epilepsy due to its broad-spectrum anti-seizure properties. The conventional formulations of VLAoften exhibit limitations related to delayed onset of action, variable absorption, and patient non-compliance [1-2]. The utilization of advanced drug delivery technologies, such as Fast Dissolving ODDS, presents a promising avenue to overcome these challenges.

This research aims to employ the principles of Design of Experiments (DoE) to systematically optimize the formulation of VLA-loaded ODDS. By leveraging DoE, a statistical methodology that allows for the efficient exploration of various factors influencing the formulation, we intend to achieve a comprehensive understanding of the interplay between formulation variables and their impact on critical product attributes [3]. This systematic approach not only facilitates the identification of optimal conditions but also enhances the reproducibility and robustness of the developed drug delivery system.

The significance of this study lies in its potential to improve the therapeutic efficacy of VLAby ensuring rapid dissolution and absorption, thereby optimizing its bioavailability. Moreover, the application of DoE adds a layer of scientific rigor to the formulation process, paving the way for a more systematic and efficient development approach. The outcomes of this research hold promise for the advancement of pharmaceutical technology, contributing to the betterment of epilepsy treatment and patient outcomes.The optimization of its formulation for enhanced therapeutic outcomes remains a critical objective. The utilizing Response Surface Methodology (RSM), a powerful statistical technique, offers a systematic approach to fine-tune the formulation variables of VLA. RSM enables the simultaneous exploration of multiple factors and their interactions, allowing for the identification of optimal conditions for the drug delivery system. By employing RSM, researchers can efficiently navigate the complex interplay of formulation parameters, optimizing critical attributes such as dissolution rate and bioavailability [4-6].

VLA is commercially available in various oral solid dosage formulations, including tablets, capsules, and extended-release formulations. These products are marketed under different brand names by pharmaceutical companies worldwide.VLA is a widely used medication for the treatment of epilepsy, bipolar disorder, and migraine headaches.Tablets are the most commonly prescribed oral solid dosage form of VLA. Marketed tablets come in various strengths ranging from 125 mg to 1000 mg. Capsule formulations of VLA provide an alternative to tablets, particularly for patients who may have difficulty swallowing or require specific dose adjustments.Extended-release formulations of VLA are designed to prolong drug release and maintain plasma concentrations over an extended period, thereby reducing dosing frequency and minimizing fluctuations in drug levels.In addition to conventional tablets and capsules, specialty formulations of VLA may be available for specific patient populations, such as pediatric or geriatric patients.

This methodology enhances the precision and efficiency of the formulation process, ultimately contributing to the development of a Fast Dissolving Oral Drug Delivery System (ODDS) for VLA, with the potential to improve patient compliance and therapeutic outcomes in epilepsy management [7]. This study aims to design and optimization of Fast Dissolving Oral Drug Delivery System (ODDS) of VLALoaded as Anti-Epileptic Category Drug with Utilization of DoE, in the optimization DoE plays an important role as scientifically.

2. CHEMICAL VIEW OF VLA

VLA, chemically known as 2-propylpentanoic acid, is a carboxylic acid with the molecular formula $C_8H_{16}O_2$. It is a branched-chain fatty acid and is classified as a short-chain fatty acid due to its relatively small carbon backbone.

Chemical Structure: The chemical structure of valproic acid consists of a straight carbon chain with a branch at the second carbon atom. The chemical structure can be represented as:

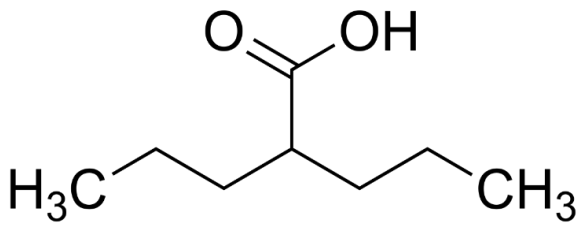

Figure. 01: The chemical stricture representation of valproic acid

The straight chain consists of four carbon atoms, and there is a methyl group (CH_3) attached to the second carbon.

2.1. Functional Groups:

- **Carboxylic Acid Group:** The carboxylic acid functional group is represented by the -COOH moiety, which is responsible for its acidic properties.
- **Methyl Group:** There are two methyl (CH_3) groups in valproic acid, contributing to its branched structure [8-9].

2.2. Mechanism of Action: The exact mechanism of action of valproic acid in the treatment of epilepsy is not fully understood. However, it is believed to involve the modulation of neurotransmitter levels in the brain, such as gamma-aminobutyric acid (GABA), and inhibition of voltage-gated sodium channels.VLA is primarily used as an anticonvulsant and mood-stabilizing drug. It is commonly prescribed for the treatment of epilepsy, bipolar disorder, and migraine headaches [10]. The MOA of VLA shown in the given flow diagram as below followings:

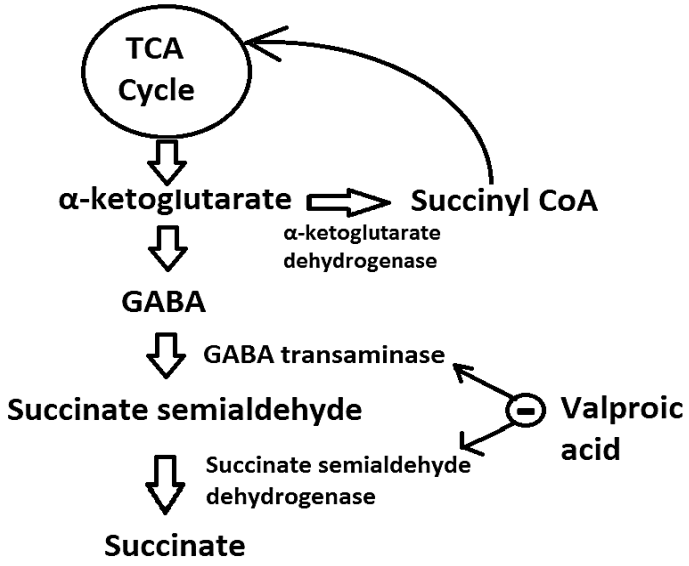

Figure. 02: The schematic representation of MOA of VLA drug

2.3. Physicochemical Properties: The several physicochemical properties mentioned in the given **Table.01** as below followings:

Table. 01: The list of physicochemical properties of Valproic acid

Property	Value	Description
Molecular Formula	$C_8H_{16}O_2$	Chemical formula indicating the types of atoms present.
Molecular Weight	144.21 g/mol	The mass of one mole of the substance.
Physical State	White Crystalline Solid	The form of matter at room temperature.
Melting Point	122-123°C	The temperature at which the solid turns into a liquid.

