RESEARCH ARTICLE

Formulation and Characterization of Gabapentin-Loaded Bigel For Transpinal Delivery to Brain

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Received: 12th February, 2024; Revised: 21st March, 2024; Accepted: 27th May, 2024; Available Online: 25th June, 2024

ABSTRACT

In this research, the focus was on the design and evaluation of novel two-phase systems known as bigels (BGs) for the transpinal (TS) drug delivery of gabapentin. BGs combine the advantages of hydrogels and organogels while mitigating the drawbacks of individual gels. The formulation involved preparing hydrogels and organogels using carbopol 940 in varying concentrations, which were later combined in a 1:1 ratio to produce BGs. The Fourier-transform infrared spectroscopy (FTIR) analysis indicated the interaction between the drug and polymer was nil. The formulated BG formulations underwent comprehensive characterization, including assessments of physical appearance, pH, viscosity, swelling index, spreadability, drug content, *in-vitro* release, *ex-vivo* permeation, skin irritation, and antiepileptic activity. Formulation B5 emerged as the optimized formulation based on various evaluation parameters. Skin irritation studies demonstrated compatibility with the skin, showing no adverse reactions. In antiepileptic activity, rats receiving gabapentin BG *via* the TS route exhibited a significant reduction in convulsion duration compared to control groups that received BG without the drug or free drug solution orally. Conclusively, the study suggests that the developed BGs containing gabapentin, when applied through the TS route on the back of the neck, hold promise for reaching the brain effectively. This method presents a potential avenue for enhanced drug delivery in the control of epilepsy.

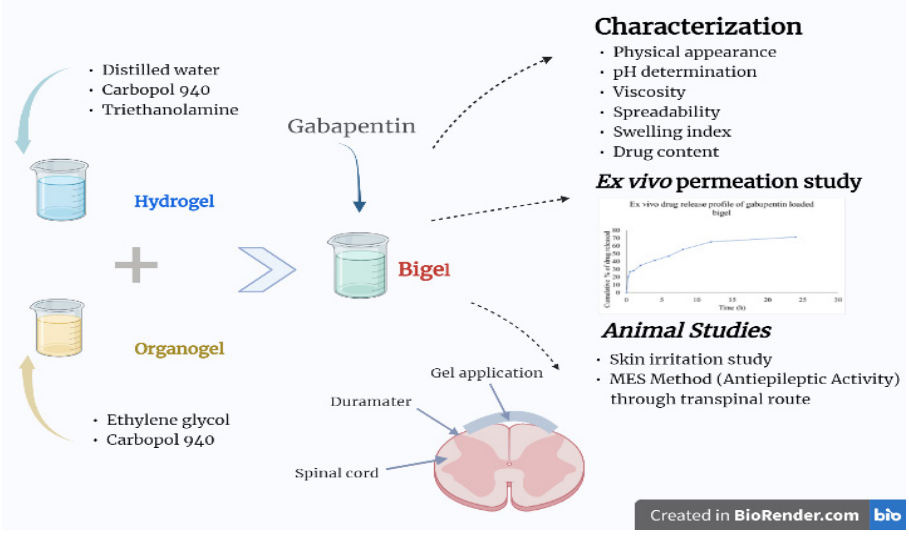
Keywords: Gabapentin, Hydrogel, Organogel, Bigel, Transpinal delivery.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.2.00

How to cite this article: Basavesh, Manjula D, Premakumari KB, Jenita JLJ. Formulation and Characterization of Gabapentin-Loaded Bigel For Transpinal Delivery to Brain. International Journal of Drug Delivery Technology. 2024;14(2):785-791.

Source of support: Nil.

