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Comparative In Vitro Release of Eletriptan Hydrobromide Formulations for Buccal Administration

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ABSTRACT

Introduction: Migraine is a neurological disease characterized by unilateral headache attacks that can last between 4-72 hours and accompanying different symptoms such as photophobia, phonophobia, osmophobia, nausea, vomiting, or movement sensitivity. Eletriptan hydrobromide (EHBR) has been recognized as a reliable and efficient treatment for severe to moderate migraine attacks, with or without aura. Buccal drug administration is the most preferred route of administration compared to other alternative routes of administration. Orally disintegrating tablets (ODT), orally disintegrating films (ODF), and in situ gel systems are popular dosage forms that can be used without the need for chewing or water when the medication is taken. With these features, they create important advantages for patients with dysphagia or problems with water intake. **Methods**: ODT, ODF, and in situ gel formulations were developed and evaluated in terms of dissolution profiles. **Results**: For the ODT formulation, more than 85% of the EHBR dissolved within the first 15 minutes. For the ODF formulation, 78% cumulative release was observed in the first 15-minutes. At the end of 4 hours, 93% cumulative drug release of EHBR from in situ gel was observed. **Conclusion**: Based on the results of these dissolution studies, ODT and ODF formulations for treatment of acute migraine attacks provide a rapid effect.

KEYWORDS: Eletriptan hydrobromide, orodispersible tablet, orodispersible film, in situ gel, dissolution

INTRODUCTION

Migraine is a neurological disorder characterized by unilateral headache attacks that can persist for 4–72 hours, accompanied by symptoms such as photophobia, phonophobia, osmophobia, nausea, vomiting, cranial allodynia, or sensitivity to movement. Patients strive for rapid control of all migraine symptoms to mitigate the impact of the condition on their professional, familial, and social obligations. Triptans are the primary treatment option for managing migraines. They function by activating 5-HT1B and 5-HT1D receptors, inducing vasoconstriction (*1*). They are particularly favored for patients who are unresponsive to nonspecific analgesics or experience severe pain, along with nausea and sensitivity to sound and light during migraine attacks, impeding their functionality (*2*, *3*).

Eletriptan hydrobromide (EHBR) was approved by the US Food and Drug Administration (FDA) on December 26, 2002 for the acute treatment of migraines in adults, with or without aura. EHBR is classified as a methylpyrrolidinyltryptamine substituted with a benzene sulfonyl derivative, and it falls under the category of organic compounds known as indoles (*4*). EHBR is a safe and effective solution for managing severe to moderate migraine headache attacks, demonstrating a favorable tolerability profile for both short- and long-term treatment in men and women of all ages. In a placebo-controlled trial focusing on a single migraine attack treated with EHBR, the medication was superior to placebo across all administered dosages (20, 40, and 80 mg) in providing headache relief within 2 hours (*5*). EHBR belongs to class I of the Biopharmaceutics Classification System (BCS), having high permeability and high solubility (*6*). The medication achieves 50% bioavailability after oral administration, with peak plasma concentrations (Tmax) reached within 1 hour. EHBR demonstrates approximately 85% protein binding. The need for an alternative route of drug administration arises due to the significant first-pass effect (*5*).

Although the oral route remains the predominant method for drug delivery, its prevalent limitations have prompted exploration into alternative administration routes. Consequently, the buccal route has garnered significant attention in research. Buccal drug delivery circumvents issues such as the first-pass effect, pre-systemic elimination by the gastrointestinal tract, and potential

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adverse drug reactions. Moreover, the ease of buccal administration positions it as a promising alternative to oral drug delivery, offering a viable option that ensures treatment compliance (*7*). Orally disintegrating tablets (ODT) are solid dosage forms that can dissolve in the mouth without the need for chewing or water when taken orally (8). With these characteristics, they offer significant advantages for patients with dysphagia or difficulties with water intake (*9*, *10*). Oral dispersible films (ODF) rapidly hydrate and dissolve upon placement in the mouth. The active ingredient is promptly released due to the formulations' quick dissolution facilitated by hydrophilic polymers present in ODF. Oral in situ gel, also referred to as environment-sensitive gel, represents an innovative dosage form utilized in drug delivery. Unlike conventional formulations, in situ gels are initially administered as low-viscosity solutions. Under specific environmental conditions, the polymer undergoes a conformational change, leading to gel formation. Consequently, this enhances the contact time and spreadability between the drug and the absorbent area (*4*).

