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Formulation And Evaluation Of Antiepileptic Medicated Jelly

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Abstract:
This study focuses on the formulation and evaluation of Brivaracetam-loaded medicated jelly designed for pediatric patients to improve drug delivery. The formulation was optimized to ensure consistent drug content, with each jelly unit containing 25 mg of Brivaracetam, and a final drug load of 491 mg per Petri plate accounting for practical losses. The physical evaluation revealed favorable characteristics such as uniform appearance, soft texture, and minimal stickiness, with slight grittiness in a few batches that may impact patient acceptability. The pH of the formulations (6.45–7.12) was compatible with oral mucosa. Syneresis studies showed minor syneresis in some batches, indicating stability and potential for optimization. Increased viscosity was observed with higher concentrations of gelatin, sodium alginate, and pectin, improving texture and drug release control. In-vitro dissolution studies will provide insights into the drug release kinetics, further validating the formulation's potential for controlled, effective drug delivery. This research lays the foundation for optimizing and scaling Brivaracetam-loaded medicated jelly formulations to meet the needs of pediatric patients.
Keywords: Brivaracetam, medicated jelly, viscosity, syneresis, oral mucosa, drug release, dissolution studies, drug stability etc.

Introduction:

Epilepsy is a chronic neurological disorder that affects millions of individuals worldwide, characterized by recurrent, unprovoked seizures. It is estimated that approximately 50 million people globally live with epilepsy, making it one of the most common neurological conditions.[1] The treatment of epilepsy primarily revolves around antiepileptic drugs (AEDs) aimed at controlling seizure activity and improving the quality of life of individuals living with this condition. However, despite the variety of AEDs available, patient adherence remains a major challenge in epilepsy management, particularly for populations that experience difficulty swallowing conventional oral dosage forms such as tablets and capsules. This issue is most pronounced in pediatric, geriatric, and special needs patients, who may struggle with pill swallowing or exhibit poor compliance due to the taste or complexity of conventional dosage forms.[2]

The need for more patient-friendly alternatives to traditional oral medications has led to the development of innovative drug delivery systems. Among these, medicated jellies have gained attention due to their ease of administration, precise dosing, and potential to improve patient adherence.[3] Medicated jellies are particularly useful for individuals who have difficulty swallowing solid dosage forms, as they offer a palatable and easy-to-swallow option. These formulations are typically designed with a thermoreversible gel matrix, which remains solid at room temperature but melts at body temperature, allowing for easy ingestion and controlled drug release. Such a system could offer a solution to the challenges of poor drug adherence, especially in pediatric epilepsy patients, who require more flexible dosing schedules and formulations that are both effective and easy to administer.[4]

One promising drug for epilepsy treatment is **Brivaracetam**, a newer second-generation AED that has shown high efficacy and a favorable safety profile in treating partial onset seizures, both in adults and children.[5] Brivaracetam is a selective synaptic vesicle protein 2A (SV2A) ligand, and its mechanism of action is thought to modulate neurotransmitter release and reduce neuronal excitability, making it effective in controlling seizure activity. Unlike older AEDs, Brivaracetam has fewer drug interactions, which makes it an ideal choice for patients who are on polytherapy or have complex comorbid conditions. It is also well-tolerated, with fewer adverse effects such as sedation, weight gain, or cognitive impairment, which are common side effects of traditional AEDs.[6]

However, despite these advantages, Brivaracetam's oral solid dosage forms (tablets and oral solutions) may not be suitable for all patients, particularly those with difficulty swallowing or those who require accurate, flexible dosing. This challenge has led to the exploration of alternative formulations, including medicated jellies, which can improve the pharmacological management of epilepsy, especially in pediatric populations.[7]

The development of a Brivaracetam-loaded medicated jelly provides a novel approach to overcoming the limitations associated with traditional tablet and capsule forms. Medicated jellies can offer controlled drug release, which ensures that Brivaracetam is gradually released over time, maintaining therapeutic plasma levels and reducing the frequency of dosing. This is especially important for preventing breakthrough seizures in patients with epilepsy, who require stable and consistent drug levels. Additionally, medicated jellies have the potential to improve bioavailability and enhance the stability of the active drug, while also being easy to administer, which is crucial for improving patient adherence and overall therapeutic outcomes.

