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FORMULATION AND IN VITRO EVALUATION BRIVARACETAM SUSTAINED RELEASE TABLET

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Abstract:

The present study was aimed at the formulation and evaluation of Brivaracetam sustained-release (SR) matrix tablets using the wet granulation method to achieve prolonged drug release and improve patient compliance by reducing dosing frequency. Brivaracetam, a third-generation antiepileptic drug with a relatively short half-life, was selected as the model drug for sustained-release formulation. Eight formulations (F1–F8) were prepared by incorporating different concentrations of sodium alginate and tragacanth as release-retarding polymers while maintaining a constant tablet weight of 400 mg. The in vitro dissolution study showed a controlled and sustained release of Brivaracetam over 8 hours, with cumulative drug release ranging from 92.53% to 97.58%. Among the prepared formulations, F6 demonstrated the highest cumulative drug release (97.58%) and was selected as the optimized formulation. The dissolution data of the optimized formulation were fitted to various kinetic models. Stability studies conducted under 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH for three months revealed no significant changes in the physical appearance or dissolution profile of the optimized formulation, confirming its stability under the tested storage conditions. Overall, the study demonstrated that tragacanth-based formulation F6 is a promising sustained-release matrix tablet of Brivaracetam capable of providing controlled drug release with good stability.

Keywords: *Brivaracetam, Sustained-release tablets, Wet granulation, Sodium alginate, Tragacanth, Matrix tablets, Drug release kinetics, Stability studies.*

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INTRODUCTION:

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal and excessive neuronal activity in the brain. It affects individuals across different age groups and represents a major therapeutic challenge because inadequate seizure control can significantly impair quality of life.[1] Brivaracetam is a newer antiepileptic drug belonging to the racetam class and is primarily indicated as an adjunctive therapy for the treatment of partial-onset seizures.[2] Brivaracetam is administered orally and is rapidly absorbed following oral administration, with high bioavailability. However, its relatively short elimination half-life necessitates repeated administration to maintain effective plasma concentrations.[3] Sustained-release drug-delivery systems are designed to release the drug gradually over a predetermined period, thereby reducing fluctuations in plasma drug concentration and potentially decreasing the frequency of administration.[4] Oral sustained-release tablets can be developed using various formulation approaches, including hydrophilic matrix systems, hydrophobic matrix systems, polymeric coatings, osmotic systems, and multiparticulate technologies.[5] In-vitro evaluation is an essential component in the development of sustained-release tablets. Hence, the present study was undertaken with the objective of formulating and evaluating brivaracetam sustained-release tablets using suitable pharmaceutical excipients and release-retarding polymers.[6] The developed formulations were subjected to pre-compression and post-compression evaluation, followed by in-vitro dissolution studies and kinetic analysis to determine the drug-release behavior and mechanism. The optimized formulation was selected based on its physicochemical properties and ability to provide a desirable sustained-release profile over the intended period.[7]

MATERIALS:

Brivaracetam was procured from Hetero Labs, HYD. Xanthan gum and Tragacanth were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Formulation Development

Table-1: Formulation of SR Tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
1	Brivaracetam	100	100	100	100	100	100	100	100
2	Xanthan gum	50	100	150	200	-	-	-	-
3	Tragacanth	-	-	-	-	50	100	150	200
4	MCC	20	20	20	20	20	20	20	20
5	Lactose	225	175	125	75	225	175	125	75
6	Magnesium stearate	3	3	3	3	3	3	3	3
7	Talc	2	2	2	2	2	2	2	2
8	Total Wt	400	400	400	400	400	400	400	400

