https://doi.org/10.31925/farmacia.2025.6.21 **ORIGINAL ARTICLE**

DEVELOPMENT OF BIGEL SYSTEMS FOR BUCCAL ADMINISTRATION OF ELETRIPTAN HYDROBROMİDE: A COMPARATIVE FORMULATION STUDY

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Abstract

The present study focused on the development and characterization of hydrogel, oleogel and bigel systems for the buccal delivery of eletriptan hydrobromide (EHBr) as an alternative to oral therapy for acute migraine management. Hydrogel and oleogel formulations were optimised for composition, homogeneity and stability, and then combined in ratios of 30:70 and 40:60 to form bigels. The formulations were evaluated through rheological analyses, including viscosity profiling, linear viscoelastic region (LVR) determination and oscillatory frequency sweeps, which confirmed pseudoplastic and weak gel-like behaviour for all systems. Texture profile analysis assessed mechanical attributes such as hardness, compressibility, adhesiveness, cohesiveness and elasticity, with bigel (40:60) exhibiting superior mechanical strength and mucoadhesive potential. Mucin interaction tests confirmed the enhanced buccal retention of bigel systems compared to single-phase gels. *In vitro* release studies revealed a biphasic profile, where bigel (30:70) showed faster drug release (~70% in 24 h), whereas bigel (40:60) achieved more sustained release (~60% in 24 h) due to its denser oleogel network. By combining the hydrophilic nature of hydrogels with the lipophilic phase of oleogels, bigel formulations demonstrated tuneable mechanical and drug-release properties. Among these, the 40:60 bigel was identified as the most promising candidate for buccal EHBr delivery, offering a patient-friendly, non-oral platform for effective migraine therapy.

Rezumat

Studiul a avut ca obiectiv dezvoltarea și caracterizarea sistemelor de hidrogel, oleogel și bigel pentru administrarea bucală a eletriptanului hidrobromid (EHBr), ca alternativă la terapia orală în managementul migrenei acute. Formulările de hidrogel și oleogel au fost optimizate din punct de vedere al compoziției, omogenității și stabilității, apoi combinate în rapoarte de 30:70 și 40:60 pentru obținerea bigelurilor. Formulările au fost evaluate prin analize reologice, incluzând profilarea vâscozității, determinarea regiunii liniare viscoelastice (LVR) și teste oscilatorii de frecvență, care au confirmat un comportament pseudoplastic și de gel slab pentru toate sistemele. Analiza profilului de textură a evaluat atribute mecanice precum duritatea, compresibilitatea, adezivitatea, coezivitatea și elasticitatea, bigelul (40:60) prezentând o rezistență mecanică superioară și un potențial mucoadeziv crescut. Testele de interacțiune cu mucina au confirmat retenția bucală îmbunătățită a sistemelor bigel comparativ cu gelurile monofazice. Studiile de eliberare in vitro au evidențiat un profil bifazic, în care bigelul (30:70) a prezentat o eliberare mai rapidă a substanței active (~70% în 24 h), în timp ce bigelul (40:60) a asigurat o eliberare mai susținută (~60% în 24 h), datorită rețelei oleogelice mai dense. Prin combinarea naturii hidrofile a hidrogelurilor cu faza lipofilă a oleogelurilor, formulările de tip bigel au demonstrat proprietăți mecanice și de eliberare a medicamentului ajustabile. Dintre acestea, bigelul 40:60 a fost identificat ca fiind cel mai promițător candidat pentru administrarea bucală a EHBr, oferind o platformă non-orală, prietenoasă pentru pacient, pentru o terapie eficientă a migrenei.

Keywords: migraine, buccal delivery, bigel, eletriptan hydrobromide

Introduction

Migraine is a complex neurovascular disorder that significantly impairs quality of life and productivity. It typically presents as unilateral, pulsating pain accompanied by neurological symptoms such as nausea, photophobia, phonophobia and sometimes sensory and motor disturbances. A range of internal and external triggers – including stress, hormonal changes, sleep deprivation and sensory overload – can initiate migraine attacks, though the precise neurovascular mechanisms remain unclear [1].

Effective migraine management depends on accurate diagnosis and timely intervention. Treatment strategies vary between acute and prophylactic approaches. Medications for acute attacks are generally classified as non-specific (*e.g.*, NSAIDs, opioids, antiemetics) or migraine-specific, such as triptans and ergotamines. Triptans – including eletriptan, sumatriptan and zolmitriptan – are widely recommended due to their efficacy and favourable safety profiles, especially in patients with severe symptoms or poor response to non-specific treatments [2, 3].

Eletriptan hydrobromide (EHBr), a selective 5-$HT_{1B/1D}$ receptor agonist, is an established first-line treatment for

moderate to severe migraine. It offers rapid symptom relief, enhances patients' ability to resume daily activities, and is generally well tolerated [4]. However, nausea, vomiting and delayed gastric emptying during migraine attacks often complicate oral drug administration, highlighting the need for alternative, non-oral delivery systems. Despite reports of experimental buccal and fast-dissolving formulations, EHBr remains commercially available only in tablet form [5].