Conflict of interest: None



Graphical Abstract

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INTRODUCTION

Epilepsy is one of the prevailing neurological ailments affecting over 50 million people globally and manifests through recurrent uncontrollable movements.[1] It occurs more in men and peaks in the elderly due to increased stroke, neurological disorders, and tumors. Partial seizures are common in children and adults compared to generalized seizures. Gabapentin, an antiepileptic drug (AED), holds approval for treating peripheral neuropathic pain disorders like vulvodynia, post-herpetic neuralgia, and diabetic peripheral neuropathy.[2] Its role extends beyond epilepsy, highlighting its efficacy in managing diverse neuropathic pain disorders. Understanding the demographic patterns and varied applications of AEDs contributes to comprehensive healthcare strategies for individuals affected by epilepsy and related conditions.[3]

Gabapentin, a biopharmaceutical class III medicine, is a white, crystalline substance with high water solubility and limited permeability, presenting a bitter taste.[4] As an antiepileptic drug, it acts by inhibiting the alpha two subunit of voltage-gated calcium channels. However, its oral bioavailability is relatively poor due to saturable absorption, leading to a short half-life of 4 to 6 hours. Addressing this limitation, alternative formulations like transspinal drug delivery could enhance drug absorption, bypass first-pass metabolism, and maintain steady plasma levels, offering a promising avenue for improved therapeutic outcomes.[5]

Gels, semisolid formulations consisting of solid and liquid phases, play a crucial role in pharmaceuticals.[6] Hydrogels, with water as the continuous phase, offer advantages for topical application, such as simple preparation, non-oily nature, and high patient acceptance.[7] However, they are more suitable for hydrophilic drugs and have limited skin penetration capabilities.[8] On the other hand, organogels, with nonpolar liquids as the continuous phase, dissolve hydrophobic drugs but face challenges in skin removal due to stickiness and oily residues, resulting in reduced patient compliance.[9] Addressing these limitations, BGs emerge as innovative formulations by combining hydrogels and organogels. This integration allows BGs to harness the benefits of both systems, accommodating both hydrophilic and lipophilic drugs. BGs offer advantages such as controlled drug delivery, improved patient compliance, enhanced washability, spreadability, and permeability of drugs.[10] The ability to manipulate drug release rates and provide hydration to the stratum corneum makes BGs promising candidates for topical drug delivery.[11] In the context of TS delivery, BGs present a potential solution. The drug can permeate from the gel through the intervertebral spaces, cross the dura, and reach the cerebrospinal fluid (CSF), eventually reaching the brain.[12] This application underscores the versatility and potential of BGs in overcoming the limitations associated with traditional hydrogels and organogels in drug delivery systems.

This research aims to create gabapentin gel formulations for TS delivery, utilizing hydrogels, organogels, and BGs with diverse polymer ratios, followed by a comprehensive assessment using established metrics.

MATERIALS AND METHODS

Gabapentin was a complimentary sample from Amines Biotech Ltd Gujarat. Carbopol 940, triethanolamine, and methylparaben from SD Fine Chemicals Limited, Mumbai, India. Isopropyl myristate was purchased from Merck Life Science Mumbai. Other materials used were of analytical grades.

Methods

Drug polymer compatibility study

In the current research, the interaction of the drug and the polymer was determined by FTIR. The FTIR was carried out for the KBr pellets of drug gabapentin, polymer carbopol-940 and drug-polymer combination, separately at a wavelength between 4000 to 400cm^{-1}.

Method of preparation of gels

- *Preparation of hydrogel*

In the hydrogel preparation, carbopol 940 served as the polymer, with 0.5, 1, and 1.5% concentrations added to distilled water and left to soak. Continuous blending over a 24-hour period at room temperature (25°C) facilitated the creation of a homogeneous gel. The subsequent addition of triethanolamine not only adjusted the pH to match skin pH but also induced polymer gelation for enhanced hydrogel characteristics.[13]

- *Preparation of organogel*

Organogel formulations were designed by dissolving 2, 3, and 4 of carbopol 940 in polyethylene glycol (PEG). Each Carbopol 940 concentration was individually dissolved in PEG 400, and the resultant mixture was subjected to homogenization using the Ultra-Turrax Ika T25 for five minutes at a speed of 24,000 rpm.[14]

- *Preparation of BG*

Preparation of BG involves combining hydrogel and organogel at a 1:1 w/w ratio, a pivotal phase in the procedure. This mixing process, including hydrogel, organogel, and 0.1% w/w of the drug, was meticulously conducted using a mechanical stirrer

Table 1: The compositions of BG formulations, designed with a fixed 1:1 ratio of hydrogel and organogel, differ based on varying concentrations of carbopol 940

BGs	*% Carbopol 940*		*% Gabapentin in BG*
	In water (hydrogel)	*In PEG 400 (organogel)*	
B1	0.5	2	0.1
B2	0.5	3	0.1
B3	0.5	4	0.1
B4	01	2	0.1
B5	01	3	0.1
B6	01	4	0.1
B7	1.5	2	0.1
B8	1.5	3	0.1
B9	1.5	4	0.1

at 50 rpm to prevent bubble formation.[15] Refer to Table 1 for formulation specifics.