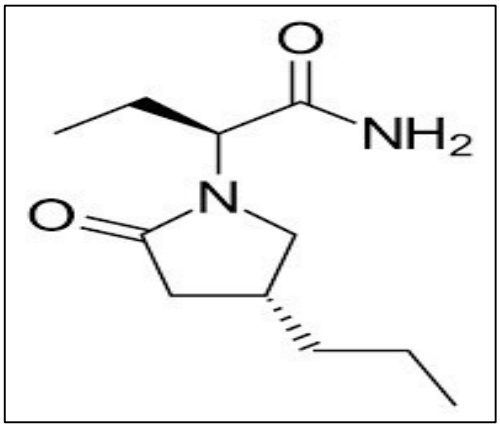

Figure 1: Structure of Brivaracetam

The formulation of an antiepileptic medicated jelly requires careful consideration of various physicochemical properties to ensure the stability, texture, and release characteristics of the drug. These include factors such as pH, viscosity, gel strength, and syneresis, all of which affect the ease of administration and the effectiveness of the formulation. Stability studies are also vital to ensure the jelly maintains its integrity over time, with minimal degradation of the active ingredient. Moreover, sensory evaluation plays an essential role in ensuring that the formulation is palatable, particularly for pediatric patients, who may be more sensitive to taste and texture.[8-10]

In conclusion, the formulation and evaluation of Brivaracetam-loaded medicated jelly represents a significant advancement in the management of epilepsy, providing a novel, patient-friendly alternative to conventional oral dosage forms. This formulation not only addresses issues related to drug adherence but also offers controlled, sustained drug release, which may improve therapeutic outcomes for individuals with epilepsy. By optimizing the physical and chemical characteristics of the jelly, the study aims to enhance the overall efficacy and safety of epilepsy treatment, ultimately contributing to better patient quality of life.

Material and Methods:

Material:

Brivaracetam (API) was obtained from Swapnroop Drugs and Pharmaceuticals, located in Shendra MIDC, Aurangabad, Maharashtra, India, a supplier compliant with GMP standards. To mask the bitter taste of the API, β-Cyclodextrin was employed as a complexing agent. The gel matrix was prepared using gelatin, sodium alginate, and pectin, which were sourced from Himedia Laboratories, Mumbai, India. Glycerin (plasticizer), methylparaben, and propylparaben (preservatives) were procured from SD Fine Chemicals Ltd., Mumbai, India. Citric acid and sodium hydroxide (for pH adjustment) were obtained from Loba Chemie, Mumbai, India. Distilled water was used as the solvent. All excipients were of analytical grade to ensure the formulation's quality and consistency.

Formulation Design of Brivaracetam Loaded Medicated Jelly

In the formulation design of a Brivaracetam-loaded medicated jelly, the dosage was carefully calculated to ensure accurate drug delivery. Each jelly unit was designed to be 4 cm^2 in size (2 cm × 2 cm) containing 25 mg of Brivaracetam. Utilizing a standard Petri plate with a diameter of 10 cm and an area of 78.54 cm^2, it was determined that approximately 19.63 jelly units could be formed per plate. Therefore, to achieve the desired drug content across all jelly units, the total drug load required per Petri plate was calculated as 490.75 mg. To compensate for any practical losses during formulation, the final amount of Brivaracetam used was rounded to 491 mg. This calculation ensured uniform drug distribution and consistency across the jelly dosage forms.[11-15]

Calculation of total drug load:

- Area of 1 jelly = 4 cm^2
- Desired drug concentration in 1 jelly of size 4 cm^2 = 25 mg
- Diameter of Petri plate: 10 cm
- Area of petri plate = 78.54 sq.cm
- No. of 2 cm x 2 cm area jelly to be made in a petri plate = 78.54 / 4 = 19.63
- Each jelly contains 25 mg drug,
- Drug to be taken per petri plate = 19.63 x 25= 490.75 mg.

Formulation of Medicated Jelly (Brivaracetam):

Brivaracetam-loaded medicated jellies were prepared using the heating and congealing method. A sugar syrup base was formed by dissolving 60 g of sugar in 100 ml water and heating at 80°C for 30 minutes with continuous stirring. The gelling polymer was then added and dispersed at 90°C, followed by 20 minutes of magnetic stirring to ensure proper hydration. Once the polymer dissolved completely, citric acid and propylene glycol were added to adjust pH and improve jelly texture. After brief boiling, preservatives, color, and flavor were incorporated. The accurately weighed drug was dissolved in a small volume of distilled water, added to the mix, and stirred well. The final solution was poured into molds, covered, and left to cool and set undisturbed.[16-20]

Table 1: Formulation Development of Briveracetam Jelly

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12

Drug : β-CD Complex (Eq. wt.)	25	25	25	25	25	25	25	25	25	25	25	25
Gelatin	2	3	4	-	-	-	-	-	-	1	1.5	1
Sodium Alginate	-	-	-	2	3	4	-	-	-	1	1.5	-
Pectin	-	-	-	-	-	-	2	3	4	-	-	1
Citric acid	1	1	1	1	1	1	1	1	1	1	1	1
Sucrose	60	60	60	60	60	60	60	60	60	60	60	60
Methyl Paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Propyl Paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Propyleneglycol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water	40	40	40	40	40	40	40	40	40	40	40	40
Coloring Agent	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Flavoring Agent	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

Evaluation of Brivaracetam-Loaded Medicated Jelly

To ensure the quality, stability, and therapeutic efficiency of the formulated pediatric jelly, various evaluation parameters were performed. These assessments aimed to analyze the physical, chemical, and release characteristics of the Brivaracetam-loaded medicated jelly.[21-26]

