Turk J Pharm Sci 2025;22(1):46-54
DOI: 10.4274/tjps.galenos.2024.83583

ORIGINAL ARTICLE

Formulation and Characterization of Etoricoxib Suppositories for the Management of Hemorrhoids

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ABSTRACT

Objectives: This study aimed to formulate and evaluate etoricoxib suppositories to improve patient compliance and drug efficacy in the management of hemorrhoids.

Materials and Methods: Suppositories were prepared using glycerin and gelatin. The prepared suppositories were evaluated for content uniformity, homogenization, hardness, weight variation, disintegration time, texture analysis, and *in vitro* drug release.

Results: Hardness, weight variation, disintegration time, and content uniformity values were found in the range of 4.00±0.50 to 7.50±0.50 kg/cm^3, 1.20±0.03 to 1.31±0.01 g, 11.00 to 19.05 min, and 66.98±0.86 to 80.76±3.60%, respectively. The SB3 gave 91.47±17.74% drug release in 6 h, whereas the SB1 gave 99.08±3.40% drug release in 12 h. Drug release from all formulations of suppositories was supported by zero-order, first-order, and Higuchi plots, except for SB4. The mechanism of drug release from all suppositories was fickian diffusion-based. The SB2 results were found to be more appropriate than those of the other batches.

Conclusion: These results confirm that the prepared formulation has a future scope and should be further explored in *in vitro* cell lines and animal studies.

Keywords: Etoricoxib, suppositories, hemorrhoids, texture analysis

INTRODUCTION

Hemorrhoids, often known as piles, indicate bulging veins in the lower part of the rectum and anus that resemble varicose veins. Hemorrhoids grow on the inner side of the rectum, which is recognized as interior or internal hemorrhoids, whereas beneath the skin surface around or surrounding the anus, which is recognized as exterior or external hemorrhoids.[1] The internal hemorrhoids occur above the dentate line and are covered by columnar epithelium, whereas the external hemorrhoids occur under the dentate line and are covered by squamous epithelium.[2-6] It commonly occurs as an inflammatory process of the hemorrhoidal plexus.[1,7] Hemorrhoids may be asymptomatic or symptomatic. The common symptoms associated with hemorrhoids are pain, the passage of bleeding in stool, itching around the anus, swelling, discomfort, lumps inside or around the anus, incomplete bowel emptying, and mucus discharge from the anus.[1,5,7] Long-term constipation, extreme pressure on the rectum, diarrhea, obesity, aging, pregnancy, and excessive use of laxatives contribute to the development of hemorrhoids owing to the irritates and enlarged blood vessels inside and around the anus.[1,7,8] Although hemorrhoids have low morbidity, they have a significant negative influence on quality of life. Available treatments for the management of symptomatic hemorrhoids include non-surgical medical procedures (like lifestyle modification and medications) and surgery. Patients try to avoid surgery, which is also expensive; however, this is also preferred by physicians as a last option for treatment. Lifestyle changes are recommended in the primary stage, which includes diet control and regular exercise.[9] Medications are preferred in the primary stage if diet control and regular

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Received: 26.11.2023, Accepted: 14.12.2024, Publication Date: 07.03.2025

Cite this article as: SONULE B, KHAIRNAR Y, MEHETRE N, KUMAR S, KUMAR L. Formulation and characterization of etoricoxib suppositories for the management of hemorrhoids. Turk J Pharm Sci. 2025;22(1):46-54.

exercise do not work well. Medicine-based treatment is associated with pain relief, control of inflammation, reduction of swelling, control of excessive blood loss, and reduction of diarrhea and constipation.

In intolerable pain conditions, patients expect immediate pain relief before other treatments. To tackle this problem, ointments, creams, and suppositories with non-steroidal anti-inflammatory drugs (NSAIDs) with or without antibiotics and anesthetic agents are available.[10,11] The suppositories are ideal for internal hemorrhoidal conditions, where they are inserted into the anus after bowel passage, whereas ointments and creams are ideal for external hemorrhoidal conditions. Furthermore, suppositories can have an immediate or prolonged effect compared to ointments and creams.[1] All these dosage forms are suitable for local application as well as can also provide immediate relief and avoid first-pass metabolism with minimal demerits of leakage and stains on clothes.

