RESEARCH ARTICLE

Formulation Development and Evaluation of Brivaracetam Extended-Release Tablets by QbD Approach

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ABSTRACT

This research article outlines a systematic and science-based approach to formulate extended-release tablets of brivaracetam (BRV) by means of quality by design (QbD) method. BRV, a potent antiepileptic drug, faces challenges due to its short half-life, necessitating twice-daily dosing and impacting patient adherence. The study focuses on addressing these challenges through the development of extended-release tablets, aiming for once-daily dosing to enhance patient compliance and adherence. QbD is a systematic approach to developing pharmaceuticals, focusing on proactive risk management and quality assurance. It is supported and recommended by regulatory bodies. QbD, seeks to enhance processes and guarantee consistent product quality by engaging in activities such as establishing target profiles and identifying crucial qualities. Feasibility trials involve the identification of optimal polymers and concentrations following USP regulations. Materials, including Vivapur 200, HPMC K4 M, Blanose 7H4XF, HPMC K-200, magnesium stearate, SYLOID 244 FPFP, and brivaracetam, are carefully selected. The formulation process includes precise weighing, blending, tablet compression, and quality control tests. Dissolution testing under simulated physiological conditions assesses drug release, with UV spectrophotometry quantifying brivaracetam release. Evaluation of pre-compression parameters ensures a thorough understanding of powder blend characteristics. The study further presents the results and discussion on physical parameters and dissolution studies of feasibility trial formulations. In conclusion, the research establishes a foundation for the formulation development of extended-release BRV tablets, emphasizing the importance of the QbD approach in achieving optimal drug release profiles. The identified formulation (BRERT-17) is highlighted as the most promising, paving the way for future advancements in epilepsy management with improved patient compliance.

Keywords: Brivaracetam, Extended-release tablets, QbD, Formulation development, Critical material attributes, Epilepsy management, Drug release.

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INTRODUCTION

Epilepsy, a widespread neurological disorder, leads to recurrent seizures with diverse symptoms affecting physical, cognitive, and emotional aspects.[1,2] Antiepileptic drugs (AEDs) are the base of treatment, with concerns about adverse effects.[3,4] Brivaracetam (BRV or Briviact), a newer AED, targets partial-onset seizures in adults. Its structural resemblance to levetiracetam enhances potency and quickens onset.[5] Operating through synaptic vesicle glycoprotein 2A (SV2A) binding, BRV modulates neurotransmitter release, reducing abnormal neuronal firing. Approved for partial-onset seizures, BRV offers advantages like high potency and good tolerability. Ongoing research explores its potential in other conditions, but long-term safety and efficacy warrant further investigation.[6]

Brivaracetam (BRV), a promising antiepileptic drug (AED) for partial-onset seizures in adults, faces challenges due to its short half-life of about 7 to 8 hours.[7] The need for twice-daily dosing poses issues related to patient adherence, impacting quality of life and increasing healthcare costs. Frequent dosing may lead to inconvenience, reduced compliance, and uncontrolled seizures. Moreover, the increased frequency of clinic visits and monitoring adds to the economic burden on both patients and healthcare systems. Addressing these challenges is crucial for optimizing the therapeutic benefits of BRV in epilepsy management.

Several potential solutions are being explored to address the challenges associated with the short half-life of BRV. One approach involves modifying the drug's formulation to develop extended-release tablets or capsules. These formulations aim to prolong the release of BRV throughout the day, reducing the need for frequent dosing. Additionally, personalized dosing strategies based on individual patient factors could optimize drug levels and potentially decrease dosing frequency for

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certain individuals. These innovative approaches seek to improve the convenience, compliance, and overall effectiveness of BRV therapy. BRV, known for its high potency, rapid onset of action, and favorable tolerability, remains a promising treatment option, and these advancements in drug delivery may further enhance its therapeutic benefits.

Extended-release tablets (ERTs) for BRV offer substantial advantages. By extending BRV release, ERTs facilitate once-daily or less frequent dosing, enhancing patient convenience and adherence. This reduction in dosing frequency may lead to more consistent drug levels, improving seizure control and potentially reducing breakthrough seizures. ERTs contribute to an enhanced quality of life by minimizing disruption to daily routines and reducing interference with activities. Additionally, the less frequent dosing schedule has the potential to lower healthcare costs due to reduced medication dispensing and clinic visits. Another notable benefit is the potential reduction in side effects, as less frequent exposure to BRV may result in a more favorable tolerability profile for patients.[8]

In addressing the challenges posed by the short half-life of BRV and its impact on patient adherence can be solved by formulation of extended-release tablets. BRV, known for its potent antiepileptic properties, faces the obstacle of twice-daily dosing. QbD, a systematic framework prioritizing quality throughout the product lifecycle, offers a transformative solution. By employing QbD principles, ERTs for BRV can be designed with optimal concentration of extended-release polymer & optimal release profiles, enabling once-daily dosing and enhancing patient adherence. The proactive risk management inherent in QbD aligns with regulatory expectations, facilitating smoother product approval processes. As an ongoing and iterative approach, QbD promotes continuous monitoring and optimization.[9]