Physical Observation

The physical appearance of the medicated jelly was examined to ensure patient acceptability, especially for pediatric use. The clarity, color uniformity, texture, and consistency were evaluated visually. Texture was assessed by gently rubbing a portion of the jelly between the fingers to detect any stickiness or grittiness, which could affect mouthfeel and compliance in children. A smooth, non-gritty, and non-sticky jelly was considered ideal.

pH Determination

The pH of the jelly formulations was measured to ensure compatibility with the oral mucosa and to prevent any irritation upon administration. For the test, 0.5 g of jelly was accurately weighed and dispersed in 50 ml of distilled water to prepare a 1% w/v solution. The pH of this dispersion was recorded using a calibrated digital pH meter at room temperature (25 ± 2°C). An acceptable pH range for oral formulations typically lies between 4.0 and 7.0.

Syneresis Study

Syneresis refers to the expulsion of water from a gel matrix during storage, indicating instability of the formulation. All prepared jellies were stored under two different temperature conditions: room temperature (25 ± 5°C) and refrigerated conditions (8 ± 1°C). The formulations were monitored over time for any signs of water separation or shrinkage. Any jelly showing significant syneresis was considered unstable and excluded from further evaluation.

Viscosity Measurement

Viscosity is a critical parameter that influences the mouthfeel, pourability, and consistency of the jelly. It also affects the drug release profile. The viscosity of the jelly formulations was determined using a Brookfield viscometer, employing spindle no. 7. Measurements were taken at a constant speed of 50 revolutions per minute (RPM) for 2 minutes. The results helped in selecting formulations with optimal rheological properties for ease of administration and controlled drug release.

Drug Content Uniformity (%)

The drug content of each formulation was evaluated to ensure dose uniformity. A known amount of jelly equivalent to 10 mg of Brivaracetam was weighed and crushed in a mortar. The crushed sample was transferred into a 100 ml volumetric flask containing 50 ml of 0.1 N hydrochloric acid. The solution was sonicated for 15 minutes to extract the drug completely, diluted to 100 ml, and filtered through Whatman filter paper. The absorbance of the resulting solution was measured at 217 nm using a UV-Visible spectrophotometer. The drug content was calculated and expressed as a percentage of the theoretical amount.

***In-Vitro* Dissolution Study**

The release profile of Brivaracetam from the medicated jelly was determined using the USP Type II (paddle) dissolution apparatus. Each test was conducted in 900 ml of 0.1 N HCl as the dissolution medium, maintained at 37 ± 0.5°C to simulate gastric conditions. The paddle speed was set at 50 RPM. At predefined time intervals (10, 20, 30, 40, 50, and 60 minutes), 5 ml samples were withdrawn and immediately replaced with an equal volume of fresh medium to maintain sink conditions. The withdrawn samples were filtered, appropriately diluted, and analyzed spectrophotometrically at 217 nm. The cumulative percentage of drug released over time was calculated to evaluate the dissolution efficiency and predict in vivo performance.

Results and discussion:

EVALUATION OF JELLY

Physical observation:

The medicated jelly was examined for physical appearance in terms of clarity, appearance, colour, texture and consistency. Texture of the medicated jelly in terms of stickiness and grittiness was evaluated by visual inspection of the product after mildly rubbing the jelly sample between two fingers.

Table 2: Physical observation of Prepared Brivaracetam Jelly

Batch No.	Appearance	Colour	Consistency	Stickiness	Grittiness
F1	Opaque	Yellowish	Soft	Sticky	Slightly Gritty
F2	Opaque	Yellowish	Soft	Sticky	Non Gritty
F3	Opaque	Yellowish	Stiff	Non Sticky	Non Gritty
F4	Opaque	Yellowish	Soft	Sticky	Non Gritty
F5	Opaque	Yellowish	Soft	Slightly Sticky	Non Gritty
F6	Opaque	Yellowish	Stiff	Non Sticky	Non Gritty
F7	Opaque	Yellowish	Soft	Sticky	Non Gritty
F8	Opaque	Yellowish	Soft	Slightly Sticky	Non Gritty
F9	Opaque	Yellowish	Stiff	Slightly Sticky	Non Gritty
F10	Opaque	Yellowish	Stiff	Non Sticky	Non Gritty
F11	Opaque	Yellowish	Stiff	Non Sticky	Non Gritty
F12	Opaque	Yellowish	Stiff	Non Sticky	Non Gritty

The physical characteristics of the formulated jelly batches were assessed based on appearance, consistency, stickiness, and grittiness. All batches showed a uniform opaque yellowish color. Batches F1, F2, F4, F5, F7, and F8 had a soft consistency, favorable for ease of administration, while F3, F6, F9, F10, F11, and F12 were stiffer, potentially offering better stability. Sticky textures were noted in batches F1, F2, F4, and F7, which may affect handling and mouthfeel, whereas F5, F8, and F9 were slightly sticky and more acceptable. Non-sticky textures were observed in F3, F6, F10, F11, and F12, ideal for patient compliance. All batches were non-gritty except F1, which showed slight grittiness, a less desirable trait due to its impact on mouthfeel.

pH:

The pH of prepared jellies was measured using a digital pH meter at room temperature (25°C). For this purpose, 0.5 g of jelly was dispersed in 50 ml of distilled water to make a 1% solution and the reading was noted.