With the growing interest in non-oral therapeutic approaches, local drug delivery systems have gained prominence due to their potential to bypass gastrointestinal limitations and improve patient compliance. Among these, mucoadhesive gel formulations – especially hydrogels – have been widely explored for various indications, owing to their favourable physicochemical properties and sustained drug release capabilities. Gel-based formulations are typically categorised according to the polarity of their continuous phase: hydrogels contain water as the external medium, whereas oleogels (or organogels) incorporate oil as the continuous phase [6].

Hydrogels are composed of various natural, synthetic and semi-synthetic biodegradable polymers and are known for their biocompatibility [7]. Due to their significant water-holding capacity, hydrogels exhibit a degree of flexibility like that of natural tissues. In addition to being effective carriers for drug delivery, they can be easily modified [8]. Oleogels are defined as semi-solid dosage forms obtained by gelation of lipophilic liquids using suitable substances known as oleogelators. The gelation process involves the formation of aggregates by the gelling agent, followed by the establishment of interactions between these aggregates, ultimately resulting in a three-dimensional network structure. Moreover, the use of lipid-based carriers in the buccal mucosa can enable prolonged controlled release, protect the active pharmaceutical ingredient from degradation in aqueous environments, and mask unpleasant tastes [6, 9]. Bigels are often preferred over single-phase gels as they combine the advantages of both aqueous and oily phases. Their benefits include the ability to carry both hydrophilic and lipophilic active substances, ease of preparation, absence of surfactants, enhanced drug permeability and controllable viscosity and drug release rates [9, 10].

Although various gel-based systems, such as hydrogels, oleogels and bigels, have been investigated for local drug delivery in different therapeutic areas, studies comparing these formulations for buccal application in migraine treatment remain limited in the literature. This study aimed to enhance the buccal delivery of EHBr by formulating and evaluating three different gel systems – hydrogel, oleogel and bigel – for potential use in migraine therapy. The gels were characterised in detail in terms of their rheological properties, including flow behaviour, viscosity profiles and linear viscoelastic regions. Oscillatory frequency sweep tests were performed to assess their viscoelastic performance. Interaction tests with mucin were conducted to evaluate its mucoadhesive potential for buccal retention. Furthermore, the mechanical properties of the gels were investigated using texture profile analysis (TPA) to determine their structural integrity and suitability for mucosal applications. Based on these comprehensive evaluations, the most promising bigel formulations were selected for *in vitro* drug release studies to gain deeper insights into the controlled release behaviour of EHBr, with the ultimate goal of developing an effective and patient-friendly buccal delivery system for migraine management.

Materials and Methods

Materials

Eletriptan hydrobromide was kindly provided by Ali Raif Pharmaceutical Industry (Türkiye). Poloxamer 407 (P407) was kindly gifted by BASF (Ludwigshafen, Germany). Aerosil® 200 (colloidal silicon dioxide), tocopheryl acetate (vitamin E), Tween 80, methyl paraben and propyl paraben were all purchased from Sigma-Aldrich (St. Louis, MO, USA). The olive oil was obtained from Kristal Yağları (İzmir, Turkey), a local oil manufacturing company.

Preparation of gel formulations

Three gel systems, namely hydrogel, oleogel and bigel, were prepared using a mechanical stirrer. During the preliminary formulation studies, critical process parameters such as mixing speed, mixing time and mixing efficiency were optimised to achieve homogenous and stable gels.

Hydrogel preparation: Poloxamer-based hydrogels were prepared using the cold method as described by Schmolka *et al*. [11]. Briefly, P407 (19%) was slowly added to a predetermined volume of distilled water under continuous magnetic stirring (300 rpm) at 4°C. The mixture was stored at 4°C until a clear and uniform solution is obtained [12]. Once homogeneity is achieved, EHBr (5%) and tocopheryl acetate (0.05%) were dissolved in 96% ethanol (10%) and the resulting solution was slowly incorporated into the cold poloxamer solution under gentle stirring. The final volume was adjusted with distilled water, and the hydrogel was kept at 4°C until use.

Oleogel preparation: Tween 80 (1%) was incorporated into pre-heated olive oil (70°C) under continuous mechanical stirring at 300 rpm. Subsequently, the gelling agent Aerosil® 200 (6%) was gradually added and dispersed thoroughly. Once complete dispersion was achieved, tocopheryl acetate (0.05%) was introduced into the system as an antioxidant. After obtaining a homogeneous mixture, heating was ceased, and the formulation was allowed to cool to room temperature, resulting in the formation of the oleogel [13]. After reaching room temperature, the calculated amount of EHBr was added and mixed into the formulation.

Bigel preparation: oleogel and hydrogel were prepared separately and subsequently combined using a mechanical stirrer at 800 rpm at room temperature. Bigel formulations were developed at various oleogel to hydrogel weight ratios, specifically 30:70, 40:60 and 70:30 [10].

The concentration of the active ingredient was set based on a commercially available product. Control gel formulations without EHBr (placebo) were also initially prepared.

Rheological evaluation

Viscosity analysis. The viscosity of the gel formulations was measured at 37°C using a TA-TX Discovery HR 1 rheometer. A stainless-steel parallel plate geometry with a diameter of 40 mm and a fixed gap of 1 mm was employed. Shear rates were incrementally varied from 0 to 100 s^{-1}, and shear stress data points (40 in total) were recorded to generate flow curves representing shear stress versus shear rate. Each sample was tested in three replicates to ensure data reliability.