MATERIAL AND METHODS

Material

A gift sample of brivaracetam recived from Kimia Bioscinece Ltd, India. Vivapure obtained from JRS Pharma, Blanose 7H4XF procured from M/s Ashland, HPMC K4M, HPMC K100 & HPMC K200 M obtained as gift specimen from Colorcon India. Syloid 244 FPFP was received from M/s Grace USA as gift sample & Magnesium Stearate obtained from M/s Suddep Pharma India and Opadry Complete Film coating system 21K58794 white Received as gift sample from Colorcon India.

Preformulation Studies

Organoleptic characteristics

Brivaracetam's organoleptic properties were performed, including appearance, color, odor, and melting point. These first evaluations laid the groundwork for later formulation efforts by providing insightful information on the active medicinal ingredient's sensory characteristics and thermal properties.

Quality target product profile

Defining the quality target product profile (QTPP) was a fundamental stage in formulating the extended-release brivaracetam tablets. This involved meticulously establishing desired features and specifications. Key parameters like dosage form, administration route, strength, drug release profile, pharmacokinetic behavior, and stability were carefully considered, laying out a comprehensive roadmap for formulation development.[10]

Critical quality attributes

Ensuring the developed and formulated product met safety, efficacy, performance, and stability requirements was fundamental, and this relied on the effective control of critical quality attributes (CQAs).[11]

Excipient compatibility studies

Fourier-transform infrared (FT-IR) studies used to check the excipient compatibility. This technique assessed the potential interactions between brivaracetam and the selected excipients in the optimized formulation. Pure brivaracetam and the final formulation were scanned, and their spectra were meticulously compared. Examining the presence or absence of common peaks provided valuable insights into potential chemical interactions between the drug and the excipients.[12]

Differential scanning calorimetry (DSC) was employed to assess thermal properties. Brivaracetam drug, was subjected to DSC analysis, and the optimized formulation blend was similarly examined. The comparison of thermograms facilitated the identification of any interactions between the drug and formulation components.

Risk assessment

The ER formulation of BRV involved a crucial risk assessment utilizing the failure mode and effects analysis (FMEA) method. This comprehensive evaluation categorized CQAs based on their risk levels and identified key formulation variables, including polymers, magnesium stearate, and syloid 244 FPFP, along with critical process variables like hardness and drug release. This risk assessment laid the foundation for a robust formulation and optimization process. Embracing QbD principles, the excipient selection process for BRV extended-release tablets employed a systematic approach. Release-controlling polymers with specific viscosity and swelling profiles and excipients like binders, lubricants, and glidants were meticulously chosen based on their CMAs and CPPs. Proactive risk assessment identified and mitigated potential interactions between components, ensuring a safe and stable formulation with the desired extended-release profile. The integration of physicochemical characterization, compatibility studies, and QbD principles further optimized excipient selection, contributing to the development of an effective extended-release formulation for BRV.[13]

Evaluation of pre-compression parameters

Understanding the flowability of the powder blend is crucial for successful tablet manufacturing. Therefore, the micrometric

properties of lubricated granules of extended-release BRV formulation were systematically evaluated. An accurately weighed blend of the granules was used to determine its bulk density, a key factor in understanding how tightly the powder particles can pack together. Tapped density was assessed using an electrolab tapped density apparatus, tapping as per USP method. The Hausner ratio and compressibility index were further calculated to provide additional insights into the powder's flow behavior. The measured values all indicated that the blend exhibited good flowability of the powder blend. The flow characteristics were evaluated using a funnel and cone setup, measuring heap radius and calculating the angle of repose (θ). This meticulous experimentation, conducted in triplicate, ensured robust assessments of the powder blend's flow properties.[14]

QbD framework for brivaracetam extended-release tablets: Formulation development

Embracing the quality by design (QbD) philosophy, developing extended-release BRV tablets involves systematically exploring diverse release mechanisms like matrix, osmotic, multiparticulate systems, and controlled-release coatings. Critical material attributes (CMAs) such as polymer viscosity and CPPs like mixing time and tablet coating thickness are meticulously optimized. This data-driven approach efficiently explores numerous combinations and statistically identifies the optimal ones, minimizing development time and resources. Ultimately, by optimizing CMAs and CPPs through DoE, we achieve extended drug release profiles that precisely match the desired delivery of BRV for improved patient outcomes. QbD tools, such as dissolution testing, mathematical modeling, and specialized software, contribute to a science-based formulation development approach, ensuring the creation of safe and effective extended-release tablets for BRV. Feasibility trials focus on identifying optimal polymers and concentrations following USP regulations, with materials including Vivapur 200, HPMC K4 M, blanose 7H4XF, HPMC K-200, magnesium stearate, syloid 244 FPFP, and brivaracetam. The process involves precise weighing, blending and tablet compression. Dissolution testing under simulated physiological conditions assesses drug release, with UV spectrophotometry used to quantify brivaracetam release. Comparative analysis of dissolution profiles guides the selection of polymers and concentrations, considering desired release characteristics. Further optimization done by using design expert software and software has suggested optimum concentration of polymer base on results of feasibility trials and criteria set in Design of Experiment software to ensures a robust process for achieving optimal extended-release brivaracetam tablet formulations.[15]