Table 3: Determination of pH of the Brivaracetam Jelly

Batch No.	pH
F1	6.52
F2	6.78
F3	6.66
F4	6.72
F5	6.56

F6	6.88
F7	6.90
F8	6.45
F9	7.08
F10	7.12
F11	7.10
F12	6.98

The pH of a formulation plays a crucial role in its **stability, drug solubility, and patient acceptability**. An ideal pH should be **compatible with physiological conditions** (typically 6.5-7.5) to ensure minimal irritation and optimal drug performance. The pH values of different batches ranged from **6.45 to 7.12**, indicating that all formulations fall within an acceptable range for oral administration.

Syneresis

Syneresis is the separation of liquid from a gel or semi-solid over time, indicating potential instability and affecting the texture, consistency, and acceptability of the formulation. All jelly batches were monitored for signs of syneresis at both room temperature (25°C ± 5°C) and refrigerated conditions (8°C ± 1°C).

Table 4: Syneresis of Brivaracetam Jelly

Batch No.	**Syneresis**
F1	No Syneresis
F2	No Syneresis
F3	No Syneresis
F4	Slightly Syneresis
F5	No Syneresis
F6	No Syneresis
F7	Slightly Syneresis
F8	No Syneresis
F9	No Syneresis
F10	No Syneresis
F11	No Syneresis
F12	No Syneresis

Formulation batches F1, F2, F3, F5, F6, F8, F9, F10, F11, and F12 showed no signs of syneresis, indicating stable formulations with well-formed gel matrices. In contrast, batches F4 and F7 exhibited slight syneresis, suggesting

minor phase separation, possibly due to lower gelling agent concentration, insufficient cross-linking, or excess water content. Although minimal, this may impact the formulation's physical stability and shelf life. Overall, the majority of the batches demonstrated good stability, making them promising candidates for further development.

Determination of Viscosity

The viscosity of the jelly formulations was carried out by using Brookfield viscometer using a non-Newtonian spindle no. 7 for the fixed time of 2 min at 50 rpm.

Table 5: Viscosity of Brivaracetam Jelley

Batch No.	Viscosity (cp)
F1	5632
F2	6425
F3	7134
F4	6127
F5	7745
F6	8086
F7	4565
F8	4829
F9	5247
F10	7245
F11	9342
F12	7310

Viscosity is crucial for the jelly's texture, stability, and administration. The study showed that increasing gelatin, sodium alginate, and pectin concentrations led to higher viscosities. Gelatin (2% to 4%) increased viscosity from 5632 cp to 7134 cp, while sodium alginate (2% to 4%) raised it from 6127 cp to 8086 cp. Pectin showed a smaller increase (4565 cp to 5247 cp) across the same range. Combination batches showed higher viscosities, with F11 (gelatin 1.5% + sodium alginate 1.5%) having the highest at 9342 cp, indicating a synergistic effect. These findings suggest that polymer combinations enhance viscosity more effectively than individual polymers.

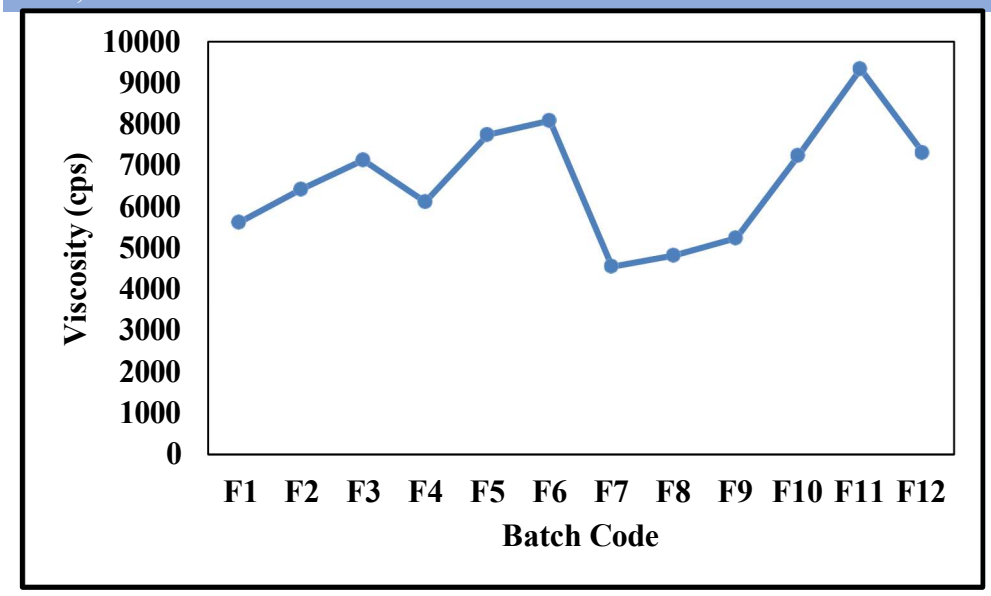

Figure 2: Viscosity of Brivaracetam Jelley formulation (F1 to F12)

Drug Content (%)

The jelly formulations were accurately weighed, crushed, and a portion equivalent to 10 mg of brivaracetam was dissolved in 0.1 N HCl, sonicated for 15 minutes, and filtered. Drug content was then measured using a UV-Visible spectrophotometer at 217 nm. The results indicated uniform drug distribution across all formulations, meeting pharmacopoeial standards.