Wet granulation method

Initially, Brivaracetam, the selected polymer (Xanthan gum or tragacanth), microcrystalline cellulose (MCC), and lactose were accurately weighed according to the formulation composition. These ingredients, except magnesium stearate and talc, were passed through #40 mesh separately to remove lumps and ensure uniform particle size. The powders were then transferred into a clean mortar or rapid mixer granulator and blended thoroughly for 10–15 minutes to obtain a homogeneous mixture. A suitable granulating fluid, such as purified water, was added slowly to the powder blend with continuous mixing until a cohesive wet mass of suitable consistency was formed. The wet mass was then passed through a #16 sieve to produce uniform wet granules. The prepared wet granules were dried in a hot air oven at 45–50°C until the moisture content reached approximately 2–3%. After drying, the granules were passed through a #20 sieve to break any agglomerates and obtain uniformly sized granules. The dried granules were then blended with the lubricants, magnesium stearate and talc, previously passed through a #60 mesh, and mixed gently for 3–5 minutes to ensure uniform lubrication while avoiding overmixing. Finally, the lubricated granules were compressed into tablets using a rotary tablet compression machine fitted with 10 mm standard concave punches. [8]

Characterization

Uniformity of weight

The uniformity of weight test was performed to ensure that all tablets contained a uniform amount of formulation and complied with pharmacopoeial specifications. Twenty tablets were selected randomly from each formulation batch (F1–F8) and carefully

cleaned to remove any dust adhering to the surface. Each tablet was weighed individually using a calibrated digital analytical balance, and the individual weights were recorded. The average weight of the 20 tablets was then calculated.[9]
Deviation (%) = Weight (individual) – Weight (average) x 100 Weight (average)

Hardness
Ten tablets were selected randomly from each formulation batch (F1–F8). The hardness of each tablet was measured using a Monsanto hardness tester (or Pfizer hardness tester, depending on the instrument available). Each tablet was placed between the anvils of the hardness tester in such a way that the force was applied diametrically across the tablet. The pressure was increased gradually until the tablet fractured. The force required to break the tablet was recorded in kilogram-force (kg/cm² or kgf) (or Newtons, if the instrument displayed SI units). The hardness of all ten tablets was determined individually, and the mean hardness along with the standard deviation was calculated for each formulation. Tablets exhibiting uniform hardness were considered suitable for further evaluation. For sustained-release matrix tablets, a hardness in the range of 5–8 kg/cm² is generally considered satisfactory to provide adequate mechanical strength while maintaining the desired drug release characteristics.[10]

Thickness
Ten tablets were selected randomly from each formulation batch (F1–F8). The thickness of each tablet was measured individually using a digital Vernier caliper (or a micrometer screw gauge) calibrated before use. Each tablet was placed between the measuring jaws of the instrument, and the thickness was measured along the central axis without applying excessive pressure that could deform the tablet. The readings were recorded in millimeters (mm).[11]

Friability test
Twenty tablets were selected randomly from each formulation batch (F1–F8), and any loose dust was removed gently. The tablets were accurately weighed together, and the initial weight (W_1) was recorded using a calibrated analytical balance. The tablets were then placed in the drum of a Roche friabilator and rotated at 25 rpm for 4 minutes, completing 100 revolutions. After completion of the test, the tablets were removed from the friabilator, dedusted carefully, and reweighed to obtain the final weight (W_2). [12]The percentage friability was calculated using the following equation:
Friability = 100 X tablet weight (before weight) – tablet weight (after test) Tablet weight (before the test)

Drug content [13]
The drug content determination was performed to estimate the amount of Brivaracetam present in the prepared sustained-release tablets and to ensure uniform distribution of the drug in each formulation. Twenty tablets were selected randomly from each formulation batch (F1–F8) and accurately weighed to determine the average tablet weight. The tablets were then finely powdered using a clean mortar and pestle. A quantity of powder equivalent to 100 mg of Brivaracetam was accurately weighed and transferred into a 100 mL volumetric flask. Approximately 70 mL of phosphate buffer (pH 6.8) was added, and the mixture was sonicated for 15–20 minutes to ensure complete extraction of the drug. The volume was then made up to 100 mL with the same phosphate buffer and mixed thoroughly. The resulting solution was filtered through Whatman No. 1 filter paper (or a 0.45 µm membrane filter) to remove any insoluble excipients. An appropriate aliquot of the filtrate was further diluted with phosphate buffer (pH 6.8) to obtain a solution within the calibration range. The absorbance of the diluted solution was measured using a UV–Visible spectrophotometer at the predetermined λmax of 210 nm (or the λmax established during your calibration study). The drug concentration was determined from the previously prepared calibration curve of Brivaracetam, and the percentage drug content was calculated.