For intolerable pain relief before or after surgery and waning inflammation, NSAIDs are mostly prescribed. NSAIDs primarily work by inhibiting the two isoforms of cyclooxygenase (COX) enzymes. The COX enzymes play an important role in the production of prostaglandins, which are elements in the body that contribute to pain and inflammation. Conventional, non-selective NSAIDs suppress both COX-1 and COX-2 enzymes. However, COX inhibitors have gastrointestinal (GI) side effects after oral administration. The major side effects of COX inhibitors extend from mild GI tract irritation to severe GI bleeding and perforation.[12-14] Other associated side effects include peptic ulcers, heartburn, dyspepsia, and nausea. The side effects of upper GI are reported more frequently.[14,15] This upper GI intolerance can be alleviated by avoiding contact with the gastric mucosa.[13]

Etoricoxib is a selective COX-2 inhibitor that is used as an anti-inflammatory painkiller. Although it is prescribed for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, for a limited duration in gout, and so on. It inhibits COX-2 in a dose-dependent manner without blocking COX-1 over the therapeutic dose range. Etoricoxib exhibits 106-fold COX-2 selectivity. Etoricoxib has fewer cardiovascular side effects compared to another coxib with a sulfone moiety, *i.e.*, rofecoxib.[16,17]

By considering the intriguing and pertinent characteristics of suppositories and identifying the upper GI intolerance to COX inhibitors, this study aimed to prepare and characterize etoricoxib suppositories for pain relief and anti-inflammatory response in hemorrhoids. In this study, etoricoxib suppositories were prepared using gelatin and glycerin as the bases, and the formulated suppositories were evaluated for homogeneity, weight variation, content uniformity, hardness, texture analysis, and drug release.

MATERIALS AND METHODS

Chemicals

Sanofi India Ltd., Verna, Goa, India, gifted Etoricoxib for research work. Gelatin powder was purchased from SRL Lab Pvt. Ltd. MIDC, Taloja, India. Glycerol was purchased from Merck Life Science Pvt. Ltd., Mumbai, India. Milli Q water was freshly prepared in our lab using MERK Millipore, ABC Enterprises, West Bengal, India.

Instrumentation and apparatus

Ultraviolet-visible spectroscopy (UV-vis) spectrophotometer (UV-1900i, Shimadzu Corporation, Kyoto, Japan), Dissolution apparatus (DS 14000 Smart, LAB INDIA, Thane, Maharashtra, India), Disintegration Tester (DT 1000, LAB INDIA, Thane, Maharashtra, India), Hardness Tester (Monsanto), Texture Analyzer (XCTX0000000S00, Ametek Brookfield, USA), Magnetic Stirrer (10 MLH, REMI, Kolkata, India), and electronic balance (Valency Lab, Kolkata, India).

Drug-excipient compatibility

Attenuated total reflectance-fourier transform infrared spectroscopy (FTIR) (Spectrum Two, PerkinElmer, UK) was used to identify etoricoxib, glycerin, and gelatin as well as to assess the drug-excipient compatibility. The drug and excipients were used at a ratio of 1:1 as a physical mixture. The FTIR spectra were logged in the infrared (IR) range of 4000 and 400 cm^{-1}. The test sample results obtained in the form of IR spectra using the PerkinElmer spectrum IR v10.7.2 software were compared with standard drug IR spectra.[18]

Method for preparing etoricoxib suppositories

In a glass beaker, glycerin was added to the required volume, and heating was applied to maintain the temperature at 120 °C. Then, a precisely weighed amount of gelatin was added, followed by continuous stirring until the gelatin was completely solubilized in glycerin. A constant temperature was maintained during the preparation. Then, the calculated amount of drug and water was continuously added until a homogeneous mixture. The obtained mixture was decanted in pre-cleaned and greased (with glycerin) suppository molds. The molds containing the formulations were then stored in a refrigerator at 4±0.5 °C. After two hours, the prepared suppositories were collected, wrapped in parchment paper, and stored in a cool, dry place.[18] The compositions of the different batches of suppositories are shown in Table 1.

Physical appearance

The color and shape of the formulated etoricoxib suppositories were assessed with the naked eye against a clear background, and observations were recorded.[18,19]

Homogeneity test

The prepared suppositories were assessed using the naked eye to determine the drug distribution pattern. The dryness

Table 1. Composition of etoricoxib rectal suppositories

Drug/Excipients	Formulation composition (*w/w*%)			
	SBI	SB2	SB3	SB4
Etoricoxib	3.00	3.00	3.00	3.00
Glycerin	60.00	60.00	65.00	65.00
Gelatin	20.00	25.00	20.00	25.00
Purified water	17.00	12.00	12.00	7.00

and/or roughness of the suppositories were also confirmed. Three suppositories from each batch were collected and cut longitudinally. The observations were recorded against a clear background.[18,20]

Weight variation

Twelve etoricoxib suppositories were randomly selected from each batch, and the suppository weight was recorded. Average weight and weight variations were calculated to compare with official limits.[18,19-21]

Content uniformity

The suppository was dissolved in 10 mL of methanol under mild heating. The final volume was made up to 100 mL with a phophate buffer (pH 7.4). The resultant solution was passed through the Whatman filter paper, and the filtrate was collected. The drug was estimated in the filtrate after appropriate dilutions with phosphate buffer at pH 7.4 using a UV-vis spectrophotometer (UV-1900i, Shimadzu Corporation, Kyoto, Japan) at a wavelength of 283 nm.[18] The study was repeated three times, and the average drug content was reported.