Characterization of BGs

Physical appearance

An assessment of color, homogeneity, and transparency was performed through visual inspection of all the prepared BGs.

pH

The pH of BGs was measured by digital pH meter (Elico, India). About 1-g of BG was measured and mixed with 25 mL of distilled water and subjected for pH determination.

Viscosity

The viscosity of all the BG formulations was measured using a Brookfield viscometer (DVRV/LV-2T) with a T-F spindle at rpm of 50 and at a temperature of 25ºC.[16]

Swelling index

To evaluate the swelling index, one-gram samples of each gel were placed in 5 mL phosphate buffer (pH 5.5) and left for a set of period. Excess buffer was removed and samples were reweighed. Tests were conducted at one and three-hour intervals. The swelling ratio was determined using the specified formula:[17]

Swelling ratio = (Ws – Wo/Wo) X 100

W_S- swollen gel weight

W_0 – initial weight of gel

Spreadability

To test the spreadability of the formulated BGs, two glass plates were employed. On the glass plate, a 1-cm circle was premarked and into that circle 0.5 gm of BG was placed. The glass plate was topped with another glass plate that was similar. The standard weight ranging from 10 to 100 g was applied to the upper plate until no further spreading was observed. The increased diameter of the spreading BG was measured.[18]

Drug Content Determination

Determination of drug content[19] in the BG involved the use of a UV spectrophotometer. The gel formulation (1 g) was mixed in 20 mL of pH 5.5 phosphate buffer and shaken for 24 hours. Subsequently, the final solution was passed through a 0.45 µm pore size membrane filter, and after dilution with pH 5.5 phosphate buffer, using UV spectrophotometer, the absorbance was measured at 207 nm.

On the basis of preliminary studies of viscosity, swelling index, spreadability and drug content, BG formulations B4, B5 and B6 gave promising results that were suitable for application to skin. Henceforth, these three formulations were selected for further evaluation.

In-vitro release studies of BG formulations

The prepared BGs (B4, B5 and B6) were subjected for *in-vitro* release by Franz diffusion cell. A cellophane membrane (CM) was used as a semipermeable membrane for *in-vitro* diffusion study. The BG formulation was placed on the CM, which was sandwiched between the receptor and donor compartments. The reservoir compartment contained 24 mL of phosphate buffer pH 5.5. The experiment was conducted for 24 hours at a temperature of 37 ± 1°*C* and 100 rpm. At regular intervals of time, samples were pipetted out from the receptor compartment, and absorbance was measured using spectrophotometrically at 207 nm. Every time, the reservoir compartment was replaced with equal volume of pH 5.5 phosphate buffer to maintain sink condition.[20]

Release kinetics

All three BG formulations were subjected to release kinetic studies to understand the drug release mechanism and determine the best fit model release kinetics. The drug release data was analysed by various kinetic models, using zero order, first order, Higuchi model, and Korsmeyer/Peppas model.[21]

Ex vivo skin permeation study

Since B5 formulation showed optimum controlled drug release of drug when compared to B4 and B6, henceforth, this formulation (B5) was further subjected for animal experiments. The animal experiment was performed after the endorsement of the Institutional Animal Ethics Committee (IAEC) bearing registration number 2076/PO/RcBiBt/S/19/CPCSEA.