In Vitro Disintegration Test
The in vitro disintegration test was performed to determine the time required for the prepared Brivaracetam sustained-release tablets to break down under specified experimental conditions. Six tablets from each formulation batch (F1–F8) were randomly selected and placed individually into the tubes of the USP disintegration test apparatus. Each tube was fitted with a perforated disc to prevent the tablets from floating during the test. The disintegration apparatus was operated using 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C as the immersion medium. The basket assembly was allowed to move vertically at a frequency of 29–32 cycles per minute. The tablets were observed continuously, and the time taken for each tablet to disintegrate completely, with no palpable core remaining on the screen, was recorded. The average disintegration time was calculated and expressed in minutes.

In- Vitro Release study[14]
The dissolution study was performed using the USP Dissolution Apparatus II (Paddle Method). One tablet from each formulation was placed separately in the dissolution vessel containing 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. The paddle rotation speed was adjusted to 50 rpm. At predetermined time intervals 5 mL of the dissolution medium was withdrawn using a syringe fitted with a 0.45 µm membrane filter. After each withdrawal, an equal volume of fresh dissolution medium maintained at the same temperature was immediately added to maintain a constant dissolution volume and sink conditions. The collected samples were suitably

diluted, whenever necessary, with phosphate buffer (pH 6.8), and the absorbance was measured using a UV–Visible spectrophotometer at the predetermined λmax of 210 nm .

Drug release kinetics[15]

The dissolution data obtained from the in vitro drug release study were fitted to different kinetic models to determine the mechanism and rate of drug release from the Brivaracetam sustained-release tablets. The cumulative percentage drug release data were analyzed using Zero-order, First-order, Higuchi, and Korsmeyer–Peppas kinetic models. The model showing the highest coefficient of determination (R^2) was considered to best describe the drug release mechanism.

Stability studies[16]

The stability study of the optimized Brivaracetam sustained-release tablet formulation was carried out according to the International Council for Harmonisation (ICH) Q1A(R2) Guidelines to evaluate the physical, chemical, and dissolution stability of the formulation during storage.

RESULTS AND DISCUSSION:

Post compression parameters

Table-2: Evaluation parameters of Brivaracetam SR tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (min)
F1	400	2.5	3.8	0.19	79.86	34
F2	399	2.7	3.5	0.23	82.43	29
F3	401	2.2	3.6	0.15	83.15	32
F4	400	2.5	3.9	0.17	78.49	25
F5	399	2.6	3.7	0.16	81.23	36
F6	400	2.8	3.1	0.18	85.92	21
F7	400	2.3	3.6	0.15	83.17	28
F8	401	2.7	3.7	0.16	80.22	32

Discussion

The weight variation of all formulations ranged from 399 to 401 mg, which was well within the acceptable pharmacopoeial limit of ±5% for tablets weighing 400 mg. The results indicate uniform die filling and consistent tablet compression, confirming the reproducibility of the wet granulation process.

The tablet thickness varied between 2.2 and 2.8 mm, indicating uniform compression and minimal variation in tablet dimensions. The slight differences observed among the formulations may be attributed to differences in polymer concentration and packing characteristics of the granules. However, these variations were not significant and did not affect tablet quality.

The hardness of the tablets ranged from 3.1 to 3.9 kg/cm². Formulation F4 exhibited the highest hardness (3.9 kg/cm²), whereas F6 showed the lowest (3.1 kg/cm²). The increase in hardness in some formulations could be due to better particle binding during wet granulation and compression. Although the tablets possessed sufficient mechanical strength for handling, the hardness values are slightly lower than the typical target range for sustained-release tablets (5–8 kg/cm²). Increasing the compression force or incorporating a suitable binder may further improve tablet hardness.

The friability values of all formulations ranged from 0.15 to 0.23%, which are well below the pharmacopoeial limit of 1.0%. Formulations F3 and F7 exhibited the lowest friability (0.15%), indicating excellent mechanical resistance, while F2 showed the highest friability (0.23%), which still remained within acceptable limits. These findings confirm that all formulations possessed adequate resistance to abrasion during handling and transportation.