Table 6: Drug Content (%) of Brivaracetam Jelly

Batch No.	Drug Content (%)
F1	96.46
F2	97.32
F3	99.14
F4	97.67
F5	98.45
F6	97.40
F7	98.41
F8	97.72
F9	98.26
F10	98.66
F11	99.84
F12	98.20

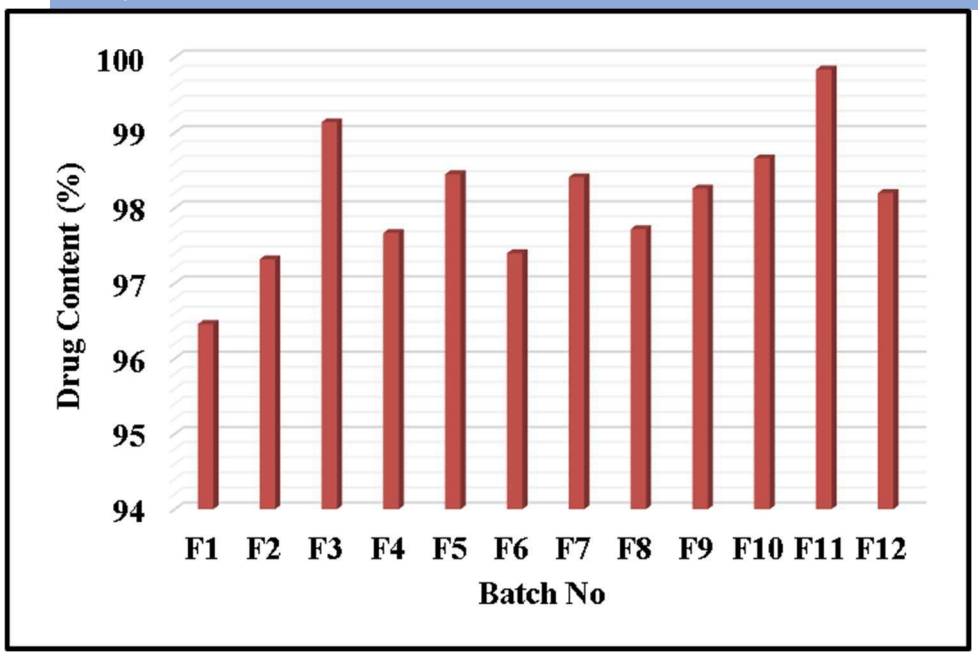

Figure 3: Drug Content (%) of Brivaracetam Jelley (F1 to F12)

***In-Vitro* Dissolution Study**

Dissolution testing evaluated the drug release profile of different jelly formulations containing gelatin, sodium alginate, and pectin. Increasing gelatin concentration (F1 to F3) slowed drug release, with F1 releasing 97.45% by 30 minutes, while F2 and F3 exhibited prolonged release. Sodium alginate (F4 to F6) also slowed release, with F4 showing 97.14% release at 30 minutes. Pectin formulations (F7 to F9) released the drug faster, with F7 reaching 97.68% at 20 minutes. Combination batches (F10 to F12) showed controlled release, with F11 (1.5% gelatin + 1.5% sodium alginate) achieving optimal release (99.78% at 30 minutes). Pectin-based formulations had quicker release but were softer and stickier, making them less suitable for handling. Higher gelatin and sodium alginate concentrations provided slower release, with more stable, less sticky formulations. Batch F11 was identified as the most optimized, offering controlled release and desirable physical properties.

Table 7: *In-vitro* Dissolution Profile of Brivaracetam Jelly (F1 to F12)

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	44.31±1.	40.26±2.	34.46±1.	44.81±1.	23.17±1.	12.56±2.	61.14±2.	45.51±1.	39.2±0.9	41.36±1.	52.03±1.	42.36±2.