The study involved the sacrifice of male albino Wistar rats (150 200 g) through spinal dislocation, followed by the surgical removal of abdominal skin. This skin was then subjected to a 6 to 8 hours immersion in a 2 M sodium bromide solution to effectively detach the epidermis and dermis from each other. Following this, the skin was positioned with the stratum corneum (SC) oriented towards the donor compartment and placed on the Franz diffusion cell, allowing hydration before its use in *ex vivo* permeation studies. pH 5.5 phosphate buffer was used in receptor compartment, while a BG containing the drug dose was applied to the SC side of the donor compartment. Drug permeation was spectrophotometrically measured at 207 nm over 24 hours, with 2 mL aliquots withdrawn at predetermined intervals. To maintain sink conditions, the retracted volume was replenished with a corresponding volume of pre-warmed receiver solution.[22]

Skin Irritation Test

The skin irritation test for B5 formulation was performed on Wistar albino rats. The rats were placed in cages with unrestricted food and water. The rats were sedated with ether anesthetics and had 3 cm^2 of their ventral side shaved. After 24 hours, the rats were used. The animals were categorized in two groups, each containing six animals, one as the control and the other as test group. The optimized gel without the drug was served as the control and the optimized gel containing the drug was used as a test. The rats were under observation for seven days for any symptoms of flushing of the skin, papules, wheals, erythema and edema.[23]

Antiepileptic activity by maximal electroshock (MES) induced convulsion model

Convulsions were induced in this model by applying a 150 mV current for 0.2 seconds near the brain using an electroconvulsiometer. The animals were separated into three

groups of six animals each. Group 1 was applied with BG without the drug which acted as the control; an oral gabapentin solution was given to group 2 and gabapentin loaded BG was applied to the group 3 over the back of neck (TS). The dose of drug given to rats was 50 mg/kg. The electrodes were positioned next to the rat's brain and subjected to 150 mV for 0.2 seconds. The lengths of various convulsion phases lengths were measured and contrasted to the control group.[24]

Statistical Analysis

All statistical calculations were done using GraphPad Prism 9.3.1. The mean and standard deviation for each piece of data were displayed. Tukey's multiple comparison test was conducted following one-way analysis of variance (ANOVA) to compare data groupings. The values were found significant statistically, at $p < 0.05$ and $p < 0.0125$.

RESULTS AND DISCUSSION

Drug Polymer Compatibility Studies

To study the compatibility of the drug (gabapentin) and the polymer utilized (carbopol 940), FTIR studies was carried out. The result revealed no possible interaction between the drug and polymer since there was neither the emergence of a new peak nor the absence of an existing peak, indicating that the polymer had no effect on the drug's performance characteristics and thereby revealing the drug's compatibility with the polymer. The FTIR spectrum of the drug, polymer and drug-polymer mixture is depicted in Figure 1.

Characterization of BG

Physical appearance

Topical administration depends heavily on the physical appearance of the formulations since it affects patient compliance. Visual assessments of all compositions' transparency, color, and homogeneity were made. All of the formulations were observed to be clear/transparent, colorless and homogeneous. The results are as depicted in Table 2.

pH

The pH of the formulated BGs was in the range of 5.5 to 6.2, which was compatible with the skin's pH, indicating no irritation upon application. Different polymer concentrations did not show much effect on pH. The results of pH measurement of BGs is shown in Table 2.

Viscosity

Viscosity is one of the essential parameters to grasp the physical performance, patient adherence and stability of the semisolid formulations. Viscosity testing of BGs was carried out at room temperature of 25°C. It was observed that as the polymer concentration increased in BG formulations, the viscosity also increased. The maximum viscosity was achieved with the B9 formulation that contained a total of 5.5% carbopol. B1, B2 and B3 showed less viscosity (0.5% of carbopol in water) that were not suitable for semisolid formulations and the formulations B7, B8 and B9 were found to have very high viscosity (1.5% carbopol in water) that were also not suitable for application onto skin as it possessed a problem in spreadability. On the other hand, B4, B5 and B6 depicted optimum viscosity with 1% carbopol in water. Among B4, B5 and B6, the viscosity increased in the order as B6 > B5 > B4. The results are as depicted in Table 2.