The drug content ranged from 78.49 to 85.92%. Among all formulations, F6 exhibited the highest drug content (85.92%), whereas F4 showed the lowest (78.49%). Although the values indicate uniform incorporation of the drug into the tablet matrix, the drug content of all formulations is below the acceptable pharmacopoeial limit (generally 95–105% of the labeled claim). This suggests incomplete drug recovery or non-uniform distribution during formulation or analytical estimation. Therefore, optimization of the formulation process and validation of the assay method are recommended to achieve acceptable drug content.

The disintegration time ranged from 21 to 36 minutes. Formulation F6 showed the shortest disintegration time (21 minutes), whereas F5 exhibited the longest (36 minutes). The increase in disintegration time with higher concentrations of the release-retarding polymers (Xanthan gum and tragacanth) may be attributed to the formation of a stronger gel matrix, which delayed the penetration of the dissolution medium into the tablets. Such behavior is expected for sustained-release formulations, where delayed disintegration contributes to prolonged drug release.

Dissolution studies

Table-3: Drug release studies of all formulations

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	17.49	18.12	16.59	19.76	20.15	21.56	20.16	17.89
2	26.82	25.73	24.83	25.83	26.89	28.95	27.49	23.32
3	38.10	37.48	38.49	39.48	36.49	40.25	42.53	38.97
4	48.43	45.83	42.80	43.28	45.87	57.89	56.25	49.81
5	65.58	66.32	63.25	65.53	64.49	68.12	67.88	62.25
6	72.15	73.59	75.89	76.81	72.15	75.86	71.23	70.15
7	83.26	84.51	85.49	83.26	81.15	86.33	83.26	84.22
8	92.53	93.56	95.86	96.39	94.46	97.58	96.38	95.13