Boiling Point	Decomposes	The temperature at which the liquid turns into a gas.
Solubility in Water	Sparingly soluble	Indicates the ability of the substance to dissolve in water.
Solubility in Ethanol	Soluble	Indicates the ability of the substance to dissolve in ethanol.

These properties provide insights into the molecular structure, state, and behavior of VLA, contributing to its pharmaceutical applications and therapeutic effects [10-11].

3. METHOD AND MATERIALS

3.1. Materials:VLAand crospovidone were received as a gift sample from Consern Pharma Pvt. Ltd., and Dr.Reddy's Lab, respectively. Microcrystalline cellulose (MCC) and directly compressible mannitol were received from Lobe chemise Pvt. Ltd. Aspartame was procured from Ipza Pharmaceutical. All other chemical used were of analytical reagent grade.

3.2. Methods: The all required steps of the formulation and pre-formulations of fast dissolving ODDS as below followings with these involving methods as follows:

3.3. Drug excipient compatibility studies: Drug compatibility studies using infrared (IR) spectroscopy provide valuable insights into the interactions between the drug (valproic acid) and various excipients or formulation components. Infrared spectroscopy is particularly useful for analyzing molecular vibrations, which can indicate changes in chemical structure or the presence of new bonds [12-13].

Table. 02: The list of typical range of peak of functional group detection by valproic acid

Functional Group	Typical Peak Range (cm^{-1})
O-H stretching (carboxylic acid)	3400-2400 (broad, complex due to hydrogen bonding)
C=O stretching (carboxylic acid)	1700-1650 (strong)
C-H stretching (alkane)	3000-2800 (medium)
C-C stretching	1400-1200 (medium)

3.4. Preparation of Fast- dissolving tablets of Valproic Acid

The preliminary screening was conducted on three different superdisintegrants, namely croscarmellose sodium (CCS), sodium starch glycolate (SSG), and crospovidone. Following the preliminary trials, the formulations were designed based on the 3^2 full factorial designs (FFD), enabling the simultaneous evaluation of the two formulation variables and their interaction. Fast dissolving tablets of VLAwere prepared using the direct compression method, following the

formulae provided in **Table 03.** All ingredients were weighed and passed through a #60 mesh before being mixed in a geometrical order. Lubricants and glidant were then added and mixed for an additional 5 minutes. The resulting blend was evaluated for pre-compression parameters and subsequently compressed into tablets of 200 mg using 7 mm flat round punches on a double compression tablet machine. For preliminary trials, a batch of 60 tablets was formulated for each designed formulation, and for data validation, 200 tablets of each formulation batch were formulated. The formulation of all batches (FFD layout) and the composition of factorial design (FD) batches can be found in **Tables 04 and 05**, respectively [14-16].

4. EXPERIMENTAL STUDIES:FFD

A 3^2 FD was implemented to optimize the formulation variables. In this design, two factors were assessed at three different levels. The experimental trials were conducted for all nine possible combinations, along with two additional check point design formulations (P1 and P2) to validate the generated mathematical model. The independent variables chosen were the amount of disintegrant and the diluent respectively. The dependent variables included disintegration time, wetting time, and the percentage of drug released [17-19]. The experimental design, response surface modeling, and statistical evaluation were performed using the ***trial version of Stat Ease 8.0.7.1 software***.

Table. 03: The 3^2factorial with their batch code factorial design layout

Formulation code	N1	N2
RP1	+1	-1
RP2	0	+1
RP3	-1	-1
RP4	+1	0
RP5	0	-1
RP6	-1	0
RP7	+1	-1
RP8	+1	+1
RP9	-1	+1

The list of several code values of formulation discussed in the given **Table. 04** as below followings:

Table. 04: The code value of diluents and superdisintegrants

Code value	Quantity of superdisintegrant (mg) R_1	Quantity of diluents (mg) R_2
+1	5	50
0	10	75
-1	14	100

The list of ingredients in the formulation in the **Table. 05** as below discussion. Due to the optimizing and variation purpose the crospovidone is not used in the RP10 formulation in the below table.

Table. 05: The list of composition of fast dissolving tablets of VLA using 3^2 factorial design

Ingredients (mg)	RP1	RP2	RP3	RP4	FRP 5	RP6	RP7	RP8	RP9	RP 10	P1	P2
Valproic acid	8	8	8	8	8	8	8	8	8	8	8	8
Crospovidone	5	5	5	10	10	10	15	15	15	- -	8	12
MCC	50	65	85	50	65	85	50	65	85	50	30	80
Aspartame	4	4	4	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
D- mannitol	200	200	200	200	200	200	200	200	200	200	200	200

RP10: The control formulation does not include a superdisintegrant. P1 and P2 are additional design check point formulations used to validate the generated mathematical model. MCC refers to microcrystalline cellulose.

5. THE EVALUATION OF BLEND FOR PRE- COMPRESSION PARAMETERS

The pre-compression parameters of the formulation blend were assessed using the official procedure, which included the evaluation of bulk density, tapped density, Carr's index (CI), Hausner's ratio (HR), and angle of repose (θ). The evaluation of post- compression parameters of Fast- dispersible tablets of VLAas follows:

5.1. Weight Variation Test: Weight fluctuation was assessed by randomly selecting 20 tablets from each batch and individually weighing them using a precise electronic balance. The weights of each tablet were then compared to the average weight to determine the extent of weight variation.

5.2. Tablet Hardness: The hardness of the tablets in each formulation was assessed by employing the Monsanto hardness tester. Three readings were taken and an average was calculated.