Linear viscoelastic region (LVR) determination. Dynamic oscillatory shear measurements were conducted to characterize the rheological properties of the prepared hydrogels, oleogels and bigels. Initially, strain sweep tests were performed across a broad strain range (0.01 - 100%) to identify the linear viscoelastic region (LVR) – the range over which the storage (elastic) and loss (viscous) moduli remain constant and the material exhibits linear behaviour. The experiments were performed in triplicate.

Oscillatory tests. Following the determination of the LVR, frequency sweep tests were carried out at a fixed strain within this region to assess the mechanical response of the gels under varying oscillation frequencies. Key parameters such as storage modulus (G′), loss modulus (G″), dynamic viscosity (η′) and phase angle (tan δ) were extracted from these measurements. All experiments were performed with a minimum of six replicates for statistical validity. The experiments were performed in triplicate.

Mucin interaction test. To investigate the interaction between mucin and the gel formulations, the interaction parameter (ΔG′) was calculated to evaluate potential synergistic or antagonistic effects on the gels' elastic properties. This parameter is defined as the difference between the elastic modulus of the mucin-gel mixture ($G'_{mixture}$) and the sum of the elastic moduli of mucin (G'_{mucin}) and gel (G'_{gel}) measured separately. The formula used is [6, 14, 15]:

$$\Delta G' = G'_{mixture} - (G'_{hydrogel,\ oleogel\ or\ bigel})$$

Measurements were typically conducted at oscillatory frequencies of 1 and 10 rad/s. The resulting ΔG′ values provide insight into the compatibility of the gels with mucin and their potential mucoadhesive characteristics. The experiments were performed in triplicate.

Mechanical evaluation. The hardness, compressibility, adhesiveness, cohesiveness and elasticity of the gel formulations were determined at 37°C based on force–time curves obtained using a software-controlled penetrometer (TA-XT Plus, Stable Micro Systems, UK) [14, 16]. The test was repeated six times for each gel formulation, and standard deviations were calculated.

In vitro release study. The analysis and quantification of EHBr were conducted using High-Performance Liquid Chromatography (HPLC). The HPLC system utilised included a UV detector, an autosampler, a degasser unit and a column oven from the Agilent 1100-1200 series. For the analyses, a C18 column (Kromasil C18, 250 mm × 4.6 mm, 5 µm) was employed. The mobile phase consisted of a mixture of phosphate buffer and acetonitrile in a 65:35 (v/v) ratio. A 20 µL sample was injected into the system at a flow rate of 1 mL/min, and detection was carried out at a wavelength of 234 nm [17].

The drug release properties of the prepared formulations were evaluated at 37°C using a water bath equipped with a magnetic stirrer. After being placed into dialysis tubing MWCO 12,000 - 14,000 Da (Spectrum Laboratories, USA), the formulations were sealed at both ends with clamps and immersed in the release medium at 37°C. At predetermined time intervals, samples were withdrawn and replaced with an equal volume of simulated saliva: ethanol mixture (80:20, v/v) to maintain a constant volume throughout the experiment and ensure sink conditions. The experiment was performed in six replicates. The collected samples were analysed using HPLC to determine the drug content, and after performing the necessary calculations, *in vitro* release profiles were plotted.

Statistical analysis

All data obtained from the experiments were statistically analysed using GraphPad Prism (version 10.3.1). One-way or two-way ANOVA, followed by Tukey's multiple comparison test, was performed where appropriate to assess differences between groups. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Preparation of Gel Formulations

As shown in Figure 1, both the hydrogel and oleogel formulations were prepared homogeneously.

Bigel (oleogel:hydrogel) formulations were prepared at ratios of 30:70, 40:60 and 70:30, and were initially assessed based on their organoleptic characteristics. As shown in Figure 2, the formulation containing 70% oleogel exhibited noticeable aggregation, phase separation and poor homogeneity. This instability at higher oleogel ratios is consistent with the literature, as shown in a study by Martins *et al.*, where increasing the oleogel fraction significantly influenced the stability and textural properties of the hybrid gel system [18]. In contrast, the bigels with lower oleogel content demonstrated a more uniform and stable structure, which can be attributed to the use of olive oil as the

lipid phase. It was evident that increasing the oleogel proportion beyond 40% adversely affected both the homogeneity and flow properties of the bigel system. Hamed *et al.*, stated that producing a stable, homogeneous bigel is essential because these biphasic systems – formed by high-shear mixing of hydrogels (aqueous phase) and oleogels (lipophilic phase) – are meant to unite the practical benefits of both matrices (simple, surfactant-free preparation) while enabling simultaneous delivery of water-soluble actives from the hydrogel phase and lipid-soluble actives from the oleogel phase in a single hybrid formulation [19].

Therefore, to maintain optimal structural integrity and handling properties, the maximum oleogel content was limited to 40%.