Procedure for brivaracetam extended release tablet dissolution testing

Film-coated brivaracetam extended release 100 mg tablet drug release examinations were conceded out using USP dissolution testing equipment type II (Paddle type; Electrolabs, Bangalore, India). A 12-hour dissolving test was conducted using 900 mL of USP-approved phosphate buffer PH 6.4 at 37°C and 50 rpm. At the 0.5, 1, 4, and 12-hour intervals, a 5 mL sample was withdrawn from the dissolution testing device and substituted with fresh dissolving media. The withdrawn sample was filtered using a 0.45 μm membrane filter; the samples were diluted with the appropriate medium to the desired concentration. With the use of a UV-visible spectrophotometer (Make: Labman Software: Meta Spec Pro), the absorbance of these samples was measured at 217 nm.

RESULTS AND DISCUSSION

Brivaracetam appeared as a white, odorless, and crystalline powder. Its melting point of 77.38°C provides valuable information for storage and processing considerations, as it suggests potential thermal sensitivity. These organoleptic properties contribute to the overall characterization of brivaracetam for its intended use.

Quality Target Product Profile

The QTPP given in Table 1 for Briv-ER, an extended-release tablet with 100 mg dosage strength, outlines key attributes such as appearance, size, hardness, and dissolution profile. Assuring quality and safety, the tablet's assay is monitored by high-performance liquid chromatography (HPLC), ensuring the right concentration of the active ingredient. The tablet is designed for a minimum 90% dissolution at 12 hours with a focus on microbial limits and stability. Packaging in Alu-Alu blister ensures protection and user convenience. The QTPP serves as a comprehensive guide, emphasizing safety, efficacy, and features throughout Briv-ER's lifecycle.

Critical Quality Attributes

CQAs provided in Table 2 for brivaracetam ER tablets are identified based on their impact on safety, efficacy, and quality. Physical attributes like appearance, size, and theoretical weight are non-critical. Identification as brivaracetam-positive and dissolution profiles at specific time points (0.5, 1, 4, 8, 12 hours) are crucial CQAs, controlled through robust quality management. The assay, with a target range of 97 to 105%, is a critical attribute influencing safety and efficacy. Meticulous control of identification, dissolution profiles, and assay values is essential for ensuring the consistent quality of the brivaracetam ER tablets drug product throughout development and production.

Excipient Compatibility Studies

These studies were conducted to ensure the absence of potentially detrimental interactions between BRV and the chosen formulation components. FTIR investigation shown no significant changes in peak intensity or the emergence of new characteristic peaks in the BRV and formulation spectra shown in Figure 1, indicating good chemical compatibility between the drug and the excipients also DSC investigations were done across a temperature series of (76–77°C) on BRV shown in Figure 2, the complete formulation, and granules to further assess potential physical interactions. The absence of significant exothermic or endothermic events in the DSC thermograms compared to BRV alone suggested no major

Table 1: Quality target product profile

QTPP components		*Target*
Dosage form		Solid oral
Dosage design		Extended-release tablets
Administration route		Oral
Dosage strength		100mg
Drug product quality attribute	Appearance	White to off white colour, round shaped, film coated tablet.
	Size	9.50–11.00 mm
	Shape	Round
	Theoretical Weight	400–500 mg
	Friability	NMT 0.8% w/w
	Hardness	100–200 N
Assay		97–105
Identification		By HPLC
Dissolution	0.5 hour	NMT 20%
	1 hours	NMT 40%
	4 hours	NLT 50%
	8 hours	NLT 70%
	12 hours	NLT 90%
Microbial limits		To comply as per IP
Packing		A) Primary: Alu-Alu Blister Pack
Stability and shelf life		Must be stable at shelf life of 24 months at a temperature not exceeding 30°C

interactions impacting the thermal behavior of the drug within the formulation. The thermograms displayed consistent melting points at 76°C and thermal behaviors, further confirming the compatibility of BRV with the formulation components and granulation process. X-ray diffraction (XRD) analysis of brivaracetam and the formulation demonstrated comparable diffraction patterns shown in Figure 3, suggesting no significant changes in the crystalline structure of BRV upon formulation. These findings collectively support the excipient compatibility and suitability of the chosen formulation for the development of brivaracetam extended-release tablets.