5.3. Friability Test: Tablet friability testing was conducted in accordance with the specifications outlined in the USP. A batch of tablets weighing 6.6 g was introduced into the Roch friability test apparatus, which underwent 100 revolutions. Subsequently, the tablets were reweighed to calculate the percentage of friability.

5.4. Wetting duration: The tablet was positioned inside a petri dish with an internal diameter of 7.6 cm, which was filled with 10 ml of water at ambient temperature. The duration required for the tablet to become completely wet was documented. In order to assess the consistency of the results, the measurements were conducted five times, and the average value was computed.

5.5. *In-vitro* Disintegration Time: The USP tablet disintegration test apparatus was utilized to determine the in vitro disintegration time for all formulations.

5.6. Drug Content: Five tablets were chosen at random and their average weight was determined to estimate the drug content. The tablets were crushed in a mortar and a precise weight equivalent to 5 mg of the drug was measured. Subsequently, the sample was transferred to a 100 ml volumetric flask and dissolved in methanol. The solution was periodically shaken, and 1 ml of it was withdrawn and diluted to 10 ml using methanol. The drug content was then determined at 232 nm using a double beam ultraviolet (UV) visible spectrophotometer.

5.7. *In-vitro* Drug Release Study: The USP type II paddle apparatus was used to perform the in vitro dissolution test. The test solution consisted of 900 ml of phosphate buffer 6.8 with using 1.0g of potassium dihydrogen phosphate and 2.0g of di-potassium hydrogen phosphate and 8.5 gm of NaCl in 900ml water) and make up t 1000ml at 37°C, with a rotation speed of 50 rpm. At various time intervals from 1 to 30 minutes, 5 ml aliquots of samples were taken and an equal volume of fresh phosphate buffer was added. The samples were then filtered, suitably diluted,

and analyzed at 232 nm using a double beam UV/visible spectrophotometer to calculate the drug content.

To choose a diluent that is compatible with the analyte and the analytical method being used. Common diluents include distilled water, buffer solutions, or solvent blends.Determine the desired dilution factor based on the concentration of the analyte in the original sample and the target concentration needed for analysis. The dilution factor is calculated as the ratio of the final volume to the initial volume of the sample.

5.8.Release Kinetics Study: Different kinetic models, such as zero-order, first-order, Higuchi's, Hixson Crowell, and Korsmeyer-Peppas models, were employed to analyze the release kinetics of the in vitro data [20-25].

5.9. Regression Analysis: VLAFast dissolving tablets were manufactured through the direct compression technique. The formulation was optimized using a 3^2 FFD, incorporating crospovidone as a superdisintegrant and MCC as a diluent. Additionally, directly compressible mannitol was included to improve the mouth feel of the tablets. Based on initial experiments, a total of nine formulations were developed, including a control group without crospovidone, as well as two additional design check point formulations. A general model equation was generated to accurately represent the collected data.

$$\mathbf{Y = k_0 + k_1A_1 + k_2X_2 + k_{12}A_1A_2 + k_{11}A_1^2 + k_{22}A} \quad \textbf{[Equation…01]}$$

In this study, the dependent variable γ is influenced by two independent variables: A_1, which represents the amount of crospovidone, and A_2, which represents the amount of MCC. The coefficient k_0 represents the average response of the nine runs, while k_1 and k_2 are estimated coefficients for A_1 and A_2 respectively. The main effect of A_1 and A_2 refers to the average effect of changing one factor at a time from its low to high value [26-27]. On the other hand, the interaction term A_1A_2 shows the change in response when both factors are simultaneously changed. Additionally, polynomial terms (A_1^2) are included to investigate non-linearity.

6. RESULTS AND DISCUSSION

The oral bioavailability of a drug, such as VLA, can be significantly different from its parenteral bioavailability, which refers to the fraction of the administered dose that reaches systemic circulation following non-oral routes of administration, such as intravenous or intramuscular injection. In the case of VLA, oral bioavailability tends to be high but variable due to factors like incomplete absorption, first-pass metabolism, and individual patient characteristics. On the other hand, parenteral administration bypasses the gastrointestinal tract and first-pass metabolism, resulting in higher and more predictable bioavailability compared to the oral route. However, the rapid onset of

action and potential for dose adjustments with parenteral administration must be balanced against the convenience and ease of oral dosing in long-term therapy.

6.1. Effect of Type and Concentration of Disintegrant

Initially, tablets containing different concentrations of superdisintegrants were tested to determine their disintegration time. It was observed that as the concentration of SSG increased, the disintegration time also increased. This was attributed to the swelling mechanism of SSG, which causes the tablets to swell upon contact with water. The swelling process may lead to the formation of a gel-like substance, which can block the pores in the tablet and delay the penetration of water, thus prolonging the disintegration time. Therefore, it can be concluded that higher concentrations of SSG have a negative impact on tablet disintegration.

On the other hand, when the concentration of CCS was increased, a significant variation in disintegration time was observed. The different tablets containing crosspovidone, however, showed no significant change in disintegration time when the concentration of crosspovidone was increased from 2% to 6%. This suggests that crosspovidone has a positive effect on disintegration time, possibly due to its higher capillary action and minimal tendency to form a viscous gel. The based on the disintegration results, the superdisintegrants can be ranked according to their ability to swell in water, with crosspovidone, CCS, and SSG in that order. To considering the findings from the preliminary screening studies, the batch containing crosspovidone exhibited the fastest disintegration. Therefore, crosspovidone was selected for the formulation of fast dissolving tablets of VLA.

6.2. Effect of Diluents on Disintegration Time: When MCC is mixed with water-soluble mannitol, it exhibits a shorter disintegration time compared to other diluents. This can be attributed to the excellent water solubility of mannitol, which creates pores within the tablet matrix. Subsequently, capillary action facilitates the penetration of the surrounding fluid into the tablet matrix, resulting in rapid disintegration [28].

6.3. Effect of Tablet Hardness on Disintegration Time: The data indicates that the hardness of the tablet does not have a significant impact on its disintegration time. However, when the concentration of crospovidone increases, the disintegration time decreases. Conversely, an increase in the concentration of MCC leads to an increase in the disintegration time. This can be attributed to the fact that MCC has excellent compaction properties. Therefore, the tablet containing 30% MCC and 6% crospovidone (RP8) exhibits a maximum hardness of 3.58 kg/cm^2 and a minimum disintegration

time of 24.3 s. This may be due to the porous particle morphology of crospovidone, which facilitates rapid water absorption through capillary action, thereby aiding in faster disintegration.