Hardness

The Monsanto tester was used to determine the hardness of the etoricoxib rectal suppositories. Three suppositories were selected from each batch, and the hardness was measured at room temperature.[22,23]

Disintegration time

Six suppositories were randomly selected from each batch and placed in cylindrical glass tubes [having a United States Pharmacopoeia (USP) type A basket with 10 mesh] of the USP tablet disintegration tester (DT 1000, LAB INDIA, Thane, Maharashtra). Suppositories holding glass tubes were allowed to be immersed in 900 mL of phosphate buffer (pH 7.4) and taken in a 1000 mL beaker while maintaining a dip speed of 30±1 DPM. The phosphate buffer temperature was maintained at 37±0.2 °C. The time taken by the suppositories to eliminate debris particles from the perforated ends of the glass tubes was recorded.[18,21]

Texture analysis

The adhesiveness, adhesive force, and stringiness of the formulated etoricoxib suppositories as mechanical properties were analyzed using a texture analyzer (XCTX0000000S00, Ametek Brookfield, USA), which was connected to a 1500 g load cell. The probe (TA39) and TA-RIF fixture were used in the analysis. The trigger load, distance, and holding time were 50.00 g, 5.00 mm, and 2.00 s, respectively. The probe traveled at a rate of 1 mm/s until the surface of the suppositories was detected.

Dissolution studies and drug release kinetics

The dissolution studies of the prepared etoricoxib suppositories were performed using a USP Type 2 Dissolution apparatus (DS 14000 Smart, LAB INDIA, Thane, India) in 250 mL of phosphate buffer (pH 7.4) by maintaining 25 rpm paddle speed. The dissolution media temperature was maintained at 37±0.5 °C using a thermostat. The 4.0 mL of sample was collected at predefined time points, and the equivalent volume of the replacement buffer was exchanged at regular time points. Collected samples were filtered through Whatman filter paper, and the drug was estimated in the filtrate after appropriate dilutions with pH 7.4 phosphate buffer using the UV-Vis spectrophotometer (UV-1900i, Shimadzu Corporation, Kyoto, Japan) at 283 nm wavelength. The study was repeated in triplicate, and the percent cumulative drug release was reported.[24] The drug release data were further assessed for *in vitro* drug release kinetics and release mechanisms. Zero-order kinetics, first-order kinetics, and the Higuchi plot were applied to evaluate the drug release kinetics, whereas the Korsmeyer-Peppas model was applied to evaluate the release mechanisms. The release mechanism was evaluated by applying the model to an initial 60% cumulative drug release.[24, 25]

Differential scanning calorimetry (DSC)

The chemical modifications in the polymeric structure, temperature transition changes, and stability of the formulations at 30 °C to 120 °C to 30 °C, 30 °C to 120 °C to 4 °C, and 30 °C to 150 °C to 30 °C were ensured by DSC studies. The study was performed using a DSC 2500, Discovery Series [TA Instruments Division, Waters (India) Private Limited, Bangalore] connected to a refrigerated cooling system 90. The 4-6 mg of drug containing suppositories were weighed, crimped in an aluminum pan, and analyzed with a heating rate of 10 °C/min and a nitrogen flow of 50 mL/min.[26]

Physical stability studies

The physical stability of the prepared suppositories was evaluated by storing them at 4±1 °C. The stability of the formulations was assessed by analyzing their homogeneity and color.

Statistical analysis

The results were calculated and presented as mean ± SD of independent assessments (n=3 or n=12). The Excel office 2019 was used for the calculation of data.