Risk Assessment

The assigned level of risk for drug product CQAs in relation to various drug substances illustrated in Table 3 attributes is justified based on a comprehensive analysis. The assay is deemed to have a low to medium risk, considering factors such as solid-state form, solubility, and process impurities, with chemical stability and flow properties posing higher risks. Dissolution risk is characterized as low to medium, contingent on particle size distribution. The assessment emphasizes that the crystalline nature of the drug substance, compliance with International Council for Harmonisation (ICH) Q3A recommendations for impurities, and low impact of solubility on dissolution contribute to a generally low-risk profile. However, attention to factors like chemical stability's remarkable effect on degradation rate and potential flow-related impacts on assay uniformity requires careful consideration during drug product development to ensure robustness and reliability.

Table 2: Critical quality attributes for brivaracetam extended-release tablet

Quality attributes of drug product		*Target*	*Is this is CAQ?*	*Justification*
Physical features Size Shape Theoretical weight Coated/ Uncoated	Appearance 9.50–11.00 mm Round 400–500 mg Film coated	White to off-white color, round shape, film-coated tablet.	No	Appearance, size, shape are not directly connected to safety and efficacy, so they are not critical.
Identification	Positive for brivaracetam		Yes	Despite this, effectiveness and safety depend on identification. The quality management can successfully handle this CQA.
Dissolution	0.5 hour	NMT 20%	Yes	Optimizing formulation and process variables is crucial to ensure consistent drug release, impacting bioavailability and therapeutic efficacy in pharmaceutical formulations.
	1 hours	NMT 40%		
	4 hours	NLT 50%		
	8 hours	NLT 70%		
	12 hours	NLT 90%		
Assay		97–105%	Yes	Assay variations can impact drug safety and efficacy, emphasizing the need for continuous evaluation throughout product and process development to address potential influences from process variables

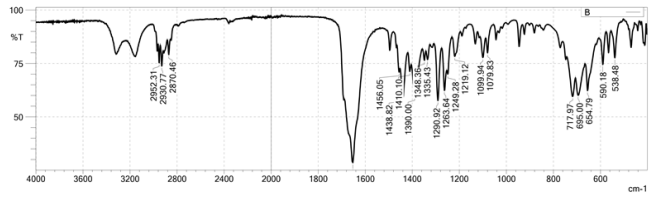

Figure 1: FT-IR spectra of API

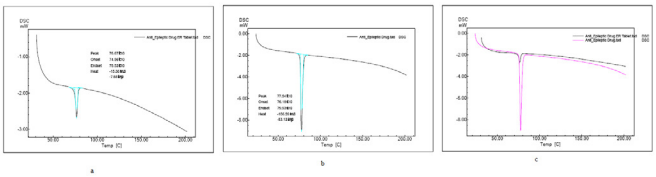

Figure 2: DSC thermogram of a) Tablet formulation b) API and c) API and formulation overlay

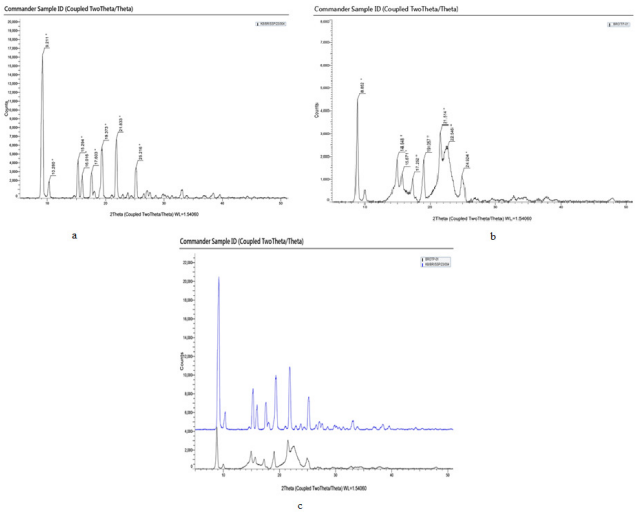

Figure 3: XRD of a) API brivaracetam b) API and formulation overlay and c) Brivaracetam lubricated granules

Evaluation of Pre-compression Parameters

The table presents tapped density data for a powder at various tap counts. The initial tap count reveals a bulk density of 0.395 g/mL, tapped density of 0.625 g/mL, Hausner's ratio of 1.583, and Carr's compressibility index of 36.84%.given in Table 4 subsequent tap counts (10, 500, 1250) lack specific volume readings. The initial data suggests fair flow properties with a moderate compressibility index. However, the incomplete dataset makes it challenging to draw definitive conclusions about the powder's flow characteristics, emphasizing the need for additional measurements at various tap counts.

Table 5 data illustrates a sieve analysis of granules, presenting the quantity retained, percentage retained, cumulative percentage retained, and the ratio of granules to fines for different mesh sizes. No granules are retained for mesh sizes #30 and #40, resulting in 0.00% and 0.10% retention, respectively. As the mesh size increases to #60, #80, and #100, the quantity retained and percentage retained gradually rise. The receiving pan, collecting particles below #100, shows significant retention, constituting 15.33 grams and 76.65% of the total. The cumulative percentage retained increases progressively, reaching 76.65% after #100 mesh size. This suggests that a considerable portion of granules falls below #100 mesh. The ratio of granules to fines provides insights into the distribution of particle sizes in the sample.