6.4. Drug Excipient Compatibility Studies: FT-IR analysis of both the pure drug and the drug combined with crospovidone revealed no evidence of any interaction between the drug and the superdisintegrant used **Fig.03**as below followings:

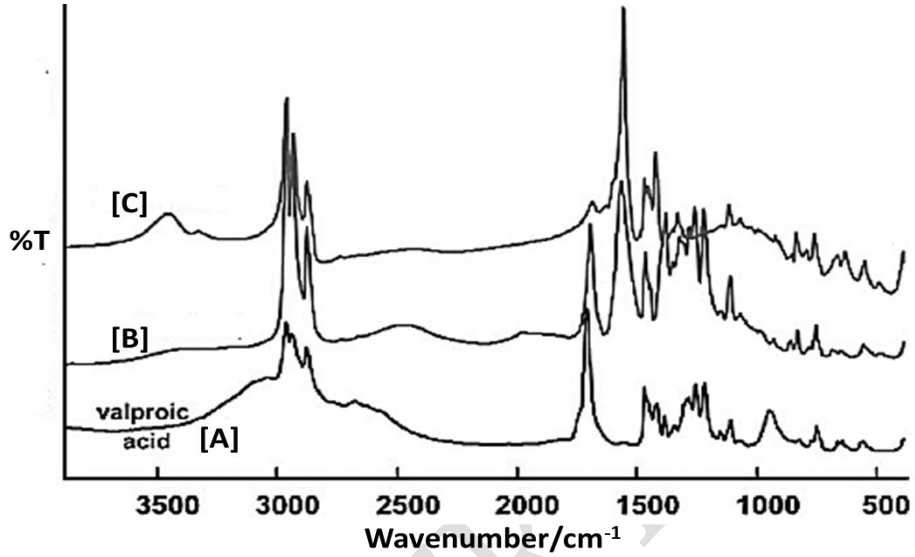

Figure. 03: The FT-IR representation of [A]. VLA, [B]. Crospovidone and [C]. The physical mixture of VLA and crospovidone

The pure VLA exhibited distinct peaks corresponding to C=O stretching vibration at 1694.7 cm^{-1}, aromatic C-H stretching at 3075.4 cm^{-1}, C- C stretching at 1493.5 cm^{-1}, C- N stretching at 1100- 1200 cm^{-1}, C-H bending at 600- 800 cm^{-1}, and CH_3bending at 1371 cm^{-1}. Interestingly, the spectra of the drug combined with crospovidone displayed all the characteristic peaks of the drug, indicating that the drug is compatible with crospovidone [29-32].

6.5. Pre- compression Parameters of Powder Blend: The different powder blends were assessed for pre-compression characteristics, including the angle of repose, bulk density, tapped density, and Carr's consolidation index (CI), in accordance with official requirements. The bulk density ranged from 0.388 to 0.349 g/cm^3, while the tapped density ranged from 0.483 to 0.377 g/cm^3. Carr's index (CI) varied between 17.09% and 11.49%, and the Hausner ratio (HR) ranged from 2.104 to 1.111. The angle of repose varied between 28.37° and 23.28°. All these parameters fell within acceptable limits, indicating satisfactory to excellent flow properties.

6.6. Post- compression Parameters of VLAFast Dissolving Tablets: The post-compression parameters of the tablets were assessed, including tablet porosity, weight variation, uniformity of

drug content, hardness, friability, in vitro disintegration time, in-vitro dissolution studies, wetting time, and water absorption ratio. The physico-chemical evaluation of all batches of VLAfast dissolving tablets is presented in **Table 06.** The weight variation of the prepared tablets ranged from 180 mg to 220 mg, which falls within the acceptable limit as per IP specifications (±7.6%) [33-36].

Table. 06: The list of evaluation of factorial design formulations ofVLAtablets

Formulation code	Hardness (kg/cm^2)	Friability (%)	Disintegration time (s)	Wetting time (s)	Drug content (%)
RP1	2.99±0.02	0.5±0.06	134.5±1.6	32±3.09	99.2±0.4
RP2	2.96±0.06	0.63±0.02	182±1.33	35±2.1	101.3±0.19
RP3	2.83±0.03	0.44±0.03	191±1.44	33±2.09	98.2±0.22
RP4	260±0.04	0.51±0.06	73±1.22	28±1.01	96.4±0.29
RP5	2.49±0.04	0.66±0.04	78±1.23	29±1.12	99.2±0.29
RP6	2.89±0.08	0.47±0.06	110±1.44	25±1.01	98.67±0.24
RP7	2.69±0.03	0.43±0.04	54±1.34	21±1.11	99.63±0.19
RP8	3.61±0.02	0.42±0.06	23.4±1.2	18±1.13	102.4±0.13
RP9	2.89±0.17	0.49±0.04	51.7±1.2	19±1.13	95.42±0.14
RP10	3.70±0.14	0.51±0.03	198±1.33	38±2.99	99.5±0.12
P1	2.94±0.09	0.52±0.04	76±1.23	26±1.18	99.5±0.18
P2	2.52±0.08	0.55±0.03	61.1±1.59	27±1.19	101.1±0.17

The drug content ranged from 103.2% to 97.44%, while the hardness of the tablets ranged from 2.43 kg/cm^2 to 2.99 kg/cm^2 respectively. The friability was below 1% (0.5% to 0.51%), and the thickness ranged from 3.40 mm to 4.7 mm.