RESULTS

Drug excipient compatibility

The FTIR spectra of etoricoxib, glycerin, gelatin, and physical mixture (etoricoxib + both gelatin and glycerin in a 1:1 ratio) are shown in Figure 1A-D, respectively. Figure 1A shows the etoricoxib spectra with the characteristic absorbance bands at 3050.8 cm^{-1}, 1594 cm^{-1}, 1428.7 cm^{-1}, 1390 cm^{-1}, 1292.7 cm^{-1}, 1139.9 cm^{-1}, 1090 cm^{-1}, 1008 cm^{-1} (in-plane: C-H bend), 955.7 cm^{-1} (in-plane: C-H bend), and 769.42 cm^{-1} for aromatic C-H stretching, stretching of C=C, aliphatic bending (asymmetric) of C-H, aliphatic bending (symmetric) of C-H, stretching vibration (asymmetric) of O=S=O, stretching vibration (symmetric) of O=S=O, aromatic stretching of C-Cl, in-plane C-H bend (aromatic), and out-of-plane C-H bend (aromatic), respectively.[27,28] The characteristic absorbance bands in the obtained spectra confirm that the present sample is etoricoxib.

Figure 1B depicts the glycerin spectra with absorbance bands of 3283.1 cm^{-1} for OH stretching, 2931.5 cm^{-1} to 2821.3 cm^{-1} for C-H stretching, 1414 cm^{-1} for C-O-H bending, 1108 cm^{-1} and 1035.2 cm^{-1} for C-O stretching, and 993.37 cm^{-1} for O-H bending.[29-31] The presence of the above-mentioned absorbance bands reveals that the present sample is glycerin.

Figure 1C illustrates the IR spectra of gelatin with characteristic absorbance bands of 2300 cm^{-1} to 3600 cm^{-1}, for amide A, 1600 cm^{-1} to 1620 cm^{-1} for amide 1 (C=O) stretching, 1560 cm^{-1} to 1300 cm^{-1} for amide 2 (NH bending), 1240 cm^{-1} to 2929.4 cm^{-1} and 670 cm^{-1} for amide 3 (C-N stretching).[32] The obtained band confirms that the given sample is gelatin.

Figure 1D shows the physical mixture of etoricoxib with both glycerin and gelatin in a 1:1 ratio of the drug and excipients. The presence of characteristic absorbance bands at 1595 cm^{-1} for C=C aromatic benzene, 1294 cm^{-1} for O=S=O stretching vibration (asymmetric), 1139 cm^{-1} for O=S=O stretching vibration (symmetric) of etoricoxib, for glycerin bands at 3297.8 cm^{-1} for OH stretching, 2929.4 cm^{-1} and 2875 cm^{-1} for C-H stretching, and for gelatin absorbance bands are observed. FTIR studies confirm the absence of interactions between etoricoxib and excipients.

Physical appearance

Table 2 lists the physical characteristics of the prepared suppositories. There were no observable differences in the suppositories among the batches. Suppositories were slightly yellowish and opaque. All the suppositories were conical with no breakage.

Homogeneity test

As shown in Table 2, the SB2 suppositories were found to be homogeneous, smooth, and free from dryness. The remaining batches of suppositories were found to be almost homogeneous, smooth, and free from dryness.

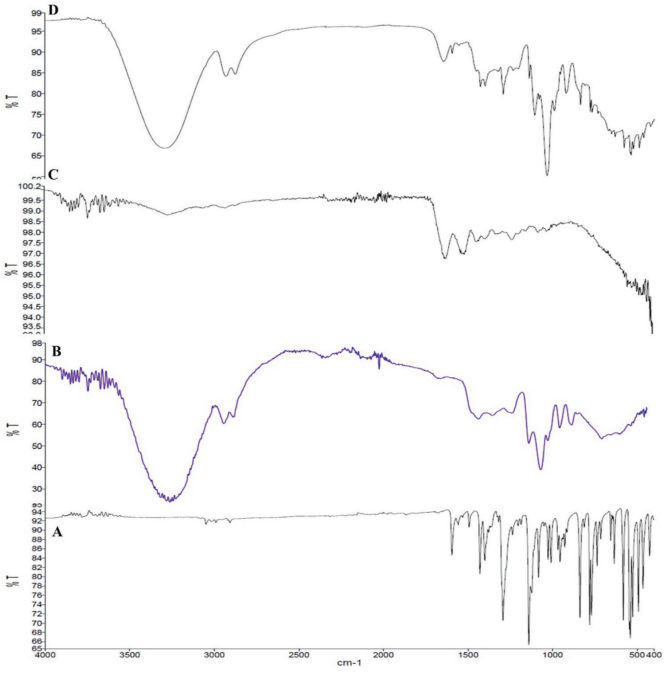

Figure 1. FTIR spectra: (A) Etoricoxib; (B) Glycerin; (C) Gelatin; (D) PM
FTIR: Fourier transform infrared spectroscopy, PM: Physical mixture

Hardness

Different hardness values were recorded for different batches of suppositories. Batch SB1 suppositories showed the lowest hardness values, *i.e.*, 4.00±0.50 kg/cm, SB2 suppositories showed the highest hardness values, *i.e.*, 7.50±0.50 kg/cm^3, whereas SB3 and SB4 presented almost the same hardness values, *i.e.*, between 5.9±0.36 and 5.5±0.50 kg/cm^3 (results are reported in Table 2). The SB2 sample had the highest hardness, which may be attributed to the higher concentration of gelatin in this batch.