Formulation Development of Brivaracetam Extended-Release Tablets Using QbD

Tables 6 & 7 provides data on various parameters for batches of extended-release tablets (BRERT-02 to BRERT-07), including average tablet weight, thickness, and hardness. The average weight of tablets is consistent across all batches, maintained at 400.00 mg, ensuring uniform dosing. In terms of tablet thickness, batches BRERT-03, BRERT-06, and BRERT-07 fall within a narrower range (4.10–4.13 mm, 4.20–4.22 mm, and 4.15–4.17 mm, respectively), indicating better control compared to other batches. Hardness values vary slightly across batches, with BRERT-02 and BRERT-04 exhibiting higher hardness (130–140 Newton's) compared to other batches. This variation in hardness may be attributed to differences in formulation or

Table 3: Assigned level of risk for drug product CQAs in relation to various drug substances attributes

Drug product CQAs	*Drug substance attributes*					
	Solid state form	*Particle size distribution*	*Solubility*	*Process impurities*	*Chemical stability*	*Flow properties*
Assay	Low	Low	Low	Low	High	Medium
Dissolution	Low	Medium	Low	Low	Low	Low

Table 4: Tapped density determination

S. No.	*Tap count*	*Volume of powder (mL)*	*Bulk density (g/mL)*	*Tapped density (g/mL)*	*Hausner's ratio*	*Carr's compressibility index*
1	0	38.00				
2	10	32.00				
3	500	24.00	0.395	0.625	1.583	36.84
4	1250	24.00				
5	1250	--				

Table 5: Sieve analysis

Mesh size	*Quantity retained (g)*	*Percentage retained (%)*	*Cumulative percentage retained*	*Ratio granules: Fines*
#30	0.00	0.00	0.00	
#40	0.10	0.50	0.50	
#60	1.27	6.35	6.85	100# retained-22.85%
#80	1.70	8.50	15.35	100# pass- 76.65
#100	1.53	7.50	22.85	
Receiving pan (below100#)	15.33	76.65	---	

Table 6: Manufacturing formula of feasibility trials using different controlled release polymer and different concentrations of polymer

Ingredients	*Brert-02*	*Brert-03*	*Brert-04*	*Brert-05*	*Brert-06*	*Brert-07*
Vivapur 200	240	240	240	230	230	230
HPMC K4 M	---	50	--	10	10	20
Blanose 7H4XF	50	----	--	50	--	20
HPMC K-200	----	---	50	--	50	20
Magnesium stearate	5	5	5	5	5	5
Syloid 244 FP	5	5	5	5	5	5
Brivaracetam	100	100	100	100	100	100
Total weight	400	400	400	400	400	400

compression parameters. Overall, while tablet weight remains consistent, there is room for improvement in ensuring tighter control over tablet thickness and hardness for enhanced batch uniformity in future formulations.

The dissolution study results given in Table 8 for different batches (BRERT-02 to BRERT-07) of formulations produced in feasibility trials are presented in the table. The data show the percentage of drug release at various time points (30 minutes, 1, 4, 8, and 12 hours). Batch BRERT-07 exhibits the highest drug release percentages at 30 minutes and 1-hour, indicating a faster initial release compared to other batches. However, BRERT-07's release plateaus at later time points, reaching lower percentages at 8 and 12 hours. Batches BRERT-03 and 04 demonstrate an extended-release profile, with drug release increasing gradually over time. These results suggest variations in the release kinetics among the batches, highlighting the importance of optimizing the formulation to achieve the desired extended-release profile for brivaracetam tablets (Table 9). Further investigation and adjustments to formulation parameters may be necessary to achieve a more consistent and controlled drug release across all batches.

Results of Physical Parameters of Experimental Batches

Results of physical parameters of experimental batches were studied using standard operating procedures. The results are reported in Table 10.

Dissolution Profile of Optimization Batches

Table 11 present the results of the effect of polymer concentrations (Blanose CMC and HPMC K4M) on various drug release responses at different time points for brivaracetam extended-release tablets. The factors studied include the concentration of blanose CMC (Factor 1) and HPMC K4M (Factor 2), and the responses measured include drug release percentages at specific time series. The data reveal notable variations in drug release across different formulations. For instance, formulations with higher concentrations of blanose CMC and HPMC K4M generally exhibit slower drug release at early time points, while concentrations and interactions among factors influence the release kinetics. Understanding these relationships is crucial for optimizing the formulation to achieve the desired extended-release profile for brivaracetam tablets. Further analysis, such as statistical modeling and design of experiments, may be employed to discern optimal polymer concentrations and their synergistic effects on drug release responses.