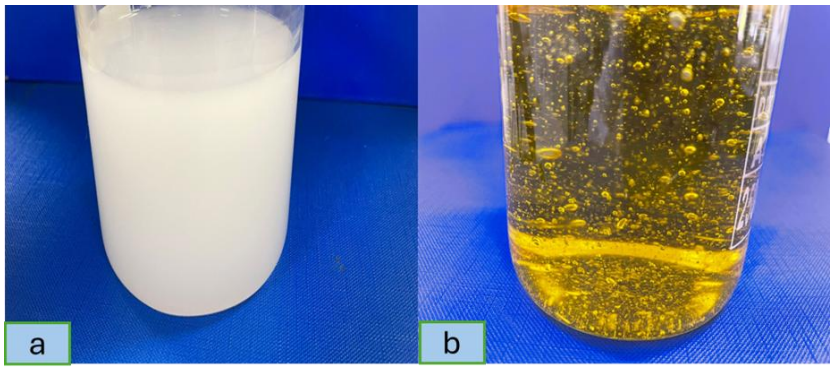

Figure 1.
Visual appearance of the prepared gels: (a) hydrogel and (b) oleogel, both exhibiting homogeneous structures

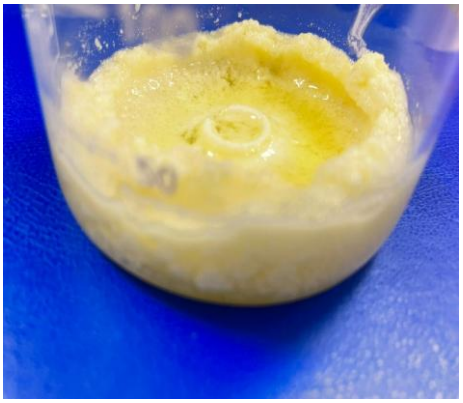

Figure 2.
Visual appearance of the bigel formulation containing 70% oleogel, showing aggregation, phase separation and poor homogeneity

Rheological evaluation

Viscosity analysis. The viscosity profiles of the hydrogel, oleogel and bigel formulations are presented in Figure 3. All formulations exhibited a clear pseudoplastic (shear-thinning) behaviour, characterised by a pronounced decrease in viscosity with increasing shear rate. According to Joița *et al.* shear-thinning behaviour is advantageous for biomedical applications such as tissue engineering and wound healing [20].This indicates that the internal structure of the gels progressively aligns and flows more easily under applied shear. Among the tested formulations, the bigel containing 40% oleogel demonstrated the highest viscosity across the shear rate range, followed by the bigel with 30% oleogel and the hydrogel. The oleogel alone showed the lowest viscosity values. Shakeel et al. demonstrated that multi-component systems (such as bigels) often exhibit higher hardness and moduli than mono-component systems due to synergistic interactions [21]. This trend suggests that incorporating higher proportions of the oleogel phase into the bigel increases the overall structural viscosity due to enhanced network interactions between the oleogel and hydrogel phases. The pseudoplastic flow behaviour observed in all samples is advantageous for topical or mucosal application, as it ensures ease of spreading under shear while maintaining structural integrity at rest. The differences in viscosity can be attributed to the specific composition and ratio of oil and water phases, as well as the interactions between the gelling agents used in the hydrogel and oleogel components.

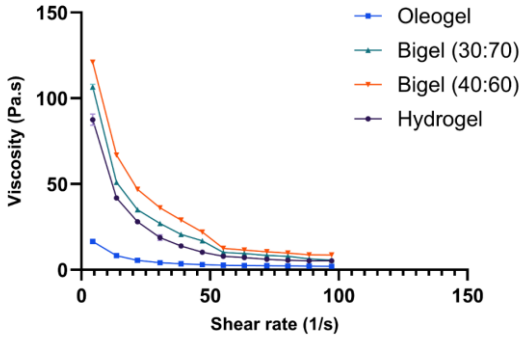

Figure 3.
Shear rate-dependent viscosity of hydrogel, oleogel and bigel formulations

Linear viscoelastic region (LVR) determination. The oscillatory strain sweep tests were conducted to determine the linear viscoelastic region (LVR) of the developed hydrogel, oleogel and bigel formulations

with 30:70 and 40:60 oleogel:hydrogel ratios for buccal delivery of eletriptan hydrobromide. The strain sweep tests were performed over a strain range of 0.02 - 2.12% for the hydrogel and oleogel, and 0.02 - 6.45% for the bigel systems. The LVR describes the strain interval where the viscoelastic properties, specifically the storage modulus (G′) and the loss modulus (G″), remain constant and independent of the applied strain. Within the LVR, the observed visco-elastic properties (G' and G") are solely determined by the material's molecular structure and not by the applied strain, ensuring the material's structure remains intact. According to Bartkowiak *et al*., increasing the elasticity of hydrogels significantly enhances muco-adhesion, because more elastic gels resist structural deformation and remain better attached to the mucosal surface [22]. Within this region, the structural network of the gel stays intact, ensuring that the measured rheological response truly represents the material's inherent structure rather than deformation-induced damage. The critical strain (γc) is defined as the strain point where G′ or G″ decreases by more than 10% from its initial value, indicating the end of the LVR [23]. As shown in Figure 4, the storage (G′) and loss (G″) moduli remained constant within the LVR and decreased markedly beyond the critical strain, confirming the structural breakdown point for each formulation. For the eletriptan-loaded gels, the critical strain values (γc) were found to be 0.79% for the hydrogel, 0.50% for the oleogel, 1.99% for the bigel with a 30:70 oleogel:hydrogel ratio and 3.19% for the bigel with a 40:60 oleogel:hydrogel ratio. From the results, a 0.3% strain was exactly within the LVE range for all samples, thus it was used for all dynamic tests. These results demonstrate that the oleogel alone possesses the narrowest LVR, suggesting a weaker network structure more prone to breakdown under applied shear deformation. In contrast, the hydrogel and both bigel systems exhibited broader LVRs, indicating a stronger and more elastic network capable of withstanding higher strain levels before structural disruption occurs. Notably, the bigel with the 40:60 ratio showed the widest LVR among all formulations, with a critical strain value of 6.13%, nearly double that of the 30:70 bigel and significantly higher than the hydrogel and oleogel. This indicates that increasing the hydrogel content in the bigel system enhances the formulation's resistance to deformation, likely due to a more continuous and reinforced hydrogel network interpenetrating the oleogel domains.