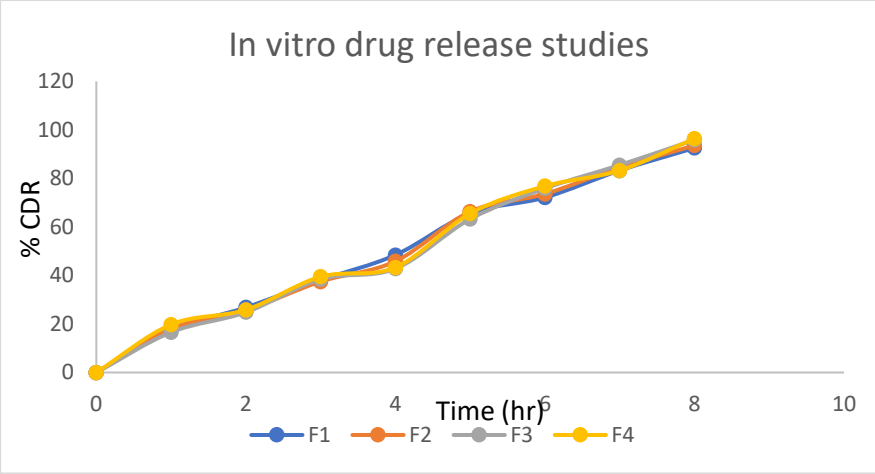


Fig-1: Dissolution Profile of F1 to F4 formulations

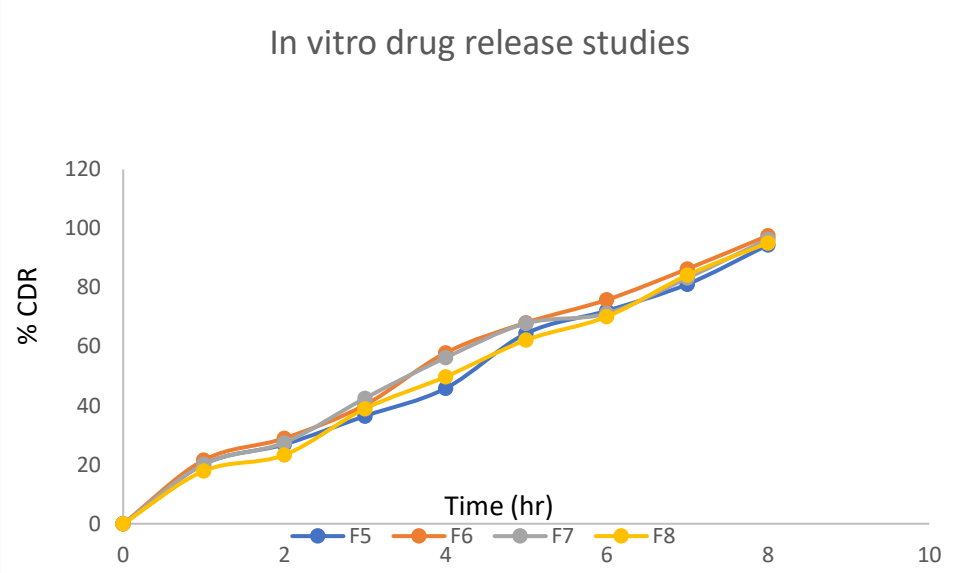


Fig-2: Dissolution Profile of F5 to F8 formulations

Among all formulations, F6 exhibited the most desirable release profile, with a gradual and consistent increase in drug release throughout the dissolution period and the highest cumulative release at 8 hours. The optimized release pattern may be attributed to the appropriate concentration of tragacanth, which formed a hydrated gel matrix capable of regulating drug diffusion while allowing complete release over the intended duration. Formulations containing higher concentrations of Xanthan gum or tragacanth generally exhibited a more controlled release due to increased gel strength and diffusion path length.