Analysis of the ANOVA results

Drug release at 30 minutes $= b0+15.32A-3.06B-7.01AB+3.08A2+3.62B2+1.75B2$

Drug release at 1 hour $= +22.89-5.49A-9.26B+4.23AB+4.98A2$

Drug release at 4 hours $= +65.28-6.77A-3.91B-3.32AB+2.12A2-2.08B2$

Table 7: Results of physical parameters of feasibility trials

Parameters	*Batch no*					
	Brert-02	*Brert-03*	*Brert-04*	*Brert-05*	*Brert-06*	*Brert-07*
Average weight of tablets (mg)	400.00	400.00	400.00	400.00	400.00	400.00
Thickness (mm)	4.08–4.10	4.10–4.13	4.15–4.17	4.05–4.10	4.20–4.22	4.15–4.17
Hardness (Newton's)	130–140	100–110	120–130	130–140	120–130	120–130

Table 8: Results of dissolution studies of formulations produced in feasibility trials

Batch number	*30 minutes*	*1 hour*	*4 hours*	*8 hours*	*12 hours*
B. No. BRERT- 02	16.8	14.6	51.0	87.6	117.3
B. No.-BRERT -03	17.8	38.9	73.2	96.1	106.0
B. No.- BRERT 04	15.3	40.1	74.6	98.1	110.4
B. No. BRERT -05	15.0	16.5	42.5	78.9	105.8
B. No. BRERT -06	14.8	32.8	70.3	96.8	110.3
B. No. BRERT -07	23.4	19.5	54.4	81.0	97.5

Table 9: Manufacturing formula of experimental batches using 3^2 factorial using design of experiment software

Ingredients	*Brert-08*	*Brert-09*	*Brert-10*	*Brert-11*	*Brert-12*	*Brert-13*	*Brert-14*	*Brert-15*	*Brert-16*
Vivapur 200 (low moisture Grade)	236.15	207.85	214.93	217	207	222	229.08	227	237
HPMC K4 M	15	15	22.07	10	20	15	7.92	20	10
Blanose 7H4XF	35.85	64.14	50	60	60	50	50	40	40
Magnesium stearate	8	8	8	8	8	8	8	8	8
Syloid 244 FP	5	5	5	5	5	5	5	5	5
Brivaracetam	100	100	100	100	100	100	100	100	100
Total	400	400	400	400	400	400	400	400	400

Drug release at 8 hours = +78.43−8.28*A*−2.96*B*+1.53*AB*+0.7 063*A*2+1.76*B*2

Drug release at 12 hour = +97.08−2.64*A*−4.23*B*−1.62*AB*−0.5 000*A*2−2.52*B*2

The analysis of the ANOVA results for the quadratic models predicting drug release at various time points indicates the significance of the model for each response. The F-values and associated *p-values* suggest that the models are highly significant, with very low chances that the observed effects are due to noise. In each case, the factors A (Blanose CMC) and B (HPMC K4M), as well as their interactions (AB), and quadratic terms (A^2 and B^2), are found to be significant contributors to the drug release. Lack of fit tests shows non-significance, indicating good model fitting. The high values of R^2, adjusted R^2, and predicted R^2, along with adeq precision ratios exceeding 4, indicate that the models are robust. The resulting equations with coded factors provide a means to predict drug release based on different levels of the factors, allowing for informed formulation decisions. Overall, the quadratic models successfully capture the relationship between formulation factors and drug release, providing a valuable tool for optimization in the design of extended-release tablets. BRERT-17 batch of brivaracetam extended-release tablets formulation was found to be best based on the parameters identified through a design of experiments

Response surface methodology surface plots shown in Figure 4 are significant in the field of experimental design and optimization as they provide visual representations of the relationship between multiple independent variables and a response or outcome. Plot observes how changes in input variables affect the response, helping to identify optimal conditions for the desired outcome. They offer valuable insights into the interactions and trends within the experimental space, facilitating informed decision-making in the pursuit of optimized processes or formulations.

Optimized formula for brivaracetam extended-release tablets (Verification Batch Suggested by Design Expert) is mentioned in Table 12 and the dissolution profile of brivaracetam extended-release tablets (Verification Batch) is presented in Figure 5. The dissolution profile of experimental batches is presented in Figure 6.

Results of Physical Parameters of Verification Batches (Uncoated Tablets)

The results of physical parameters of verification batches (Uncoated tablets) were studied and reported in Table 13.