From the patient's perspective, some currently available ODT products are excessively delicate and prone to breakage, whereas ODF formulations are sturdier, offering enhanced ease of administration and improved adherence. Many elderly patients encounter difficulties in swallowing solid dosage forms such as tablets or capsules. Despite ODT being designed for rapid disintegration in the mouth, concerns persist regarding the fear of swallowing solid tablets and the risk of choking, particularly for specific patient populations (*10*). The adoption of ODF has the potential to address the issue of swallowing difficulties and subsequently improve adherence. Moreover, in situ gelling formulations represent drug delivery systems that typically remain in a liquid state at room temperature and transition into a gel state upon application to the body, triggered by various stimuli like temperature changes, pH shifts, or alterations in ionic composition. These systems aim to reduce dosing frequency and enhance therapeutic outcomes for patients; however, developing such highly functional yet intricate dosage forms presents significant challenges (*11*). These innovative dosage forms have the potential to enhance patient adherence. Clinical research findings suggest a preference among patients for orally dissolving dosage forms over conventional solid oral dosage forms. From a clinical perspective, this innovative dosage form shows significant promise in addressing issues of inconvenience (*12*).

In the current study, ODF, ODT, and in situ gel dosage forms containing EHBR for migraine treatment were developed. This study aimed to compare the release of EHBR from these three different formulations.

METHODS

Materials

EHBR was gifted from Ali Raif Pharmaceutical Industry, Turkey. Acetonitrile was of HPLC grade from Merck. Potassium dihydrogen phosphate and ortho phosphoric acid were of analytical grade, also from Merck.

Analytical Method Development and Validation

Analysis and quantification of EHBR was determined using high pressure liquid chromatography (HPLC). The HPLC system used consists of a UV lamp, automatic sampler, degas unit, and column oven (Agilent 1100-1200 series). A C18 column (Kromasil, 250 × 4.6 mm, 5 µm) was used for analyses. For the phosphate buffer, acetonitrile mixture (65:35) was used as the mobile phase; 20 µL of sample was injected into the system at a flow rate of 1 mL/min, and 234 nm was used as the wavelength (*13*).

The HPLC method was validated for specificity, linearity, recovery, precision, repeatability, and stability in aqueous solution according to International Council for Harmonization (ICH) guidelines (*14*).

For linearity studies, stock solution was prepared by dissolving 10 mg EHBR in 100 mL of phosphate buffer. Solutions were prepared at concentrations of 5, 10, 15, 20, 25, and 30 µg/mL, by making the necessary dilutions with phosphate buffer from the stock solution. Three parallel samples were prepared for each concentration. The equation and correlation coefficient of the calibration curve for EHBR were obtained.

A calibration curve was created with solutions prepared at different concentrations. The concentrations of the standards prepared for the calibration curve were 5, 10, 15, 20, 25, and 30 µg/mL.

Samples at three concentrations (15, 20, and 25 µg/mL) were prepared for accuracy and recovery studies. Repeatability was studied by injecting six replicates of the EHBR solution in phosphate buffer at a concentration of 15 µg/mL. Solution stability was evaluated using solutions of EHBR in phosphate buffer at concentration of 15 µg/mL. The solutions were analyzed at 0, 24, and 48 h.

Solubility Study

Low aqueous solubility is the main problem encountered in the formulation development of new active substances, as well as in generic development. In addition, the active substance must be dissolved to be absorbed from the application site. For this reason, we examined the solubility

of EHBR in artificial saliva fluid and distilled water media (15 mL) (n = 6). An excessive amount of active ingredient was added to the prepared media and placed in a water bath preheated to 37 ± 0.5 °C and stirred with a magnetic stirrer. Samples (1 mL) samples were taken at 15, 30, 45, 60, and 90 minutes. The volume of medium was kept constant by adding 1 mL of solvent to the medium. The solubility study continued until a constant field value was reached in the samples taken. Using the area values obtained from the solubility study, the amount of EHBR was calculated using standard curve equations.

Dissolution Studies

Dissolution studies of ODT and ODF were carried out using United States Pharmacopeia (USP) dissolution apparatus type 2 (Varian VK7010).

For in situ gel formulations, studies were performed using a water bath with magnetic stirrer. A calculated amount of in situ gel formulation was placed in a dialysis membrane (12–14 kDa), then the membrane was closed from the top and bottom with the help of clamps.

For all formulations, pH 7.4 artificial saliva (250 mL) was used as the dissolution medium, with a 1-L vessel and a paddle of appropriate size for these vessels. The ambient temperature was set at 37 °C, and the stirring speed was set at 50 rpm. A 2-mL sample was taken from the medium at predetermined time intervals, the same amount of dissolution medium was added to maintain sink conditions. The samples were filtered through a 0.45-µm filter, then the amount of drug was determined with HPLC, and the in vitro release graph was drawn after the necessary calculations were made. The studies were carried out in six replicates.