Kinetic modelling of drug release

Zero order kinetics

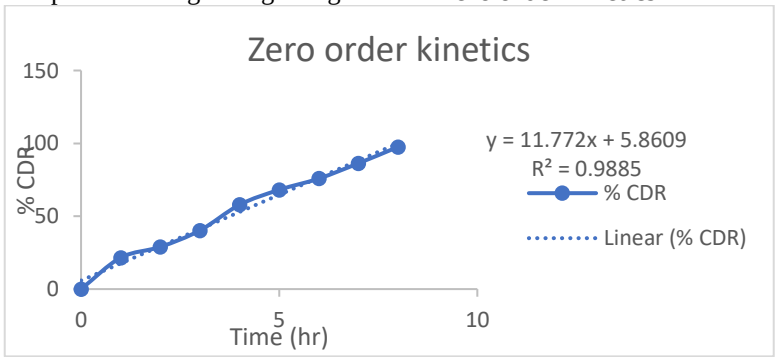


Fig-3: Zero order kinetics of optimized formulation

First order kinetics

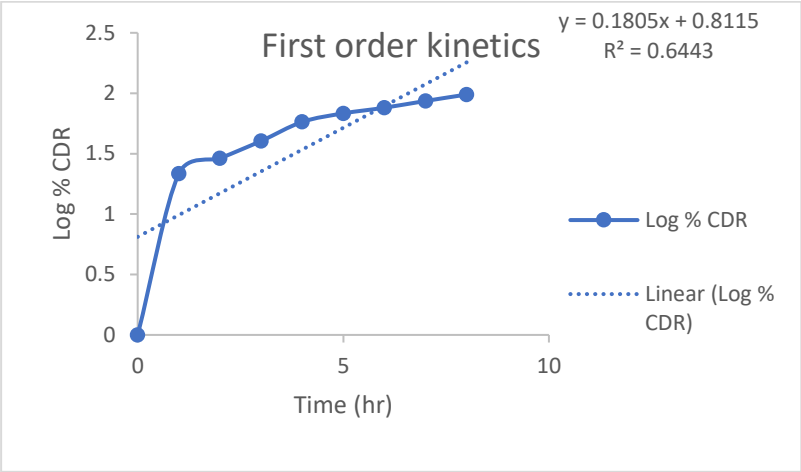


Fig-4: First order kinetics of optimized formulation

Higuchi model

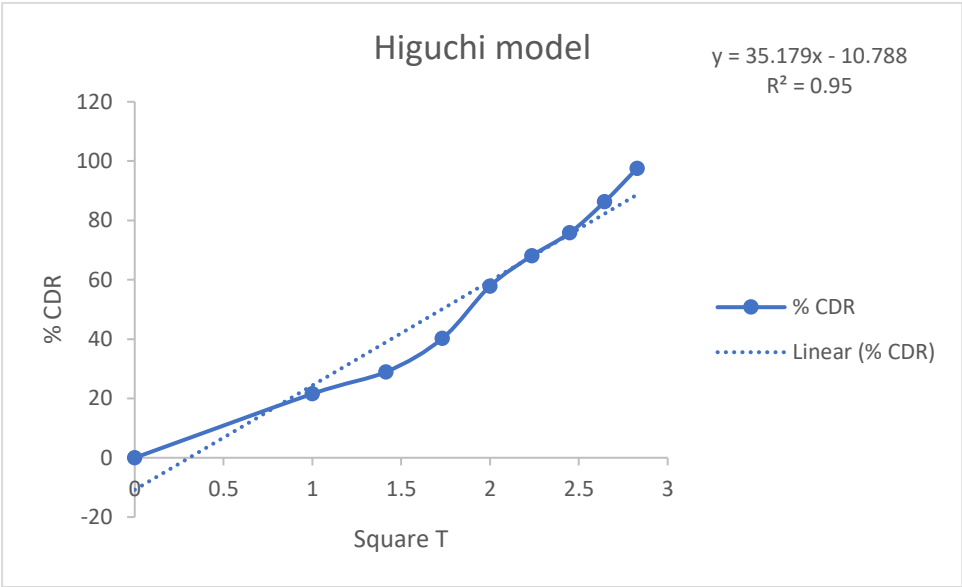


Fig-5: Higuchi model of optimized formulation

Korsmeyer peppas

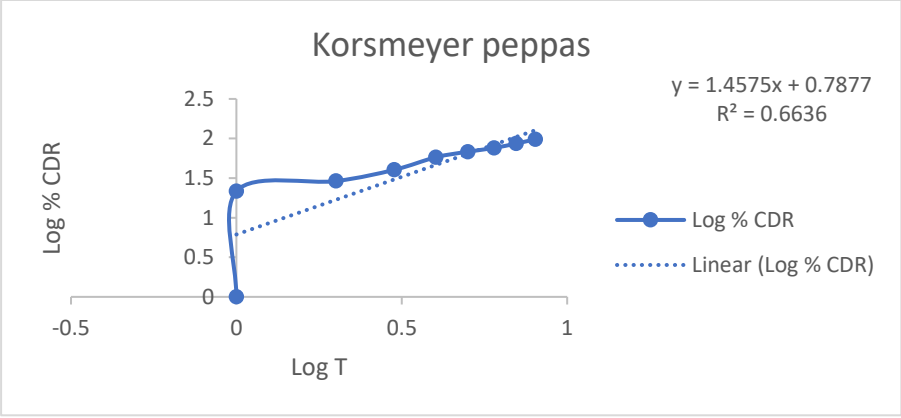


Fig-6: Korsmeyer peppas of optimized formulation

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix and Peppas.

Regression values are higher with Zero order release kinetics. Therefore, all the Brivaracetam tablets follows Zero order release kinetics.

Discussion

The highest regression coefficient obtained with the Zero-order model confirms that the optimized formulation F6 follows Zero-order release kinetics. The high correlation with the Higuchi model further indicates that diffusion through the hydrated polymer matrix significantly contributed to drug release. Overall, the results suggest that the optimized sustained-release tablets provide a controlled and nearly constant release of Brivaracetam over the study period, making the formulation suitable for prolonged drug delivery.

Stability Study

Table-4: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	**25^{0}C/60%RH % Release**	97.58	96.37	95.48	94.88	**Not less than 85 %**
F-6	**30^{0}C/75% RH % Release**	97.58	96.25	95.22	94.57	**Not less than 85 %**
F-6	**40^{0}C/75% RH % Release**	97.58	96.30	95.13	94.53	**Not less than 85 %**

Discussion

Overall, the stability study confirms that the optimized Brivaracetam sustained-release tablet (F6) is stable for at least three months under the tested ICH storage conditions. The formulation maintained its physical integrity and drug release profile throughout the study, indicating that it is suitable for storage and has the potential for an acceptable shelf life.