Weight variation

The weight variation values (shown in Table 2) were within the acceptable weight variation limits, with values between 0.00 and 1.09%. SB2 exhibited the highest content uniformity, *i.e.*, 80.76±3.6%.

Content uniformity and disintegration time

The content uniformity (results are depicted in Table 2) for all batches was found to be between 66.98 and 80.76% with a very low standard deviation. As reported in Table 2, the disintegration time was noticed in the following order: SB2>SB4>SB1>SB3. SB2 exhibited a longer disintegration time, which may be due to the presence of a higher gelatin concentration in this batch. SB3 showed the least disintegration time, which may be due to the lowest concentration of gelatin in these suppositories.

Texture analysis

The texture analysis of the formulated suppositories is presented in Table 3. Suppositories SB1 and SB3 showed the highest adhesive forces, *i.e.*, 4.70±1.20 and 3.90±2.80 g, respectively, compared with the other batches of suppositories, which may be due to the presence of a higher glycerin-to-gelatin ratio, *i.e.*, 3.00 and 3.25, respectively. These two batches of suppositories also gave higher standard deviation values than the SB2 and SB4 suppositories. The SB2 suppositories showed the least adhesive force, *i.e.*, 3.73±0.90 g) among all remaining batches. The standard deviation values of SB2 and SB4 were also lower.

The SB1 and SB3 suppositories (with adhesiveness values of 0.07±0.04 and 0.14±0.01 mJ, respectively) also showed the highest adhesiveness compared with the SB2 and SB4 suppositories (with adhesiveness values of 0.06±0.01 and 0.09±0.01 mJ, respectively).

Stringiness was found to decrease with increasing glycerin concentration but to increase with increasing gelatin concentration. SB2 showed the highest stringiness (1.36±0.24 mm), whereas SB3 showed the lowest stringiness (0.20±0.15 mm).

Dissolution studies and drug release kinetics

Figure 2 shows the *in vitro* drug release profile of the drug from the prepared batches of suppositories in phosphate buffer (pH 7.4) to mimic the physiological condition of the rectal. SB3 gave the fastest drug release (*i.e.*, 91.47±17.74% in 6 h) because it had a gelatin-to-glycerin ratio of 0.31. SB1

induced complete drug release within 12 h (*i.e.*, 99.08±3.40%). The drug release from SB2 and SB4 was found to be almost the same, (*i.e.*, 98.14±13.50% and 97.12±26.66%, respectively) within 10 h.

The obtained drug release data was assessed for drug release kinetics and mechanisms (the data is reported in Table 4). The drug release from all the formulated batches of suppositories except SB4 was appropriately supported by zero-order and first-order drug release kinetics. The release of drugs from SB4 was noticed to be first-order-based. The release of drugs from the suppositories was also supported by the Higuchi plot.

Differential scanning calorimetry

To confirm the changes in the polymeric structure of gelatin between 30 °C and 120 °C, the prepared suppositories underwent DSC analysis. The study was executed by scanning the samples between 30 °C and 120 °C and then reversing the thermal cycle from 120 °C to 30 °C at a rate of 10 °C/min. The absence of modifications was recorded in the thermogram during the study, as reported in Figure 3A, confirming that gelatin retains its polymeric structure at the mentioned temperature range.

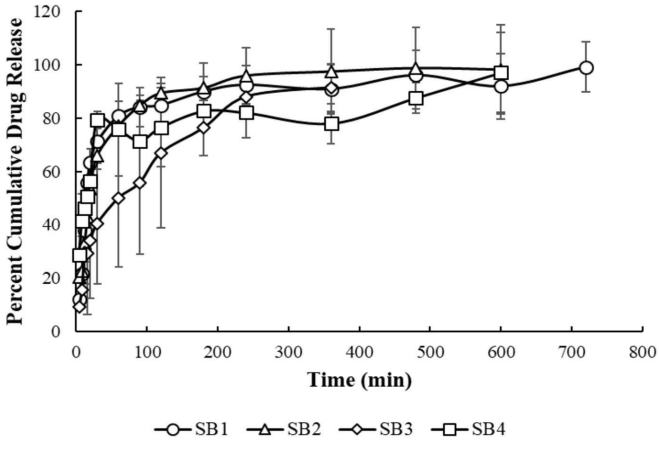

Figure 2. In vitro drug release profile of formulated suppositories. *Above data are presented as mean ± SD, n=3