Kinetic Modeling of Drug Release

Numerous kinetic models are available to characterize drug release from various dosage forms. Given the potential impact of formulation changes on drug release and subsequent in vivo performance, there is a continuous drive to develop tools that streamline product development, minimizing the reliance on extensive biostudies. Hence, leveraging in vitro drug dissolution data to forecast in vivo bioperformance is a rational approach. The in vitro drug release data were fitted into multiple kinetic models including zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson-Crowell to assess the release mechanism. The model demonstrating strong linearity, reflected by a high-value correlation, is deemed the most suitable to characterize the release kinetics of the formulations.

RESULTS AND DISCUSSION

Development and Validation of the Analytical Method

The EHBR calibration curve demonstrated linearity within the specified concentration range of 5–30 µg/mL. The equation of the calibration curve was y = 37.376x + 2.7775, and R^2 = 0.9998 (Fig. 1). Samples of the three given concentrations showed satisfactory recovery of EHBR. For concentrations of 15, 20, and 25 µg/mL, the mean recovery was found to be 101.58%, 100.78%, and 99.86%, respectively (Table 1). Thus, the method was found to be accurate as per ICH guidelines. The precision study results were suitable for guidelines outlined by ICH, demonstrating satisfactory outcomes, as shown in Table 2.

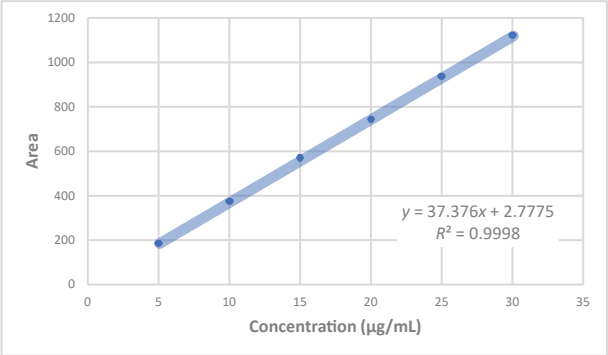

Figure 1. Calibration curve of eletriptan hydrobromide in phosphate buffer solution.

Table 1. Results of Accuracy Studies (n = 3)

Concentration	Sample	Area (AU)	Amount recovered (µg/mL)	Recovery%
15 µg/mL	1	572.43	15.24	101.61
	2	571.00	15.20	101.35
	3	573.46	15.27	101.79
	Average	**572.30**	**15.24**	**101.58**
	SD	**1.24**	**0.04**	**0.22**
	RSD %	**0.22**	**0.23**	**0.22**
20 µg/mL	1	755.63	20.14	100.71
	2	756.53	20.17	100.8
	3	756.49	20.17	100.83
	Average	**756.22**	**20.16**	**100.78**
	SD	**0.51**	**0.02**	**0.06**
	RSD %	**0.07**	**0.09**	**0.06**
25 µg /mL	1	934.97	24.94	99.76
	2	936.12	24.97	99.89
	3	936.62	24.98	99.94
	Average	**935.90**	**24.96**	**99.86**
	SD	**0.85**	**0.02**	**0.09**
	RSD %	**0.09**	**0.08**	**0.09**

RSD: relative standard deviation.

Table 2. Results of Precision Studies (15 µg/mL EBHR in Phosphate Buffer), n = 6.

Sample	Area (AU)	Mean Area (AU)	RSD %
1	572.43	571.71	0.18
2	571.00		
3	573.46		
4	571.07		
5	571.45		
6	570.88		

AU: arbitrary units; RSD: relative standard deviation.

The stability study data showed no noteworthy decrease in the amount of active substance at the end of 48 hours (Table 3).

Table 3. Results of Stability Studies (15 µg/mL EBHR in Phosphate Buffer)

Time	Area (AU)	Concentration (µg/mL)
0 h	566.24	15.08
24 h	552.46	14.71
48 h	548.79	14.61

AU: arbitrary units.

Solubility Studies

Solubility of EHBR in two different solution (distilled water and simulated saliva fluid) was evaluated. Findings were presented in Figure 2. The solubility of EHBR in artificial saliva was found to be substantially higher compared to its solubility in distilled water. This is thought to be due to the ions present in the saliva.

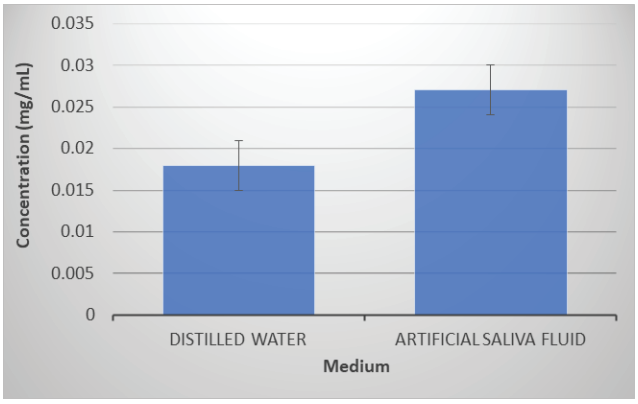

Figure 2. Results of solubility study. Error bars represent SD

Dissolution Studies

Dissolution profiles are presented in Figure 3. For the ODT formulation, more than 85% of EHBR dissolved within the first 15 minutes. These results indicate that ODT formulations can exert their effect rapidly, especially in situations where quick action is anticipated. For the ODF formulation, 78% of EHBR was released in the first 15 minutes, and complete drug release was achieved in 45 minutes.