CONCLUSION:

The present investigation successfully demonstrated the formulation of Brivaracetam sustained-release matrix tablets using the wet granulation technique. Sodium alginate and tragacanth effectively functioned as release-retarding polymers, producing tablets with satisfactory pharmaceutical characteristics and sustained drug release behavior. Among all formulations, F6 was identified as the optimized formulation, as it provided the most desirable balance between tablet quality and sustained drug release. The formulation released 97.58% of Brivaracetam over 8 hours, followed Zero-order release kinetics, and exhibited a strong correlation with the Higuchi diffusion model, indicating controlled drug release through the hydrated polymer matrix. The stability study confirmed that the optimized formulation remained stable under long-term, intermediate, and accelerated storage conditions without significant changes in dissolution behavior or physical properties. Although the optimized formulation demonstrated promising sustained-release performance, the drug content values obtained during evaluation were below the pharmacopoeial acceptance range (95–105%). This indicates that further optimization of the formulation process and analytical method is required to improve content uniformity before the formulation can be considered for large-scale manufacturing. Overall, the study concludes that Brivaracetam sustained-release tablets prepared by wet granulation using tragacanth as the matrix-forming polymer represent a promising oral sustained-release dosage form capable of providing controlled drug release, improved patient compliance, and the potential to reduce dosing frequency.

REFERENCES:

1. Mathew AV, Rampal V, Jose A, et al. Brivaracetam: a novel antiepileptic drug for the treatment of partial-onset seizures. Journal of Pharmacy and Bioallied Sciences. 2016;8(1):1-6.
2. Ben-Menachem E. Brivaracetam: a novel antiepileptic drug with a unique mechanism of action. Epilepsy Research. 2010;89(1):1-7.
3. Kenda BM, Matagne AC, Talaga PE, et al. Discovery of brivaracetam, a selective high-affinity ligand for synaptic vesicle protein 2A. Journal of Medicinal Chemistry. 2004;47(21):5308-5319.
4. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. Nature Reviews Neuroscience. 2004;5(7):553-564.
5. Gillard M, Fuks B, Michel P, et al. Binding characteristics of brivaracetam to synaptic vesicle protein 2A and its anticonvulsant properties. Epilepsia. 2011;52(12):2321-2330.
6. Klein P, Schiemann J, Sperling MR, et al. Brivaracetam for the treatment of uncontrolled partial-onset seizures in epilepsy. Neurology. 2015;85(11):945-952.
7. Biton V, Berkovic SF, Abou-Khalil B, et al. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a randomized, double-blind, placebo-controlled trial. Epilepsia. 2014;55(1):57-66.
8. Ben-Menachem E, French JA, Kwan P, et al. Efficacy and safety of brivaracetam for partial-onset seizures: a systematic review. Epilepsy & Behavior. 2016;62:56-62.
9. Kwan P, Brodie MJ. Early identification of refractory epilepsy. New England Journal of Medicine. 2000;342(5):314-319.
10. Vongluecha P, Pattanawongsa A, Suksiriworapong J, et al. Oral sustained-release

drug delivery systems: formulation approaches and evaluation. Drug Development and Industrial Pharmacy. 2018;44(8):1259-1271.
11. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. Pharmaceutical Science & Technology Today. 2000;3(6):198-204.
12. Colombo P. Swelling-controlled release in hydrogel matrices for oral route. Advanced Drug Delivery Reviews. 1993;11(1-2):37-57.
13. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews. 2012;64:163-174.
14. Colombo P, Bettini R, Massimo G, Catellani PL, Santi P, Peppas NA. Drug diffusion front movement is important in drug release control from HPMC matrices. Journal of Pharmaceutical Science. 1995;84(8):991-997.
15. Nokhodchi A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery. Journal of Controlled Release. 2012;163(2):121-134.
16. Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. Journal of Controlled Release. 2011;154(1):2-19.