SD: Standard deviation

To assess the stability of the prepared suppositories at 4 ºC, the DSC runs were recorded in the thermal cycle from 30 to 120 °C and then reversed from 120 to 4 ºC. The absence of modifications in the thermogram was observed (data presented in Figure 3B), indicating the stability of the prepared suppositories between 4 °C and 120 ºC.

The DSC thermogram shown in Figure 3C confirms the stability of the active molecule over the temperature range of 30 °C to 150 ºC.

Physical stability studies

The prepared suppositories exhibited good homogeneity over a period of 21 days (Figure 4). No observable differences in homogeneity or physical appearance were recorded during storage at 4 °C. However, a slight color change was observed in the formulated suppositories.

DISCUSSION

As reported in the literature,[33,34] etoricoxib has good permeability, with a log P of approximately 2.8. However, its solubility was reported to be 0.0245, 0.0103, 0.0772, and 0.0785 mg/mL in water, acetate buffer pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4, respectively.[35] Hence, the drug solubility was better at the rectal pH, *i.e.*, between pH 7 and 8, compared to all other regions. Another reason is that because the drug has a pKa value of 5,[33,34] it can also have better absorption at rectal pH.

Long-term constipation contributes to the development of hemorrhoids owing to the presence of irritates and enlarged blood vessels inside and around the anus.[36,37] Glycerin in suppositories is also most commonly used in the treatment of constipation.[38] Hence, the presence of glycerin in the suppositories for the management of constipation-based hemorrhoids may be preferable. Another reason is that the addition of glycerin to the suppositories enhances their lubrication and imparts their moisturizing properties, which further, in contact with the minimal amount of water from the surrounding tissue, enhances the dissolution of the suppositories.[39,40] On the other hand, the presence of gelatin in the suppositories dissolves slowly and

Table 2. Physical characteristics of etoricoxib rectal suppositories

Physical characteristics	Formulation batch			
	SB1	SB2	SB3	SB4
Color and opacity	Slight yellowish and opaque	Slight yellowish and opaque	Slight yellowish and opaque	Slight yellowish and opaque
Shape*	Conical	Conical	Conical	Conical
Homogeneity*	Almost homogeneous and smooth with no dryness	Homogeneous and smooth with no dryness	Almost homogeneous and smooth with no dryness	Almost homogeneous and smooth with no dryness
Hardness* (kg/cm^3)	4.00±0.50	7.50±0.50	5.90±0.36	5.50±0.50
Weight variation (g)#	1.20±0.03	1.30±0.02	1.31±0.01	1.25±0.02
Content uniformity (%)*	66.98±0.86	80.76±3.60	74.34±5.70	78.66±1.48
Disintegration time (min.)	13.45	19.05	11.00	18.00

*Results present as mean ± SD, n=3, #Results present as mean ± SD, n=12. min.: Minimum, SD: Standard deviation

maintains long-term drug release at the site.[38] The combination of glycerin and gelatin is complementary to each other to maintain sustained drug release.

Furthermore, drugs that are not completely soluble and have been dispersed in suppositories with opposing properties encourage the drug to leave the fluid.[38,41,42] Considering this useful fact, lipophilic drugs (such as nifedipine, diclofenac sodium, *etc.*) have been incorporated in hydrophilic bases for better delivery on the application site.[39,43]

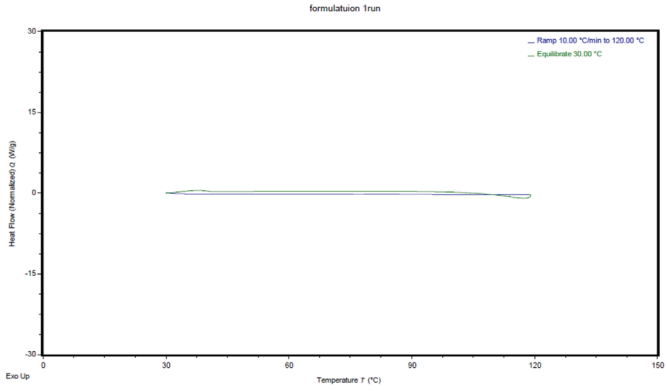

Figure 3A. DSC thermogram of suppositories from 30 °C to 120 °C and 120 °C to 30 °C