6.7. *In-vitro* Disintegration Time: The in vitro disintegration time ranged from 25.6 to 190 seconds. Among all the formulations, Formulation RP8, which contained 6% crospovidone and 30% MCC, exhibited the shortest disintegration time. The wetting time, which indicates the ability of the disintegrant to swell in the presence of water, closely matched the disintegration time and ranged from 19 to 38 seconds with RP8 having a wetting time of 19 seconds. A shorter wetting time suggests a highly porous tablet matrix. Additionally, increasing the concentration of crospovidone decreased the disintegration time, while increasing the concentration of MCC increased the disintegration time. This delay in disintegration time may be attributed to strong binding between molecules, which hinders water uptake and prevents the superdisintegrant from swelling adequately. The decreased disintegration time of the RP8 formulation can be attributed to increased porosity, possibly due to the addition of a water-soluble filler that affects the internal structure of the tablet matrix. It was also observed that wetting time, disintegration time, and porosity were positively correlated [37].

6.8. In vitro Drug Release Study: In vitro dissolution testing in phosphate buffer pH 6.8 reveals that more than 80% of the drug gets released within 22 min for all the formulations with RP8 showing maximum release of 99% **Fig. 04.** Further formulation RP8 was compared with marketed formulation for its *in-vitro* release profile and it was found to be comparable to the marketed formulation of VLA **Fig. 05** respectively**.** This result correlates well with disintegration time and wetting time. Addition of water soluble filler mannitol greatly affected the inner structure of the tablet with subsequent impact on the wetting time, disintegration time and drug dissolution profile.

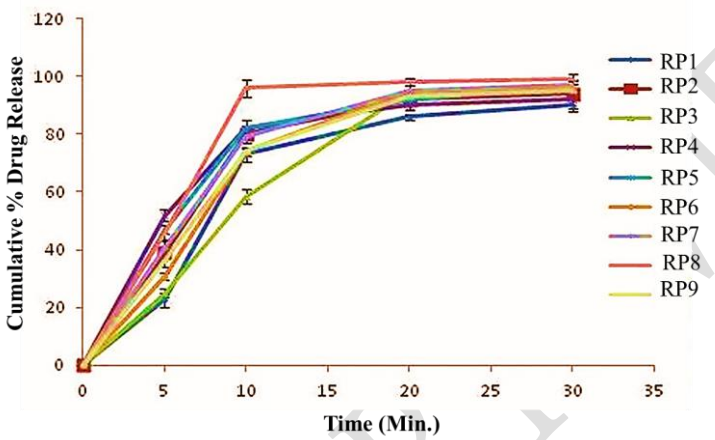

Figure. 04: The mean ± SD (n = 3) represents the comparative in vitro drug release profile of VLA tablet formulation batches RP1-RP9 using graphical representation in the *In-vitro* release study

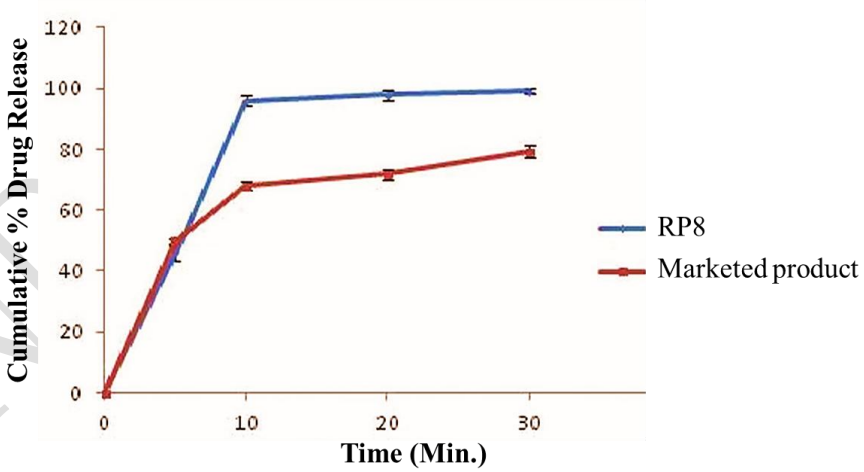

Figure. 05: The average release of drugs in a laboratory setting was compared between the optimized formulation (FRP8) and the commercially available formulation of VLA. The data is presented as the mean value plus or minus the standard deviation, with a sample size of three

6.10. Release Kinetic Study: The drug release of VLAwas analyzed using various models, including the Korsmeyer-Peppas model, Higuchi's model, zero order kinetics, and first order kinetics. The

results, presented in **Table. 07**, revealed that the first order release kinetics provided the best fit for VLAFast dissolving tablets. The correlation coefficient (r^2) was used to determine the suitability of each model, and it was found that all developed formulations followed the first order release model. The drug release mechanism was identified as non-Fickian diffusion, with an "n" value less than 1, indicating that the release is influenced by both swelling and diffusion mechanisms. [35-38]

Table. 07: The regression coefficient (r^2) values of drug release data obtained from various kinetic models and 'n' value (diffusional exponent) according to Korsmeyer-Peppas mode

Formulation code	Zero order	First order	Higuchi kinetics	Korsemeyer-Peppas equation	
	r^2	r^2	r^2	r^2	N
RP1	0.889	0.819	0.792	0.788	0.877
RP2	0.749	0.917	0.822	0.813	0.667
RP3	0.855	0.801	0.904	0.919	0.667
RP4	0.679	0.979	0.865	0.826	0.456
RP5	0.801	0.853	0.796	0.839	0.545
RP6	0.742	0.944	0.927	0.842	0.624
RP7	0.740	0.864	0.916	0.849	0.712
RP8	0.509	0.965	0.508	0.701	0.822
RP9	0.759	0.846	0.549	0.863	0.644

6.11. Regression Analysis: The mathematical relationship derived from the analysis of multiple linear regression for the variables under study can be represented by the following equations as follows:

$$\textbf{Disintegration time} = +78.64 - 64.8A + 16.23A_2 - 15.53A_2 - 16.22A_1A_2 + 24.22A_1^2 + 6.55A_2^2$$

[Equation. 02]

$$\textbf{Wetting time} = 27.8789 - 6.669A_1 + 1.1695A_2 - 3.12A_1A_2 - 1.340A_1^2 + 0.93A_2^2$$

[Equation. 03]

$$\textbf{DR (\%)} = +97.03 + 1.89A_1 + 1.43A_2 - 2.13A_1A_2 + 0.54A_1^2 - 2.05A_2^2$$

[Equation. 04]

All polynomial equations were determined to be statistically significant ($P < 0.01$) through the use of analysis of variance (ANOVA). **Table.08** provides a summary of the ANOVA results for all three responses.