This improved mechanical stability of the bigel (40:60) could be advantageous for buccal administration, where the formulation must retain its integrity under mechanical stress from the oral cavity and mucosal movement. The higher critical strain implies that the bigel can maintain its structure longer during application, potentially supporting sustained drug release and prolonged mucosal adhesion.

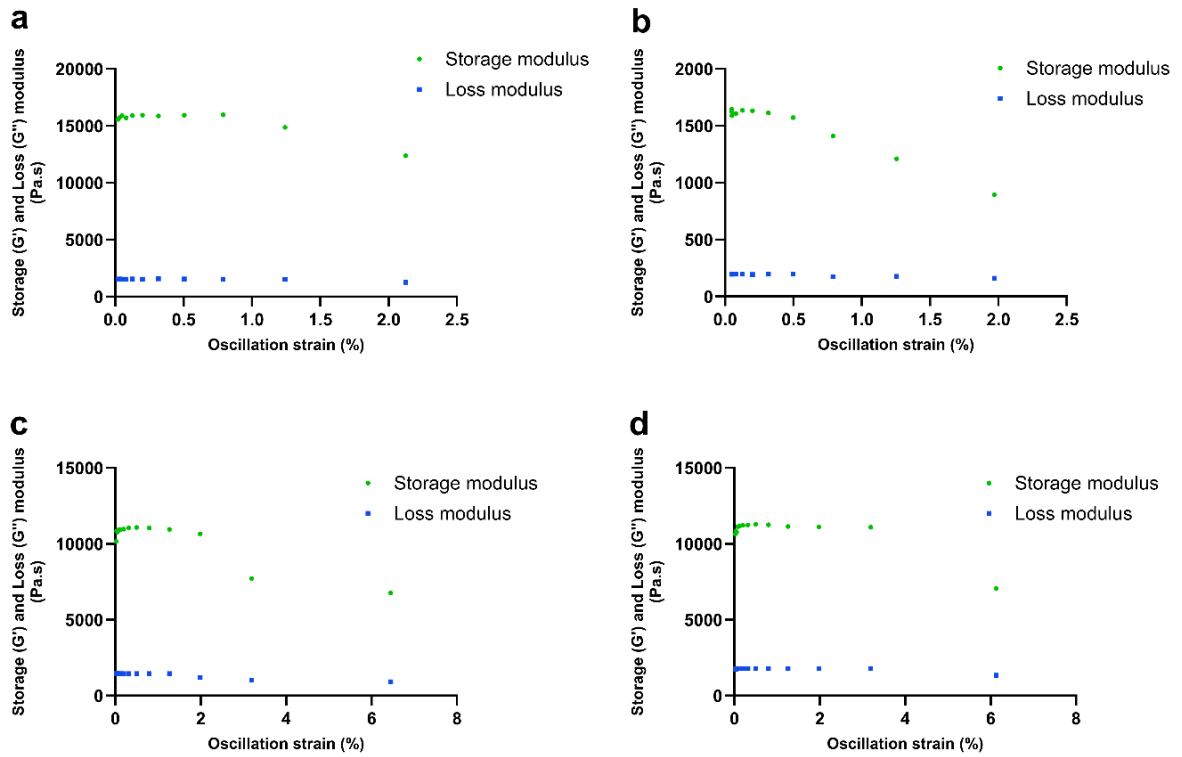

Figure 4.
Strain sweep curves for determination of the linear viscoelastic region (LVR) of the formulations: (a) Hydrogel, (b) Oleogel, (c) Bigel (30:70) and (d) Bigel (40:60)