	12	87	56	10	78	30	15	77	8	40	12	12
10	56.28±0.76	51.18±0.67	49.16±2.17	56.38±0.62	34.18±0.75	24.34±1.93	77.34±1.55	57.44±1.08	55.16±1.55	50.34±1.34	74.53±2.19	50.15±1.44
15	70.56±1.30	63.41±2.10	60.54±1.83	64.1±0.78	46.32±1.82	37.14±2.06	83.57±1.78	70.1±1.15	62.18±1.80	67.35±1.64	85.18±1.90	60.46±1.88
20	87.82±2.16	73.6±1.04	74.28±1.20	73.46±1.23	59.78±1.34	48.62±1.13	97.68±2.19	87.45±2.28	70.34±2.42	77.3±2.32	96.36±2.83	77.78±1.56
25	97.45±1.88	86.3±2.51	80.24±0.80	86.37±2.04	77.28±1.72	66.31±0.68	-	97.48±2.89	88.51±1.22	89.15±1.55	97.22±1.50	90.34±1.89

30	-	95.18±1.45	90.26±2.18	97.14±2.76	87.4±2.31	79.46±1.54	-	-	96.17±1.66	96.68±1.29	99.78±0.95	98.31±0.27

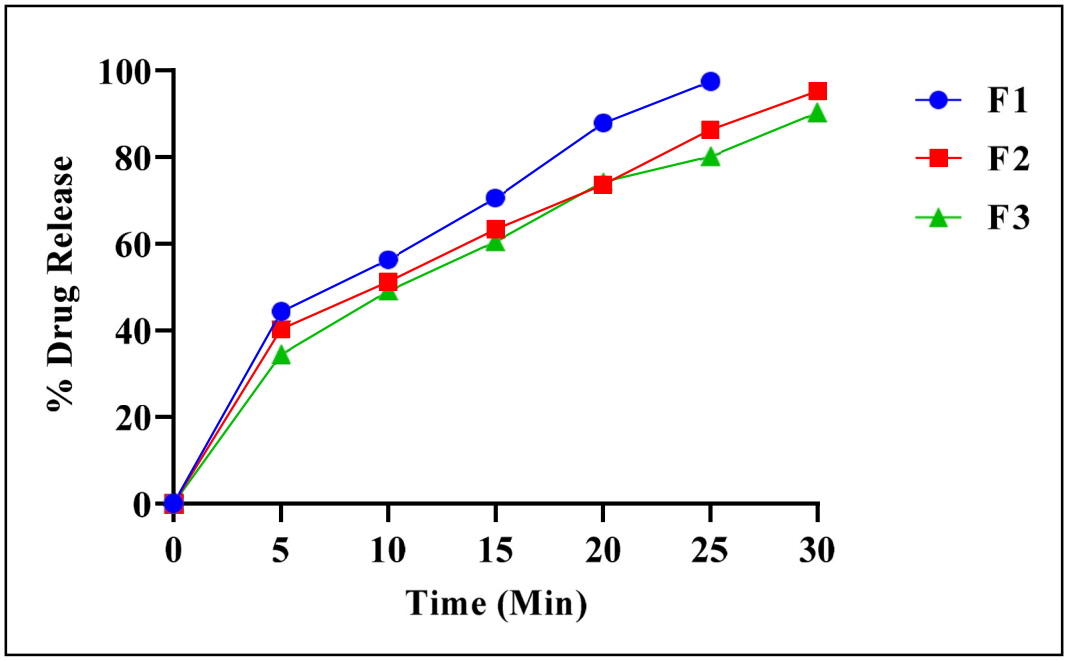

Figure 4: *In-vitro* Dissolution Profile of Batch F1 to F3

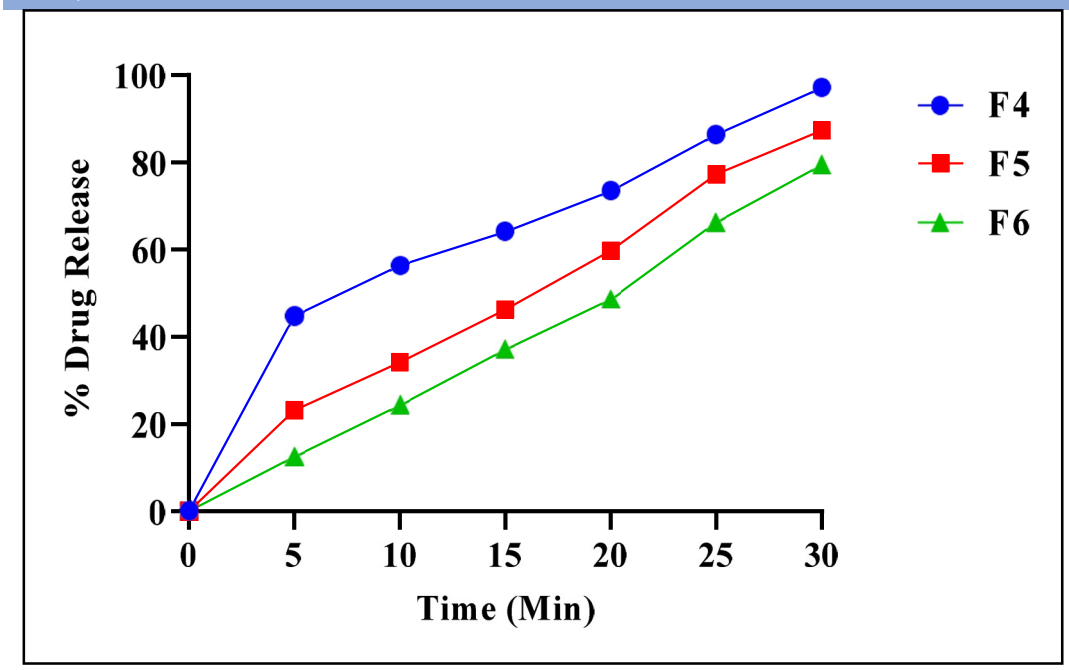

Figure 5: *In-vitro* Dissolution Profile of Batch F4 to F6

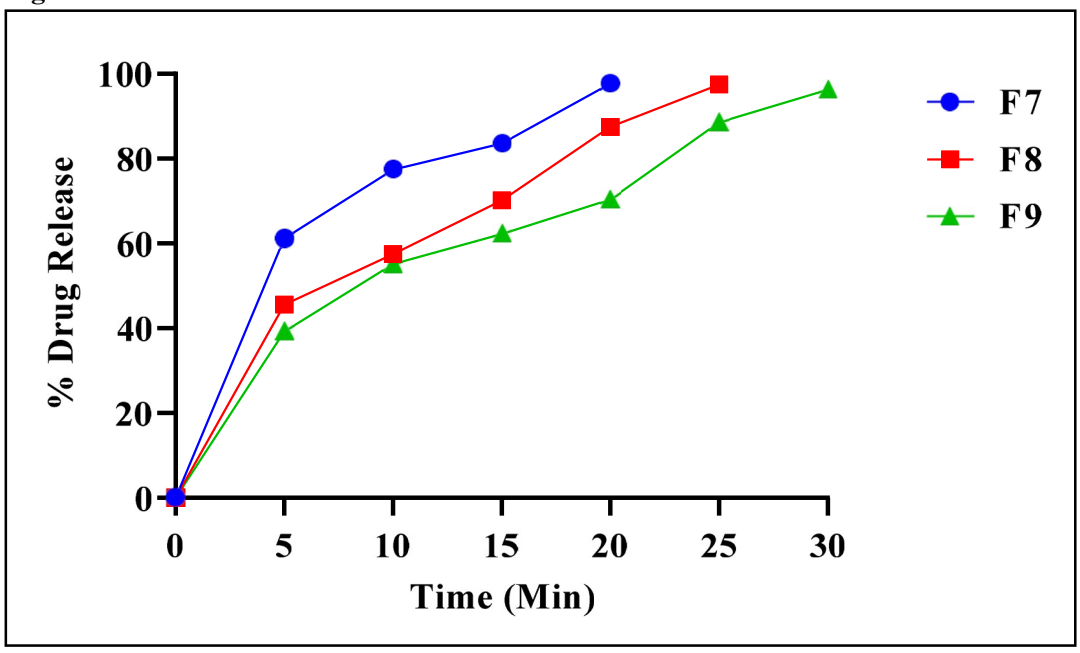

Figure 6: *In-vitro* Dissolution Profile of Batch F7 to F9

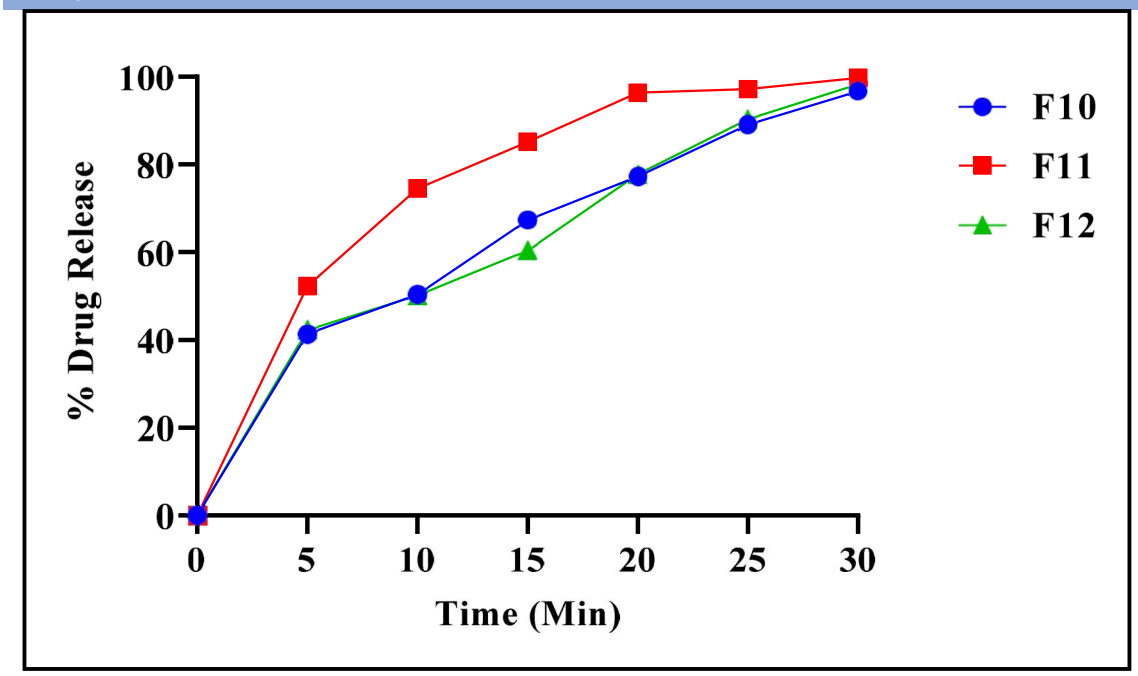

Figure 7: *In-vitro* Dissolution Profile of Batch F10 to F12

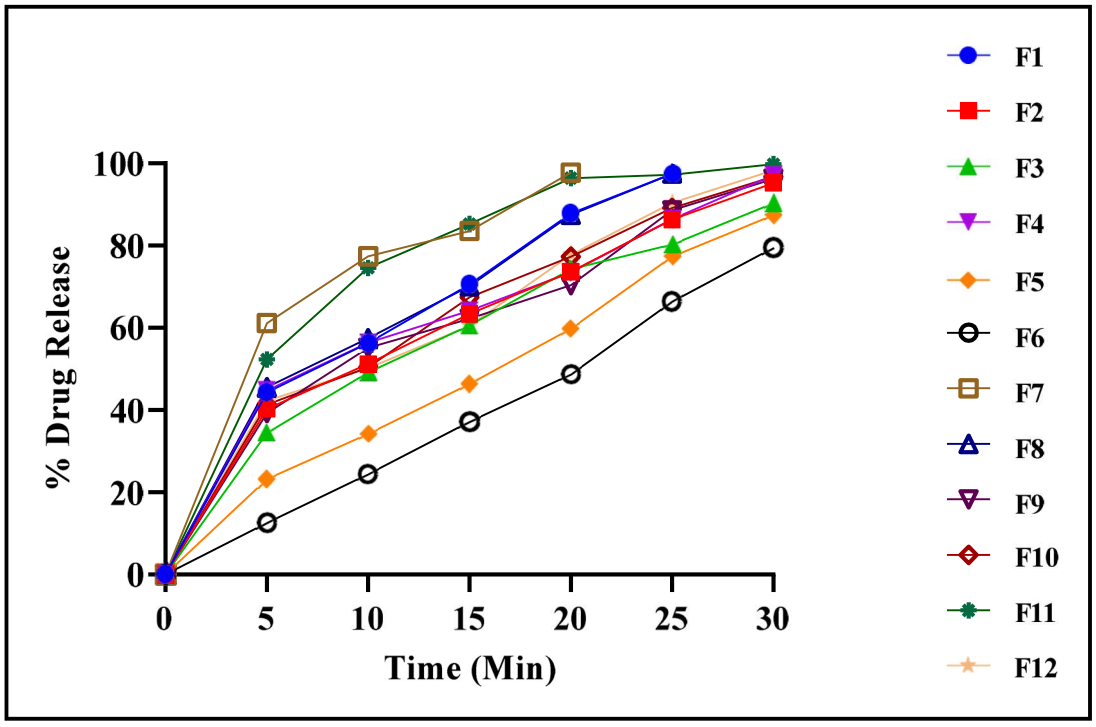