Model	Disintegration Time (Dt Time)		Wetting Time		DR %	
	F	P Value	F	P Value	F	P value
Model	18.86	0.0167	22.03	0.0162	12.99	0.0348
M1	89.34	0.0037	95.76	0.0025	22.98	0.189

M2	4.99	0.1226	2.80	0.1891	12.42	0.0434
M1M2	4.02	0.1914	6.78	0.0878	18.14	0.0257
$M1^2$	4.89	0.1549	1.29	0.3528	0.66	0.0578
$M2^2$	0.23	0.6813	0.48	0.5423	9.98	0.0564

Table. 08: The list of ANOVA for all three generated responses

The **Table. 09**presents the results of multiple linear regression analysis, which reveal that the amount of crospovidone (M1) has a negative effect on all responses, namely disintegration time, wetting time, and % drug release. Conversely, the concentration of MCC (M2) has a positive effect. This means that as the amount of crospovidone increases, both the wetting time and disintegration time decrease, while there is an increase in % DR [39]. On the other hand, increasing the amount of MCC leads to an increase in both the wetting time and disintegration time.

Coefficients	K_0	K_1	K_2	K_{12}	K_{11}	K_{22}	R^2
Disintegration time (Dt)	78.73	- 64.89	16.23	−15.53	24.21	6.59	0.9809
Wetting time	27.99	−7.78	−1.13	−3.00	−1.34	−0.84	0.9623
DR %	97.03	2.89	1.43	−3.00	0.54	−2.04	0.9624

Table 09: Summary of regression analysis results

To achieve rapid disintegration of the tablets, it is recommended to select a high level of crospovidone and a medium level of MCC. The relationship between the dependent and independent variables was further elucidated through surface response plots. These plots, depicted in **Fig.06**, demonstrate that both M1 and M2 have an impact on the disintegration time, wetting time, and % DR respectively.

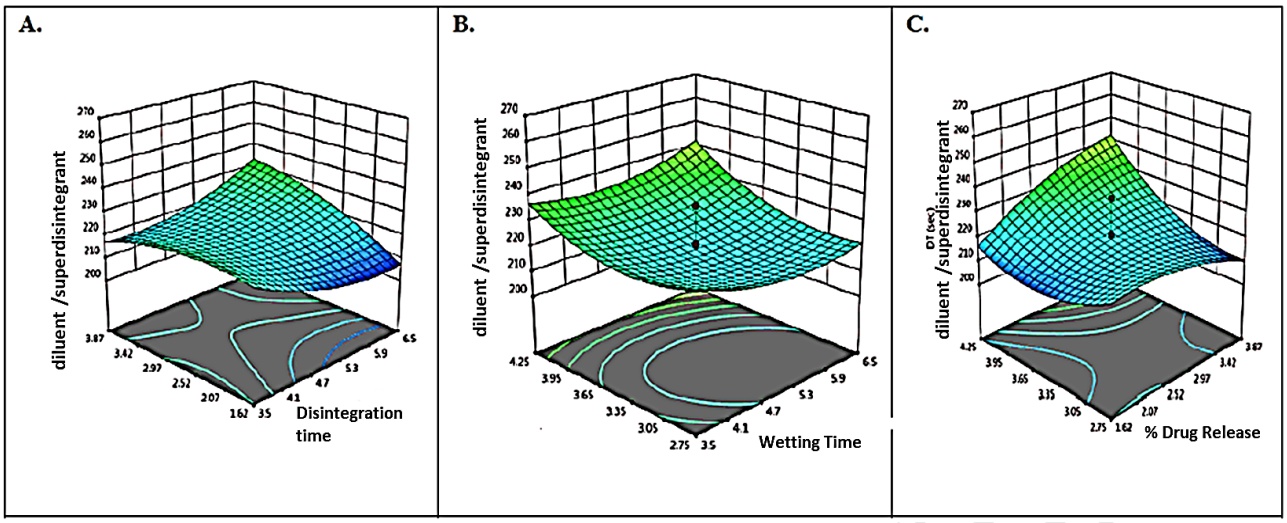

Figure 06: The RSM plot showing the influence of diluent microcrystalline cellulose and superdisintegrant (A) disintegration time, (B) wetting time, (C) % DR

6.12. Comparison between Conventional Marketed Product and Selected Formulation: The **Table. 10** presents the findings of a comparative study between a commercially available Valproic acid tablet and the specifically chosen formulation RP8 is the optimized formulation.

Table. 10: The comparison between one marketed product and selected formulation (RP8)

Formulation code	Hardness (kg/cm^2)	Wetting time (s)	Friability (%)	Content uniformity	Disintegration time (s)
Marketed product	4.04±0.56	156±2.36	0.664±0.19	98.78±0.19	304±1.52
RP8	3.16±0.02	18±1.13	0.42±0.06	102.4±0.13	23.4±1.2

The results indicate that formulation RP8 exhibits superior efficacy when compared to the conventional VLA formulation [38-42].

7. CONCLUSION

This study successfully employed Design of Experiments (DoE) to design and optimize a fast-dissolving oral drug delivery system (ODDS) for valproic acid, an anti-epileptic drug.DoE analysis revealed significant interactions between superdisintegrants, diluents, and lubricants, influencing the dissolution rate of valproic acid ODDS.The optimized formulation, containing sodium starch glycolate, lactose, and minimal magnesium stearate, achieved a rapid dissolution rate exceeding 85% within 10 minutes.This formulation demonstrated significantly faster drug release compared to conventional tablets, potentially enhancing patient compliance and therapeutic efficacy.This study showcases the effectiveness of DoE in optimizing pharmaceutical formulations for improved

performance. By systematically evaluating the impact of various factors, DoE facilitates the development of ODDS with desired drug release profiles.Further investigations could explore the in-vivo performance of the optimized ODDS in animal models or clinical trials to confirm its efficacy and safety in humans.Additional studies could optimize other aspects of the formulation, such as taste, stability, and scalability for mass production.