Oscillatory tests. Frequency sweep tests were conducted to comprehensively evaluate the viscoelastic behaviour of the hydrogel, oleogel and bigel formulations. As shown in Figure 5, all samples exhibited typical weak gel-like behaviour, where the storage modulus (G′) representing the elastic (solid-like) response remained consistently higher than the loss modulus (G″) representing the viscous (liquid-like) component over the entire angular frequency range tested (0.1 - 100 rad/s). The absence of a crossover point and the slight frequency dependency of both moduli confirm the formation of stable, predominantly elastic gel networks that maintain their structural integrity under oscillatory stress [24]. Among the tested formulations, the bigel with a 40:60 hydrogel-to-oleogel ratio demonstrated the highest G′ and G″ values, indicating the strongest and most rigid network structure. The bigel with a 30:70 ratio showed intermediate viscoelastic moduli, whereas the hydrogel exhibited lower values and the oleogel displayed the weakest mechanical properties, with the lowest storage and loss moduli. These findings clearly suggest that the synergistic interaction between hydrogel and oleogel phases enhances the overall network strength in bigel systems. The dominance of G′ over G″ in all formulations implies that the gels behave more like solids, exhibiting predominantly elastic and recoverable deformations, confirming the formation of a stable, three-dimensional gel-like structure. Consistent with our findings, a study conducted by Min *et al*. on dual-crosslinked composites composed of glycol chitosan and amino-functionalised bioactive glass nanoparticles also demonstrated a hydrogel structure in which the storage modulus (G′) was significantly higher than the loss modulus (G″), with a G′/G″ ratio of approximately 20, further confirming the formation of a strong and elastic network [25] Furthermore, the tunability of viscoelastic properties by adjusting the hydrogel-to-oleogel ratio highlights the potential for optimizing bigel formulations for desired mechanical strength, stability and application performance, which is particularly advantageous for topical delivery systems.

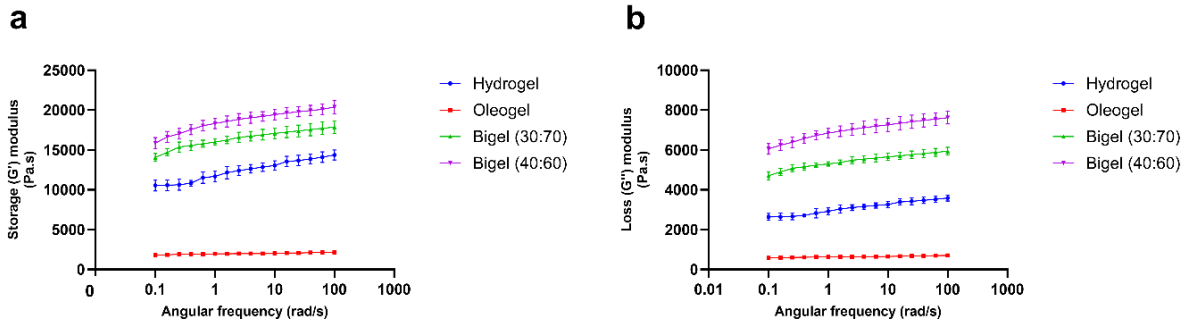

Figure 5.
Storage (a) and Loss (b) moduli as a function of angular frequency

Mucin interaction test. The interaction of mucin with various gels was evaluated by analysing the change in storage modulus (G') at two different frequencies (1 and 10 rad/s), represented by the interaction parameter ΔG', as shown in Table I. The results reveal both positive and negative interactions depending on the type of mixture and frequency. The mucin/hydrogel mixture showed a positive interaction at both frequencies, with ΔG' values increasing as the frequency increased. This indicates that mucin weakly enhances the structural properties of the hydrogel, albeit in a moderate manner. The results suggest that mucin interacts positively with the hydrogel matrix but with relatively weak synergy compared to other mixtures. The mucin/oleogel mixture showed negative interaction values at both frequencies, with ΔG' becoming more negative as the frequency increased. This indicates that mucin has a disruptive effect on the oleogel structure, suggesting poor mucoadhesion and indicating that mucin may not effectively strengthen oleogels under the conditions tested. The mucin/bigel (30:70) mixture showed a positive interaction at both frequencies, with ΔG' values increasing at the higher frequency. This suggests that mucin interacts positively with bigels, contributing to their structural stability. The results indicate moderate synergy between mucin and the bigel (30:70) mixture, suggesting that mucin enhances the rheological properties of bigels, though not as significantly as it does with other gel types. The mucin/bigel (40:60) mixture showed similar positive interaction, with ΔG' values slightly increasing at the higher frequency. This mixture exhibited stronger positive interactions compared to the 30:70 ratio, suggesting that a higher concentration of mucin in the bigel further strengthens the mixture's structure. This is consistent with the findings of Cardoso *et al.*, who reported similar pH-dependent effects of mucin on the rheological properties of gel systems. At pH 1.2, the ΔG′ values for mucin-gellan gum and mucin-retrograded starch demonstrated both positive and negative interactions, respectively, with the negative values indicating weaker mucoadhesive behaviour in mucin-retrograded starch and stronger interactions in mucin-gellan gum. These results suggest that mucin's effect on gel systems is strongly influenced by both

the type of gel and the pH, highlighting the complex nature of mucin's interactions in different formulations [26].

The results reveal that mucin has varying effects depending on the type of gel used. Mucin enhances the structural properties of bigels (30:70 and 40:60 mixtures), with stronger positive interactions observed at both frequencies, especially at 10 rad/s. On the other hand, mucin has a detrimental effect on oleogels, where it weakens the structure, as indicated by the negative ΔG' values. The interaction between mucin and hydrogel is moderate, with a positive but weak effect on the hydrogel structure. These findings provide insights into the potential use of mucin in different gel systems, particularly in bigels, where it enhances structural integrity, while its role in oleogels requires further investigation.