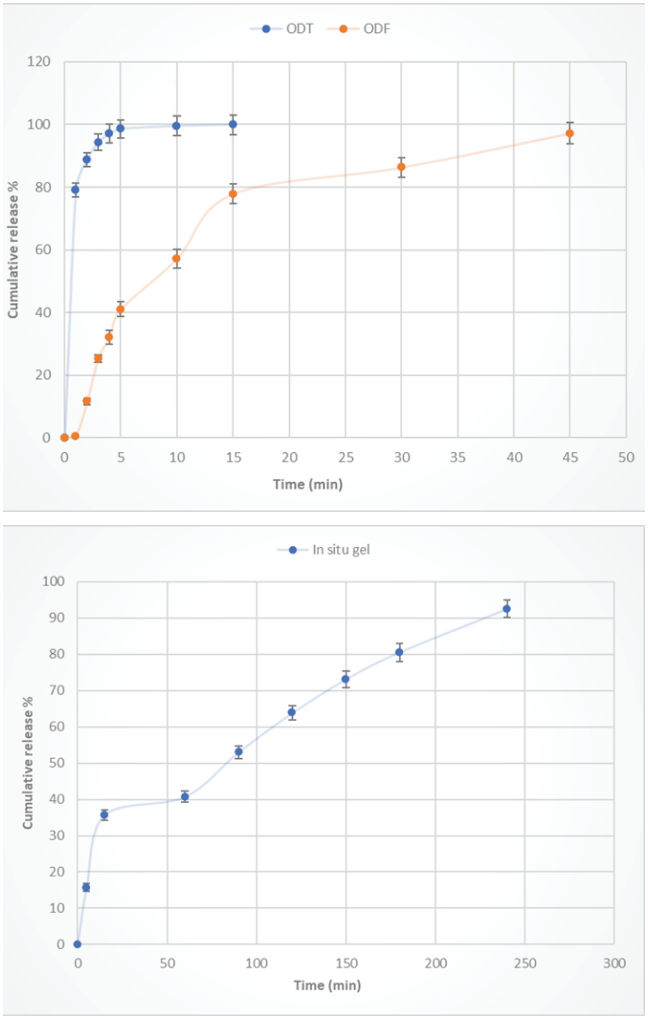

Figure 3. Dissolution profile of formulations for ODT and ODT (top) and in situ gel (bottom). Error bars represent standard deviation of n = 6. ODT: orodispersible tablet; ODF: orodispersible film.

Gel formulations generally exhibit slower drug release compared to colloidal systems. The drug is expected to be released by erosion of the gel system and diffusion from it. At the end of 4 hours, 93% cumulative drug release was observed.

Because ODT includes the use of excipients that can induce fast disintegration, it exhibited the fastest drug release. The results showed that creating a 3D network structure by using a polymer affected dissolution of the drug.

Kinetic Modeling of Drug Release

The dissolution study data were fitted into distinct kinetic models to evaluate their linearity, assessed through regression coefficients. Notably, each of the three formulations (ODT, ODF, and in situ gel) displayed

distinct behavior and mechanisms in drug release (Table 4). Specifically, the findings indicated that the first-order model best described the release kinetics for ODT and ODF, while the Higuchi model exhibited the best fit for the in situ gel.

Table 4. Results of Kinetic Modelling

Kinetic Model		ODT	ODF	In situ gel
Zero Order	R^2	-1.698	0.605	0.768
	k_0	10.305	2.765	0.455
First order	R^2	0.991	0.975	0.907
	k_1	1.442	0.078	0.01
Higuchi Model	R^2	0.132	0.930	0.972
	kH	37.119	15.865	5.934
Korsmeyer-Peppas Model	R^2	0.989	-0.005	0.968
	kKP	83.483	4.238	8.932
	n	0.082	0.656	0.415
Hixson-Crowell Model	R^2	0.059	0.972	0.893
	kHC	0.084	0.025	0.002
Best Fit Model		**Korsmeyer-Peppas**	**First order**	**Higuchi**

ODT: orodispersible tablet; ODF: orodispersible film.

CONCLUSION

This study compared the drug release profiles of ODT, ODF, and in situ gel formulations. Based on the results of these dissolution studies, ODT and ODF formulations for treatment of acute migraine attacks will provide a rapid effect.

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DISCLOSURES

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