The findings of this study have also demonstrated that RSM can effectively be utilized to optimize and create VLAFast dissolving tablets. In conclusion, it can be inferred that by conducting a limited number of experiments, a well-designed formulation with the desired drug release and disintegration time can be achieved using suitable statistical experimental design and optimization techniques.

REFERENCES

1. Celebioglu, A., & Uyar, T. (2019). Fast dissolving oral drug delivery system based on electrospunnanofibrous webs of cyclodextrin/ibuprofen inclusion complex nanofibers. *Molecular pharmaceutics*, *16*(10), 4387-4398.
2. Bhalla, D., Godet, B., Druet-Cabanac, M., & Preux, P. M. (2011). Etiologies of epilepsy: a comprehensive review. *Expert review of neurotherapeutics*, *11*(6), 861-876.
3. Činčárová, L., Zdráhal, Z., & Fajkus, J. (2013). New perspectives of valproic acid in clinical practice. *Expert opinion on investigational drugs*, *22*(12), 1535-1547.
4. Pal, R., Pandey, P., Rizwan, M., Koli, M., Thakur, S. K., Malakar, R. K., ... & Chawra, H. S. (2023). The Utilization of Response Surface Methodology (RSM) In the Optimization of Diclofenac Sodium (DS) Liposomes Formulate through the Thin Film Hydration (TFH) Technique with Involving Computational Method. *Journal of Advances in Medicine and Medical Research*, *35*(22), 287-300.
5. Bhadani, K., Asbjörnsson, G., Hofling, K., Hulthén, E., &Evertsson, M. (2024). Application of design of experiments (DoE) in evaluating crushing-screening performance for aggregates production. Minerals Engineering, 209, 108616.
6. Thakur, S. K., Pal, R., Jha, D., Dutta, P., Pandey, P., Tripathi, B. D., ...& Singh, R. P. (2023). The Application of Response Surface Methodology (RSM) In the Computational Optimization of Sustained Release (SR) For Phenothiazine Derivative Matrix Tablet. *Journal of Pharmaceutical Research International*, *35*(35), 13-27.
7. Kushwaha, V., Akhtar, J., Usmani, S., & Singh, S. P. (2015). A review on fast dissolving formulation technologies. *World Journal of Pharmacy and Pharmaceutical Sciences*, *4*(7), 574-85.
8. Bialer, M., &Yagen, B. (2007). Valproic acid: second generation. *Neurotherapeutics*, *4*, 130-137.
9. Mishra, M. K., Kukal, S., Paul, P. R., Bora, S., Singh, A., Kukreti, S., ... & Kukreti, R. (2021). Insights into structural modifications of valproic acid and their pharmacological profile. *Molecules*, *27*(1), 104.
10. Wiltse, J. (2005). Mode of action: inhibition of histone deacetylase, altering WNT-dependent gene expression, and regulation of beta-catenin—developmental effects of valproic acid. *Critical reviews in toxicology*, *35*(8-9), 727-738.
11. Mondal, S., Dhondge, S. S., Paliwal, L. J., Tangde, V. M., &Jengathe, S. P. (2015). Physicochemical properties of an anticonvulsant drug sodium valproate in aqueous and in mixed aqueous solutions at different temperatures. *The Journal of Chemical Thermodynamics*, *90*, 147-157.
12. Odi, R., Bibi, D., Wager, T., & Bialer, M. (2020). A perspective on the physicochemical and biopharmaceutic properties of marketed antiseizure drugs—From phenobarbital to cenobamate and beyond. *Epilepsia*, *61*(8), 1543-1552.
13. Khajir, S., Shayanfar, A., Monajjemzadeh, F., &Jouyban, A. (2021). Crystal engineering of valproic acid and carbamazepine to improve hygroscopicity and dissolution profile. *Drug Development and Industrial Pharmacy*, *47*(10), 1674-1679.
14. Muñoz, H., Castan, H., Clares, B., & Ruiz, M. A. (2014). Obtaining fast dissolving disintegrating tablets with different doses of melatonin. *International Journal of Pharmaceutics*, *467*(1-2), 84-89.

15. VARSHNEY, A. P., & AKHTAR, S. (2020). Fast dissolving tablet: An Opportunity for treatment of Epilepsy. *International Journal of Pharmaceutical Research (09752366), 12*(2).

16. Pal, R., Pandey, P., Jha, D., Dutta, P., Sahoo, S., Gupta, R., ... & Chawra, H. S. (2023). The Utilization of 32Full Factorial Design (FFD) for Optimization of Lincomycin Hydrochloride (LNH) Loaded Nanogel Involving; Design of Experiments (DoE) an Advanced Approach. *Advances in Research*, *24*(6), 272-281.

17. Myers, R. H., Montgomery, D. C., & Anderson-Cook, C. M. (2016). *Response surface methodology: process and product optimization using designed experiments*. John Wiley & Sons.

18. Bezerra, M. A., Santelli, R. E., Oliveira, E. P., Villar, L. S., &Escaleira, L. A. (2008). Response surface methodology (RSM) as a tool for optimization in analytical chemistry. *Talanta*, *76*(5), 965-977.

19. Pal, R., Pandey, P., Nogai, L., Anand, A., Suthar, P., SahdevKeskar, M., & Kumar, V. (2023). The future perspectives and novel approach on gastro retentive drug delivery system (GRDDS) with currrent state. *Journal of Population Therapeutics and Clinical Pharmacology*, *30*(17), 594-613.

20. Albert, J. (2017). *Formulation and Evaluation of Immediate Release Tablets of Metoclopramide Hydrochloride* (Doctoral dissertation, Cherraan's College of Pharmacy, Coimbatore).

21. Rajesh, R. (2018). *Formulation Development and Invitro Evaluation of Mouth Dissolving Tablets of Lercanidipine Hydrochloride by Direct Compression Method: An Approach to Improving Oral Bioavailibility* (Doctoral dissertation, JKK Nattraja College of Pharmacy, Komarapalayam).

22. Pal, Rahul & Pandey, Prachi & Waheed, Saman& Thakur, Shiva Kant & Sharma, Vidhi& Chanana, Arsh& Singh, Ravindra. (2023). TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS) AS A NOVEL TOOL FOR DRUG DELIVERY. 12. 688-711. 10.20959/wjpr20232-26997.