Table I

Interaction Parameter (ΔG') of Storage Modulus (G') for mucin/plain hydrogel, oleogel, bigel mixtures and their individual components at 1 and 10 rad/s

	Hydrogel	**Mucin/Hydrogel mixture**	**ΔG' (Pa)**
G' (1 rad/s)	11669.6	4199.04	6983.06
G' (10 rad/s)	13056.8	4912.72	7729.08
	Oleogel	**Mucin/Oleogel mixture**	**ΔG' (Pa)**
G' (1 rad/s)	1960.26	2022.91	-62.65
G' (10 rad/s)	2002.905	2175.83	-172.925
	Bigel (30:70)	**Mucin/Bigel (30:70) mixture**	**ΔG' (Pa)**
G' (1 rad/s)	15990.85	3649.92	12340.93
G' (10 rad/s)	17083.15	4199.61	12883.54
	Bigel (40:60)	**Mucin/Bigel (40:60) mixture**	**ΔG' (Pa)**
G' (1 rad/s)	18331.4	3298.35	15033.05
G' (10 rad/s)	19436.7	4200.92	15235.78

Mechanical evaluation. The mechanical properties of the different formulations – including hardness, compressibility, adhesiveness, cohesiveness and elasticity – were comprehensively evaluated, and the statistical comparisons are summarised in Table II. Significant differences ($p < 0.05$) were observed between the single-phase gels (hydrogel and oleogel) and the bigel systems, as well as between the bigel formulations with different hydrogel-to-oleogel ratios.

Table II

Mechanical properties of gel formulations

Code	**Hardness (g) ± SD**	**Compressibility (g·s) ± SD**	**Adhesiveness (g·s) ± SD**	**Cohesiveness ± SD**	**Elasticity ± SD**
Hydrogel	15.84 ± 1.60	27.08 ± 5.296	75.99 ± 6.55	0.87 ± 0.02	1.03 ± 0.05
Oleogel	8.07 ± 0.13	43.61 ± 1.97	1.61 ± 0.56	7.83 ± 0.60	1.02 ± 0.09
Bigel (30:70)	14.97 ± 1.35	23.62 ± 3.37	40.36 ± 3.03	1.08 ± 0.25	0.93 ± 0.04
Bigel (40:60)	35.58 ± 0.74	45.38 ± 1.92	94.28 ± 5.80	1.14 ± 0.18	0.96 ± 0.09

Hardness, which reflects the force required to compress a substance, varied significantly across formulations. The bigel (40:60) formulation (40% oleogel, 60% hydrogel) exhibited the highest hardness (35.58 ± 0.74 g), which was significantly greater than both the hydrogel (15.84 ± 1.60 g) and bigel (30:70) (14.97 ± 1.35 g) ($p < 0.05$). This indicates that increasing the oleogel content from 30% to 40% markedly strengthens the gel network, making it more rigid. In contrast, oleogel alone showed the lowest hardness (8.07 ± 0.13 g), confirming its softer texture ($p < 0.05$ *vs*. hydrogel). A similar increase in consistency and structure strengthening upon combining multiple gelators or phases has been observed in other lipid-based systems, in a study conducted by Zima *et al.*, where synergistic interactions lead to a more robust gel network [27].

Compressibility, representing the extent to which a material deforms under compressive force, was also influenced by the formulation composition. The Bigel (40:60) and oleogel exhibited the highest compressibility (45.38 ± 1.92 g·s and 43.61 ± 1.97 g·s, respectively), both significantly higher than the hydrogel (27.08 ± 5.30 g·s, $p < 0.05$) and Bigel (30:70) (23.62 ± 3.37 g·s). The significant difference between Bigel (30:70) and Bigel (40:60) ($p < 0.05$) confirms that a higher oleogel fraction enhances compressibility, resulting in greater deformability under load.

Adhesiveness, which indicates the ability of the material to stick to a surface, was markedly affected by the bigel composition. Hydrogel showed high adhesiveness (75.99 ± 6.55 g·s), while oleogel alone had minimal adhesiveness (1.61 ± 0.56 g·s). Bigel (40:60) showed the highest value (94.28 ± 5.80 g·s), significantly greater than both Bigel (30:70) (40.36 ± 3.03 g·s, $p < 0.05$) and the hydrogel ($p < 0.05$). This result suggests that increasing the oleogel fraction up to 40% significantly reinforces the cohesive interactions within the bigel matrix, enhancing stickiness and mucoadhesive potential.

Cohesiveness and elasticity showed no significant differences ($p > 0.05$) among the formulations, indicating that the internal structural integrity and ability to recover shape after deformation were not strongly influenced by the hydrogel-to-oleogel balance in this system.

Taken together, the mechanical test results reveal that the oleogel phase plays a dominant role in defining the hardness, compressibility and adhesiveness of the bigels. Specifically, increasing the oleogel content from 30% to 40% significantly enhanced the hardness, compressibility and adhesiveness, confirming that the network becomes more robust, more adhesive and more deformable under force ($p < 0.05$). Conversely, a higher hydrogel fraction (Bigel 30:70) resulted in lower hardness and adhesiveness, implying a softer and less sticky structure.