Table 10: Results of Physical Parameters of Experimental Batches

Parameters	*Batch no:*								
	Brert-08	*Brert-09*	*Brert-10*	*Brert-11*	*Brert-12*	*Brert-13*	*Brert-14*	*Brert-15*	*Brert-16*
Average weight of tablets (mg)	400.00	400.00	400.00	400.00	400.00	400.00	400.00	400.00	400.00
Thickness (mm)	4.08–4.10	4.10–4.13	4.15–4.17	4.05–4.10	4.20–4.22	4.15–4.17	4.15–4.20	4.15–4.17	4.05–4.10
Hardness (Newton's)	120–130	100–110	120–125	125–135	130–135	130–140	125–130	120–130	135–140

Table 11: Results of dissolution studies of experimental batches

Batch number	*30 minutes*	*1 hour*	*4 hours*	*8 hours*	*12 hours*
B. No. BRERT- 08	28	42.1	78.2	91.2	99.7
B. No.-BRERT -09	18.8	24.1	60.2	68.5	92.5
B. No.- BRERT10	10.1	9.6	55.3	78.2	85.7
B. No. BRERT -11	21.2	27.5	65.7	74.1	96.9
B. No. BRERT -12	12.8	18.5	51.2	70.6	85.7
B. No. BRERT -13	14.3	21.3	64.3	78.1	96.3
B. No. BRERT -14	29.2	37.3	66.3	85.7	98.4
B. No. BRERT -15	12.4	19.3	72.2	84.6	94.4
B. No. BRERT -16	33.1	45.2	73.4	94.2	99.1

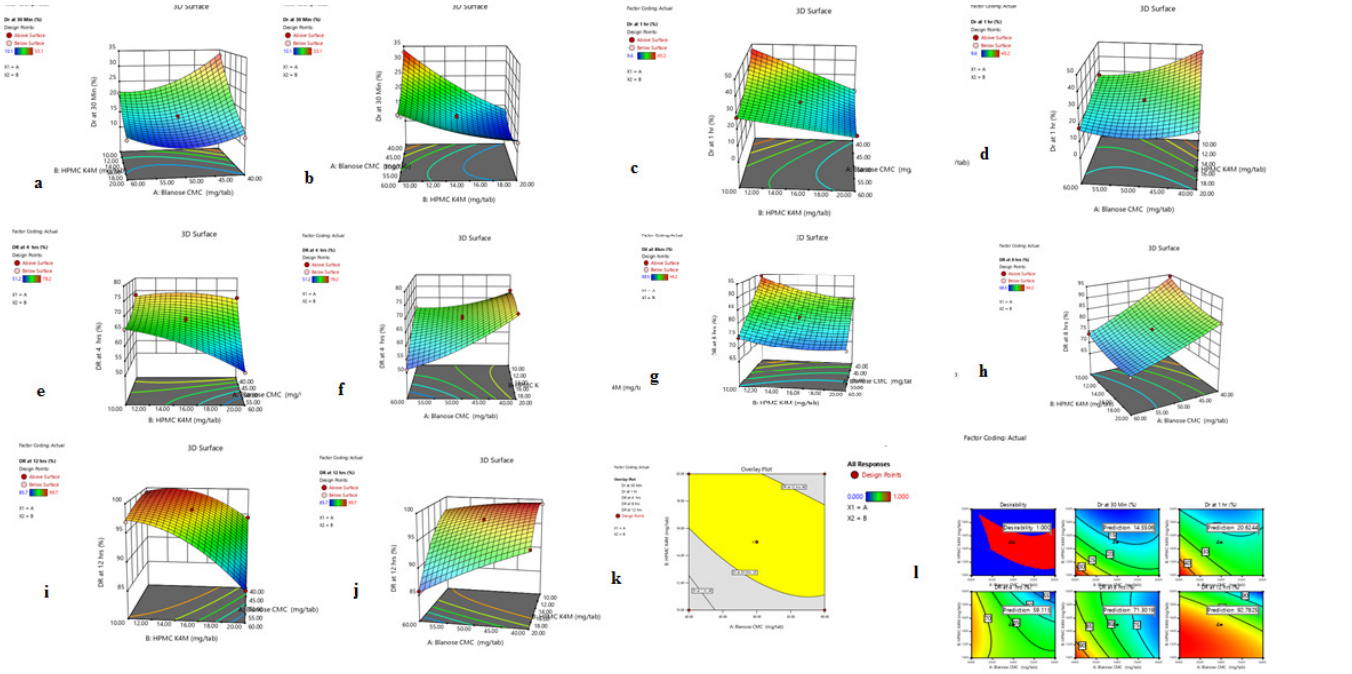

Figure 4: Response surface methodology surface plots, a& b) Response 1 drug release at 30 minutes c& d) Response 1 drug release at 1-hour e & f) Response 1 drug release at 2 hours g& h) Response 1 drug release at 4 hours h& i) Response 1 drug release at 8 hours I & j) Response 1 drug release at 12 hours k) Overlay plot l) all responses

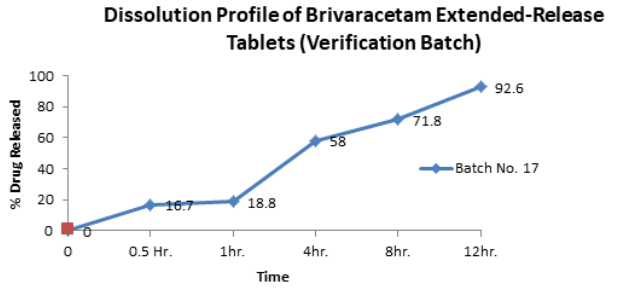

Figure 5: Dissolution profile of brivaracetam extended-release tablets (Verification Batch)