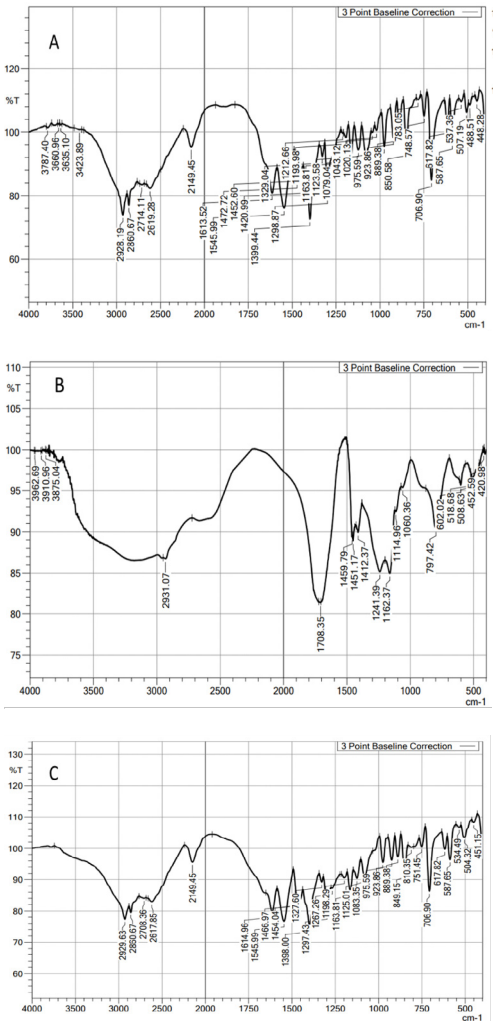


Figure 1: FTIR Spectrum (A) FTIR spectrum of gabapentin (B) FTIR Spectrum of carbopol 940 (C) FTIR spectrum of physical mixture of gabapentin and carbopol

Among the various BG formulations, B5 was subjected for viscosity determination at a varying shear rate up to 500 rpm and the results are as depicted in Figure 2. It was observed that as the rate of shear increased from 0 to 500 s^{-1}, the viscosity of B5 formulation decreased, thereby depicting the BG formulation as shear-thinning system. The behavior is graphically represented in Figure 2.

Spreadability

The spreadability of the BGs was evaluated and the values are shown in Table 2. According to the findings, formulations with optimum viscosity (B4, B5 and B6) demonstrated good spreadability compared to other formulations, as spreadability and viscosity are inversely proportional to each other.

Table 2: Characterization of BG formulations

Formulation code	*Physical appearance*	*pH*	*Viscosity (Cps)*	*Spreadability (cm)*	*Swelling index %*	
					1 hour	*3 hours*
B1	Transparent and homogeneous	5.9 ± 0.09	30458 ± 0.12	6.8 ± 0.35	31.52	51.6
B2		5.8 ± 0.12	31270 ± 0.35	6.5 ± 0.28	35.63	53.1
B3		6.1 ± 0.18	32384 ± 0.42	6.0 ± 0.32	38.11	55.35
B4		5.8 ± 0.21	32938 ± 0.18	6.2 ± 0.12	27.21	32.31
B5		5.6 ± 0.16	33167 ± 0.43	6.3 ± 0.26	29.53	35.63
B6		5.5 ± 0.21	35321 ± 0.51	6.1 ± 0.25	31.27	36.52
B7		6.2 ± 0.13	38616 ± 0.12	5.9 ± 0.32	8.32	12.96
B8		6.1 ± 0.17	39132 ± 0.35	5.7 ± 0.19	10.51	14.24
B9		5.9 ± 0.24	40718 ± 0.41	4.9 ± 0.21	12.54	15.87

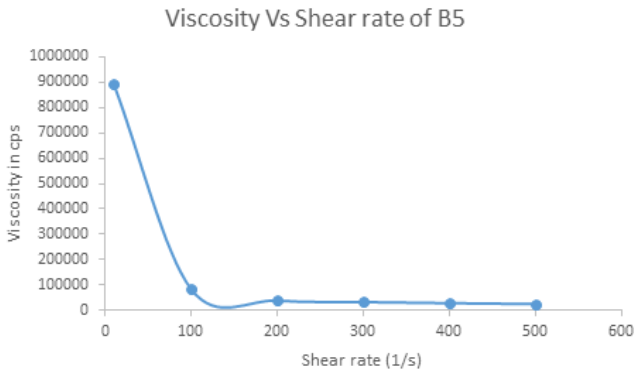


Figure 2: Viscosity *vs* shear rate profile of B5

Swelling index

The swelling index plays a pivotal role in understanding gel drug delivery from gels. Too high a swelling index may lead to rapid drug release and too low may hinder drug diffusion. The formulations B4 to B6 have an optimum swelling index, which makes them ideal BGs. The results are depicted in Table 2.