These findings demonstrate that mechanical performance of bigel formulations can be precisely tailored by adjusting the hydrogel-to-oleogel ratio, allowing for the customization of textural and application properties depending on the desired performance in topical or mucoadhesive systems. The high adhesiveness of the bigel is a crucial requirement for a buccal dosage form, as it ensures prolonged residence time and potential sustained drug absorption, according to Reddy *et al*. [28].

In vitro release profiles of bigel formulations

The HPLC method was developed and validated in accordance with the ICH guidelines for validating analytical procedures. The calibration curve for Eletriptan Hydrobromide exhibited linearity across the concentration range of 15, 20 and 25 µg/mL, with a correlation coefficient (r^2) of 0.9998 and a linear regression equation of $y = 37.376x + 2.7775$. For each calibration point, the average of three replicate peak areas was used, and each sample was analysed in triplicate.

The *in vitro* release profiles of EHBr from two different bigel formulations – Bigel (30:70) and Bigel (40:60) – were investigated in artificial saliva containing 20% ethanol to enhance the solubility of the poorly water-soluble drug. Both bigel systems exhibited a biphasic release pattern characterised by an initial burst release within the first few hours, followed by a slower sustained release phase (Figure 6). This is typical for biphasic semi-solid systems where the drug is partly located near the gel surface and partly embedded within the oleogel-hydrogel network. When comparing the two formulations, bigel (30:70) (30% oleogel, 70% hydrogel) exhibited a higher cumulative release (~ 70% at 24 hours) than bigel (40:60) (40% oleogel, 60% hydrogel), which reached approximately 60% at the same time point. This result indicates that increasing the oleogel content from 30% to 40% led to a slightly slower drug release profile. This could be explained by the higher oleogel fraction forming a more lipophilic and viscous network, which may hinder the diffusion of the poorly water-soluble drug into the hydrophilic release medium. This prolongation of drug release, attributed to the highly complex and viscoelastic gel network that lengthens the diffusion pathway, has also been reported in a similar study conducted by Hamed *et al*. [19]. In contrast, a higher hydrogel content supports greater water uptake and swelling, which facilitates the release of eletriptan hydrobromide by creating aqueous channels for diffusion. Therefore, the relative proportions of oleogel and hydrogel phases are critical for tuning the release behaviour, and an increased oleogel fraction appears to slow the release rate by providing a more substantial barrier to drug diffusion. A study by Shelke *et al.* formulated eletriptan hydrobromide into a muco-adhesive and thermoreversible intranasal gel using ethosomes for brain targeting. The ethosomal gel demonstrated high mucoadhesive strength and sustained drug release, resulting in enhanced *in vitro* and *ex vivo* bioavailability over 24 hours. These findings indicate that mucoadhesive formulations with controlled release may offer clinical advantages for eletriptan by over-coming extensive first-pass metabolism associated with oral administration [29]. In addition, Begum *et al.* reported the formulation and *in vitro* evaluation of eletriptan transferosomal gels aimed at reducing dosing frequency, and overall, their findings suggest that Eletriptan-loaded transferosomal gels represent a promising approach to maintaining therapeutic drug levels at the target site while minimizing the dosing frequency [30].

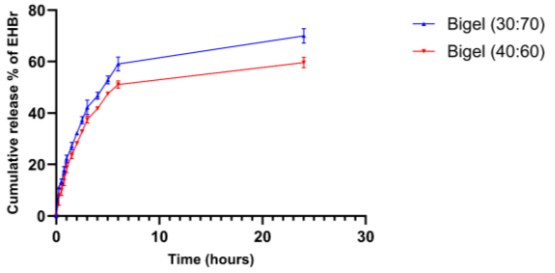

Figure 6.
In vitro release profile of bigel formulations

Conclusions

The development of bigel systems for buccal delivery of eletriptan hydrobromide demonstrated that combining hydrogel and oleogel phases offers significant advantages over single-phase formulations. The prepared gels exhibited desirable physicochemical and rheological characteristics, including pseudoplastic flow behaviour and stable viscoelastic properties, which are favourable for buccal application. Mechanical tests confirmed that the bigel with a 40:60 oleogel-to-hydrogel ratio displayed the highest hardness, compressibility and adhesiveness, suggesting the enhanced mucoadhesive potential and the structural integrity. Mucin interaction studies further revealed that bigels, particularly the 40:60 formulation, achieved stronger positive interactions with mucin compared to hydrogels and oleogels, highlighting their superior buccal retention properties.

In vitro release studies indicated that drug release could be tailored by adjusting the oleogel content, with the 30:70 bigel achieving a faster release profile due to its higher hydrophilic content, while the 40:60 formulation allowed for more controlled and sustained drug delivery. These findings underscore the potential of bigel-based systems as an effective and patient-friendly alternative for eletriptan administration, offering improved drug release modulation, enhanced muco-adhesion and ease of application. The optimised bigel formulation, particularly the 40:60 system, emerges as a promising candidate for non-oral migraine therapy, warranting further *in vivo* and clinical evaluation.

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Conflict of interest

The authors declare no conflict of interest.

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