Figure 8: Comparative *In-vitro* Dissolution Profile of Batch F1 to F12

Conclusions:

The Brivaracetam-loaded medicated jelly formulations were successfully developed with a focus on optimizing physical, chemical, and release characteristics to ensure appropriate drug delivery for pediatric patients. The drug was accurately incorporated into the jelly units, with each unit containing 25 mg of Brivaracetam. The formulation design ensured consistency in drug content, and the final drug load per Petri plate was calculated to be 491 mg to

account for practical losses. The evaluation of the physical properties revealed that the majority of batches had favorable characteristics such as uniform appearance, soft texture, and minimal stickiness, with the exception of a few batches showing slight grittiness or stickiness, which could potentially affect patient acceptability. The pH of the formulations was within the acceptable range (6.45 to 7.12), ensuring compatibility with the oral mucosa. Additionally, syneresis studies showed that most batches were stable, with only slight syneresis observed in a couple of batches, which may require optimization in future formulations. Viscosity measurements revealed that higher concentrations of gelatin, sodium alginate, and pectin led to increased viscosity, with a synergistic effect observed in combination formulations. This increase in viscosity is beneficial for controlling the texture and release profile of the jelly. The *in-vitro* dissolution studies will further provide insights into the drug release kinetics, which are essential for predicting the in vivo performance of the formulation. Overall, the formulation development and evaluation of Brivaracetam-loaded medicated jelly showed promising results, with stable, well-formed gel matrices and suitable release characteristics. The study lays the foundation for future optimization and scaling up of these formulations, ensuring that they meet the needs of pediatric patients for controlled, effective drug delivery.

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Conflict of Interests:

The authors declare that there is no conflict of interest regarding the publication of this research.

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