After the preliminary investigation of the BGs with respect to physical appearance, pH, viscosity and spreadability, the formulations B4, B5 and B6 showed good results, henceforth, these three BG formulations were selected for further evaluation.

Drug Content

The drug content was assessed to confirm that the drug was dispersed uniformly in the BG. The drug content of the BG ranged from 78.46 to 87.46%. The outcomes are depicted in Table 3

In-vitro release of drug

The cumulative drug released from BG formulations ranged from 71.17 to 79.63% over a 24 hour period, depending on the concentration of polymer in the prepared BG. As the concentration of the polymer rose, the gel layer in its rubbery state thickened as the solvent penetrated towards the core. This increased the gel layer thickness, creating a longer diffusion path for drug release. Consequently, the diffusion coefficient decreased, thereby reducing the drug release rate.[25]

Table 3: Drug content of gabapentin-loaded BG

Formulation code	*Drug content (%)*
B4	87.46 ± 0.78
B5	83.55 ± 0.89
B6	78.46 ± 0.91

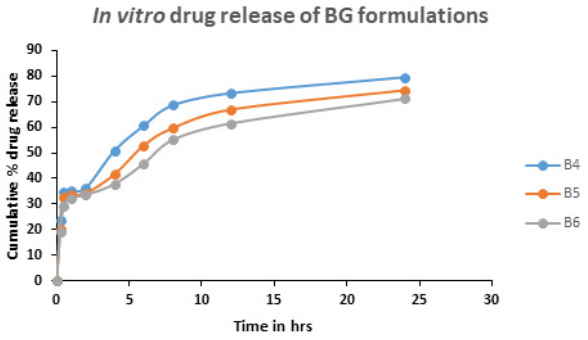


Figure 3: *In-vitro* drug release profile of BG formulations

The findings (Figure 3) indicated that formulated BG was appropriate for sustained and controlled drug delivery. For the *ex-vivo* skin penetration study, the B5 formulation was chosen.

Ex-Vivo skin permeation study

Formulation B5 was further subjected to *ex-vivo* permeation study as the *in-vitro* release study of the same formulation depicted an optimally controlled release of gabapentin at the end of 24 hours. The *ex-vivo* skin penetration profile of gabapentin-loaded BG over rat abdominal skin is depicted in Figure 4. The *in-vitro* release of the drug and the skin penetration profile both displayed similar patterns of release. *Ex-vivo* cumulative drug release from formulation B5 was reported to be71.29% after 24 hours.

Release kinetics

To calculate the release constant (n) and regression coefficient (r^2), the release data was analysed using various kinetic models.

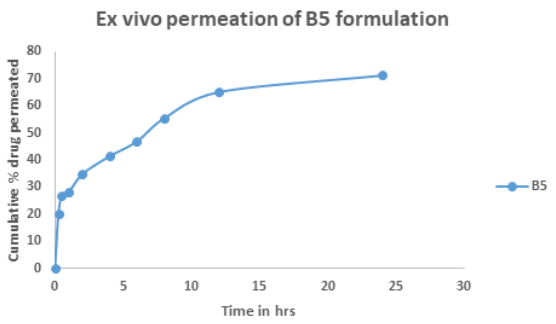


Figure 4: *Ex-vivo* skin permeation study of gabapentin-loaded BG (B5)

The obtained data is depicted in Table 4. The BG from batches B4 to B6 and *ex-vivo* had the highest regression coefficient value, demonstrating the controlled release of a drug, and was thus best matched to the Higuchi model. The n value of the Korsmeyer-Peppas model of B4 to B6 and *ex-vivo* was found to be less than 0.45. This leads to the conclusion that it adheres to the Fickian diffusion model.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) image of BG is shown in Figure 5. The SEM image depicted that the formulated BG (B5) was homogenous in nature.

Animal Studies

Skin irritation test

The animals were observed for signs of skin flushing, papules, wheals, erythema, and edema. For the entire 7-day period, no rat displayed any of the above reactions. It had no adverse effects on the skin.