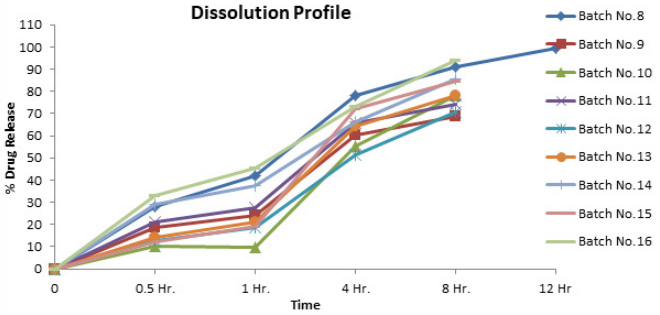

Figure 6: Dissolution Profile of Experimental Batches

Table 12: Optimized formula for brivaracetam extended release tablets

S. No	*Ingredients*	*Quantity (mg/Tablets)*
1	Vivapur 200 (low moisture Grade)	211.47
2	HPMC K4 M	16.13
3	Blanose 7H4XF	59.40
4	Magnesium stearate	8
5	Syloid 244 FP	5
6	Brivaracetam	100
	Total	400

Table 13: Results of physical parameters of uncoated tablets

Parameters	*Batch No.: BRERT-08*
Average weight of tablets (mg)	400.00
Thickness (mm)	4.20–4.25 mm
Hardness (Newton's)	110–125 N

Table 14: Formula for film coating

S. No	*Ingredients*	*Quantity (mg/Tab)*
1.	Opadry complete film coating system 21K58794 white (Moisture barrier film coating system)	10
2.	Isopropyl alcohol	Qs
3.	Methylene chloride	Qs

Solid Content: 8%
Solvent System: 60:40 (Isopropyl Alcohol:Methylene Chloride)

Table 15: Results of physical parameters of coated tablets

Parameters	*Batch NO.: BRERT-08*
Average weight of tablets (mg)	410.00
Thickness (mm)	4.35–4.40 mm
Hardness (Newton's)	130–140 N

Table 16: Dissolution studies

Batch Number	30 min	1 hr	4 hrs	8 hrs	12 hrs
B. No. BRERT- 17	16.7	18.8	58.0	71.8	92.6

Formula for Film Coating

Film coating was performed using a specified formula from Table 14.

Results of Physical Parameters of Verification Batches (Coated Tablets)

After successful film coating, results of physical parameters were obtained by experiments and reported in Table 15.

Results of Dissolution Studies of Verification Batch

Dissolution studies of verification batch (BRERT 17) are mentioned in Table 16.

CONCLUSION

The formulation development of BRV extended-release tablets using the QbD approach represents a systematic and science-based strategy to optimize extended-release polymer concentration. The need for twice-daily dosing can impact patient adherence, and extended-release formulation gives a transformative solution to optimize the therapeutic benefits of BRV in epilepsy management. The initial steps involved in the formulation development included pre-formulation studies, organoleptic evaluations, and QbD implementation. Excipient compatibility studies using FTIR, DSC, and risk assessments were conducted to ensure the suitability of the selected excipients and identify potential risks in the formulation.

Feasibility trials were conducted to identify optimal polymers and concentrations based on the United States Pharmacopeia (USP) regulations. The materials used included Vivapur 200, HPMC K4 M, Blanose 7H4XF, HPMC K-200, magnesium stearate, Syloid 244 FP, and brivaracetam. The formulation process involved precise weighing, blending, tablet compression, and optional hardness and disintegration tests. Dissolution testing under simulated physiological conditions and UV spectrophotometry were employed to assess and quantify brivaracetam release. Results from feasibility trials demonstrated variations in physical parameters and dissolution profiles among different batches, highlighting the need for further optimization. The QbD approach was then employed to conduct a systematic study on the effect of polymer concentrations on drug release responses. Statistical analysis, including Analysis of Variance (ANOVA) and quadratic models, helped identify optimal polymer concentrations for achieving the desired extended-release profile. The formulation (BRERT-17) identified through Design of Experiments was found to be the most promising, balancing the release characteristics at different time points. Response surface methodology surface plots provided insights into the interactions between polymer concentrations and drug release responses.

The QbD approach, coupled with systematic feasibility trials and statistical optimization, has paved the way for the development of an effective extended-release formulation for brivaracetam. The formulation addresses the challenges associated with the short half-life of BRV and aligns with regulatory expectations, leading to potential improvements in patient adherence, seizure control, and overall quality of life for individuals managing epilepsy. Continuous monitoring and optimization within the QbD framework will further enhance the robustness of the formulation and contribute to its successful market launch.

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