DSC: Differential scanning calorimetry

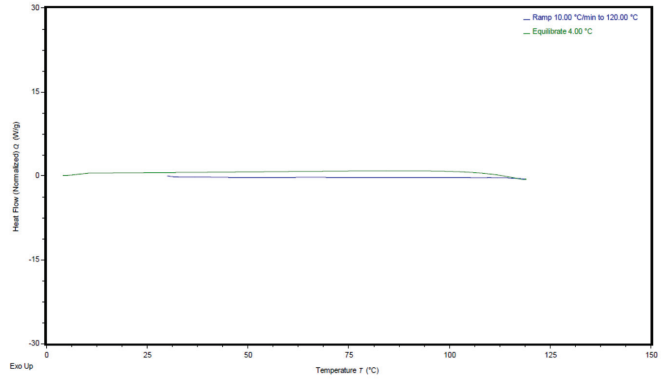

Figure 3B. DSC thermogram of suppositories from 30 °C to 120 °C and 120 °C to 4 °C

DSC: Differential scanning calorimetry

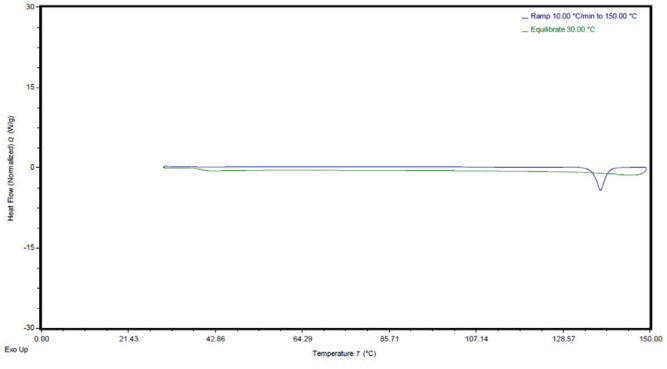

Figure 3C. DSC thermogram of suppositories from 30°C to 150°C and 150°C to 30°C

Abbreviations: DSC: Differential scanning calorimetry

USP 1151 recommends a glycerin: gelatin: water ratio of 70:20:10 for suppositories. However, this study was planned with slight modifications to the above-mentioned ratio to obtain a suitable sustained-release formulation. The study used glycerin: gelatin: water in ratios of 60 to 65:20 to 25:7 to 17. The study was planned to sustain the release of the drug from the formulated suppositories for a period of 8-10 h, as this is preferred during bedtime.

FTIR spectroscopy was conducted to confirm etoricoxib and its compatibility with the excipients planned in the study. The study showed all characteristic absorbance bands positioned as per the literature[27-32] in the obtained spectra, which confirms that the present sample is etoricoxib and also ensures its compatibility with the selected polymers. This study is in line with the earlier findings reported[24] for other molecules such as gelatin and glycerin.

The formulated suppositories were wrapped in parchment paper, which is a cellulose-based paper with properties such as non-stickiness, grease resistance, humidity resistance, and heat resistance. This paper was used to wrap the suppositories to prevent moisture loss during storage at 4 ºC.

Although color, size, and shape have negligible effects on the effectiveness of the suppositories,[38] they are considered parameters for their attractive appearance. This study demonstrated that the use of glycerin and gelatin in the suppositories not only maintains their shape but also helps in the homogeneous distribution of the drug.

The hardness of the suppositories has been given the least importance in the literature; however, this parameter is assumed to be important as it may influence drug release, therapeutic response, and packaging and transportation hazards. It is assumed that as the hardness of the material increases, drug release and response decrease. The formulation with glycerin: gelatin: water in a ratio of 60:25:12 produced uniform suppositories with optimal hardness, least weight variation, and sufficient disintegration time. This combination is considered suitable and anticipated to be useful for sustaining the release of the formulation due to the slightly higher concentration of the gelatin.[38]

The highest adhesive force was noted with a higher glycerin-to-gelatin ratio. The findings are similar to earlier research in this area, in which researchers showed an increase in bio-adhesive force with glycerin.[44] Glycerin enhances the bioadhesive strength by enhancing the degree of penetration of the polymer chains.