Antiepileptic activity of B5 BG formulation by maximal electroshock induced convulsion model

The MES-induced convulsion model was used to examine the efficacy of BG formulations in treating epilepsy. In the maximal electroshock model, a high-voltage current of 150 mV for 0.2 seconds was applied near the animal's brain to cause a convulsion. The capacity formulations to halt or postpone the various convulsion phases was regarded as a sign of their anticonvulsant effectiveness. In comparison to the oral route, the BG formulation considerably decreased not only the length of time for each phase but also the average time for each phase of convulsion. The results are presented in Table 5. All

Table 4: Release kinetics of gabapentin loaded BG (B4, B5 and B6 and *ex-vivo*)

Formulation code	*Release kinetics model*			
	Zero-order	*First order*	*Higuchi*	*Korsmeyer Peppas*
	r^2	r^2	r^2	*n*
B4	0.6578	0.0029	0.8872	0.2677
B5	0.7024	0.0001	0.9193	0.2923
B6	0.6973	0.0013	0.9127	0.2800
Ex-vivo	0.7248	0.0007	0.9274	0.2789

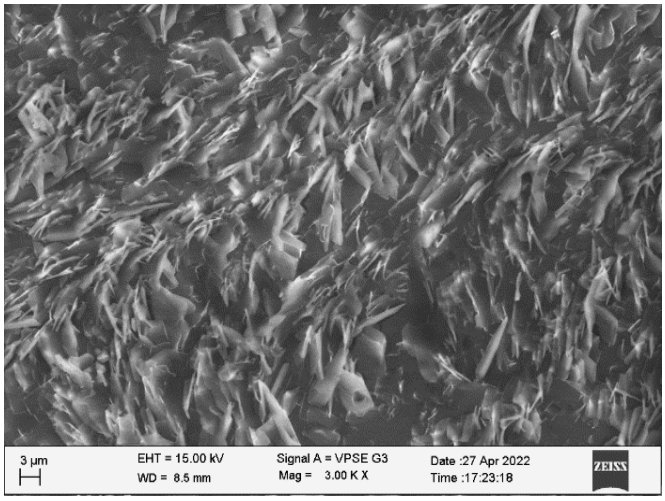
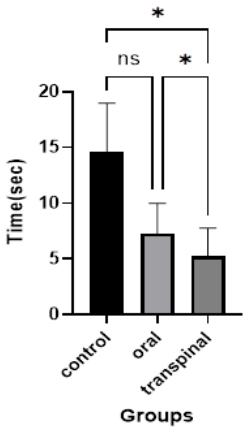


Figure 5: SEM image of BG

Table 5: Antiepileptic activity of B5 BG formulation by MES model

Phases of convulsion	*Control*	*Oral route*	*TS route*
Flexion	18 ± 2.1	11.2 ± 2.1	9 ± 2.2
Tonic extensor	8.2 ± 2	6.1 ± 2.2	4 ± 1.1
Clonic convulsion	17 ± 2.6	5 ± 2.8	4 ± 2.4
Stupor	15 ± 1.1	6.8 ± 1.2	4 ± 1.1
Average time (all phases)	14.5 ± 1.9	7.2 ± 2.1	5.25 ± 1.7
Recovery/death	4/2	6/0	6/0



Note: * p <0.1oral *vs* TS route
p <0.1 control vs TS route

Figure 6: Statistical analysis comparing different groups

statistical calculations were done using GraphPad Prism 9.3.1. The values were found significant statistically, at $p < 0.05$ and $p < 0.0125$, as shown in Figure 6.

CONCLUSION

This study aimed to develop gabapentin-loaded TS BGs using Carbopol 940 polymer and was characterized for pH, viscosity, spreadability, swelling index, drug content, and *in-vitro* drug

release. Batch B5 emerged as the ideal formulation. Subject to *ex-vivo* skin permeation and *in-vivo* study, the selected method consistently produced BGs suitable for transspinal application. Skin irritation studies confirmed compatibility with rat skin. Notably, the TS route of the optimized BG formulation significantly reduced convulsion duration and average time in comparison to the oral route in antiepileptic activity studies in rats. In conclusion, the study indicates promising results for drug delivery through the transspinal route, suggesting its potential applicability for brain-targeting drugs.

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