23. Pawar, A. Y., Patil, S. H., Jadhav, K. R., &Baviskar, S. R. (2014). Formulation and evaluation of matrix tablet of venlafaxine HCl by using directly compressible co-processed excipient. *International Journal of Pharmacy and Pharmaceutical Sciences*, *6*, 504-11.

24. Pal, R., Pandey, P., & Nogai, L. (2023). The Advanced Approach in The Development of Targeted Drug Delivery (TDD) With Their Bio-Medical Applications: A Descriptive Review. *International Neurourology Journal*, *27*(4), 40-58.

25. Brumett, R., Danai, L., Coffman, A., Radwan, Y., Teter, M., Hayth, H., ...&Khisamutdinov, E. F. (2024). Design and Characterization of Compact, Programmable, MultistrandedNonimmunostimulatory Nucleic Acid Nanoparticles Suitable for Biomedical Applications. Biochemistry.

26. Jain, A., & Jain, S. K. (2016). In vitro release kinetics model fitting of liposomes: An insight. *Chemistry and physics of lipids*, *201*, 28-40.

27. Pandey, P., Pal, R., Thakur, S. K., Sharma, V., Chanana, A., & Singh, R. (2022). FUTURE ASPECTS & MODIFICATION IN CARBON-NANOPARTICLES IN TREATMENT AND DIAGNOSIS.

28. Molinuevo, J. L., & Arranz, F. J. (2012). Impact of transdermal drug delivery on treatment adherence in patients with Alzheimer's disease. *Expert review of neurotherapeutics*, *12*(1), 31-37.

29. Berardi, A., Bisharat, L., Blaibleh, A., Pavoni, L., & Cespi, M. (2018). A simple and inexpensive image analysis technique to study the effect of disintegrants concentration and diluents type on disintegration. *Journal of Pharmaceutical Sciences*, *107*(10), 2643-2652.

30. Pal, Rahul & Pandey, Prachi & Koli, Manju & Rizwan, Mohammad & Saxena, Archita. (2023). Chitosan: As Highly Potential Biopolymer Obtainable In Several Advance Drug Delivery Systems Including Biomedical Applications "Research Paper", European Chemical Bulletin (ECB). European Chemical Bulletin. 12. 322-344. 10.48047/ecb/2023.12.si10.0036.

31. Yamamoto, Y., Fujii, M., Watanabe, K. I., Tsukamoto, M., Shibata, Y., Kondoh, M., & Watanabe, Y. (2009). Effect of powder characteristics on oral tablet disintegration. *International Journal of Pharmaceutics*, *365*(1-2), 116-120.

32. Pal, R., Pandey, P., Rai, B., Koli, M., Chakrabarti, M., Thakur, P., ... & Saxena, A. Chitosan: as highly potential biopolymer obtainable in several advance drug delivery systems including biomedical applications. *Environmental science*, *3*(4).

33. Patel, P., Ahir, K., Patel, V., Manani, L., & Patel, C. (2015). Drug-Excipient compatibility studies: First step for dosage form development. *The Pharma Innovation*, *4*(5, Part A), 14.

34. Pal, R., Pandey, P., Anand, A., Saxena, A., Thakur, S. K., Malakar, R. K., & Kumar, V. (2023). The Pharmaceutical Polymer's; A current status in drug delivery: A Comprehensive Review. *Journal of Survey in Fisheries Sciences*, 3682-3692.

35. Van Snick, B., Grymonpré, W., Dhondt, J., Pandelaere, K., Di Pretoro, G., Remon, J. P., ... &Vanhoorne, V. (2018). Impact of blend properties on die filling during tableting. *International Journal of Pharmaceutics*, *549*(1-2), 476-488.

36. Pal, R., Pandey, P., Maurya, V. K., Saxena, A., Rizwan, M., Koli, M., ...& Pinki, K. OPTIMIZATION AND FORMULATION OF DOXORUBICIN (DOX) LOADED LIPOSOME WELL-USED IN CHEMOTHERAPY INVOLVING QUALITY BY DESIGN (QBD): A TRANSITORY RESEARCH.

37. Pal, R., Pandey, P., Thakur, S., Chanana, A., & Singh, R. P. (2022). BIODEGRADABLE POLYMER'S ENHANCING DRUG DELIVERY ACTIVITY IN DIFFERENT NOVEL DRUG DELIVERY SYSTEM.

38. Fujii, A., Yasui-Furukori, N., Nakagami, T., Niioka, T., Saito, M., Sato, Y., & Kaneko, S. (2009). Comparative in vivo bioequivalence and in vitro dissolution of two valproic acid sustained-release formulations. *Drug design, development and therapy*, 139-144.

39. Pal, Rahul & Pandey, Prachi & Thakur, Shiva Kant & Chanana, Arsh& Singh, Ravinder. (2023). DRUG DESIGN AND DEVELOPMENT INVOLVING NOVEL SOFTWARE IN PHARMACEUTICALS. Asian Journal of Pharmaceutical Analysis. 10. 90-106. 10.36673/AJPAMC.2022.v10.i03.A12.

40. Ciurba, A., Todoran, N., Tăurean, A., Antonoaea, P., Hancu, G., Moisei, A., & Sipos, E. (2014). Kinetic analysis of in vitro drug release from valproic acid and sodium valproate suppositories. *Farmacia*, *62*(6), 1143-1156.

41. Drisaldi, A., Weeda, E., Neyens, R., Orvin, N., Bonilha, L., Campbell, Z., & Bohm, N. (2019). Accuracy of valproic acid concentration correction based on serum albumin. *Neurocritical care*, *30*, 301-306.

42. Pandey, P., Pal, R., Bharath, K. S., Akilandeshwari, A., Koli, M., Rizwan, M., ... & Chawra, H. S. (2023). Design of Experiments (DoE) manipulation in the formulation and optimization of a traditional Ayurvedic medicine derived from dried extract of Senegalia catechu enhanced through statistical analysis. *Journal of Pharmacognosy and Phytochemistry*, *12*(6), 159-169.