Both SB2 and SB4 contained a higher concentration of gelatin, which retarded drug release from formulated suppositories compared with the other batches. On the other hand, these studies showed that glycerin enhances drug release with an increase in its concentration owing to its wetting properties.[18] SB2 can provide complete drug release throughout 8 to 10 hours, which is essential for a patient to achieve complete drug release during bedtime. According to the reported n-value

Table 3. Texture analysis of etoricoxib suppositories

Formulation	Adhesive force (g)	Adhesiveness (mJ)	Stringiness (mm)
SB1	4.70±1.20	0.07±0.04	1.10±1.30
SB2	3.73±0.90	0.06±0.01	1.36±0.24
SB3	3.90±2.80	0.14±0.01	0.20±0.15
SB4	4.20±0.20	0.09±0.01	0.25±0.05

All results represent as mean ± SD, n=3. SD: Standard deviation

Table 4. Drug release kinetics

Formulation code	Zero-order		First-order		Higuchi plot	Korsmeyer-Peppas	
	r^2	K	r^2	K	r^2	r^2	N
SB1	0.92±0.05	13.50±0.98	0.92±0.03	0.24±0.03	0.92±0.03	0.77±0.14	0.20±0.04
SB2	0.85±0.14	9.44±1.61	0.89±0.12	0.16±0.02	0.93±0.08	0.87±0.08	0.10±0.01
SB3	0.88±0.07	7.85±3.20	0.83±0.13	0.12±0.05	0.88±0.07	0.93±0.05	0.12±0.03
SB4	0.57±0.26	3.53±0.99	0.84±0.13	0.13±0.01	0.85±0.09	0.82±0.06	0.065±0.01

*Above data are presented as mean ± SD (n=3), r^2: Correlation coefficient, and K: Reflecting rate constant, SD: Standard deviation

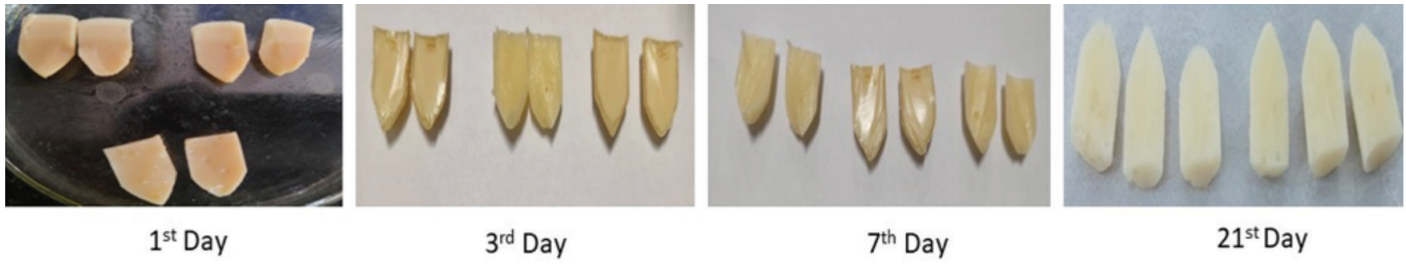

Figure 4. Appearance of formulated suppositories at 4 °C for a period of 21 days

(release exponent), all batches of the formulated suppositories showed the Fickian diffusion mechanism.[24,25,45]

The formulations are physically stable; this may be due to the presence of gelatin, which may contribute to maintaining the shape and size of the suppositories. However, chemical stability studies (especially for the estimation of drug content) are preferred for these formulations in the future.

CONCLUSION

This study was initiated to develop novel etoricoxib rectal suppositories to provide instant pain relief and anti-inflammatory activity in hemorrhoids. Drug-containing suppositories were formulated using glycerin and gelatin as a suitable base. From the evaluation studies of the formulated suppositories, we conclude that the SB2 suppositories have a very good physical appearance with optimum hardness, disintegration time, and weight variation. Further, from the texture analysis studies, we also concluded that the formulated suppositories have good adhesive force and adhesiveness, demonstrating their suitability for preventing rectal leakage and entry of the drug into the colon. The elasticity of the formulated suppositories, as stringiness, was also found to be suitable. The *in vitro* drug release, as an important study to predict the fate of formulated suppositories *in vivo,* showed a desirable release pattern with etoricoxib release of 98.14±13.50% in 10 h, and this drug release was diffusion-based, which is expected to be suitable for this type of formulation. Therefore, based on the *in vitro* evaluations of the formulated suppositories, we conclude that the present work has future scope and should be explored for further investigation of their activities in cell lines and *in vivo*.

Ethics

Ethics Committee Approval: This work does not involve any studies or research that needs approval from any review or ethics board.

Informed Consent: Not required.

Authorship Contributions

Concept: L.K., Design: L.K., Data Collection or Processing: B.S., Y.K., N.M., S.K., Analysis or Interpretation: B.S., Y.K., N.M., S.K., Literature Search: B.S., Writing: B.S., L.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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