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Development and evaluation of gastroretentive mucoadhesive microspheres of gabapentin

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Abstract: Epilepsy and neuropathic pain are two of the most prevalent neurological condition affecting millions of people worldwide, necessitating effective treatments like gabapentin. The purpose of this research was to develop and analyze gabapentin sustained-release mucoadhesive microspheres using hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) as polymers. Using varying polymer ratios, gabapentin microspheres were produced by solvent evaporation technique. Scanning electron microscopy was used to assess the (DSC & IR spectroscopy), swelling index, percentage yield, content uniformity, particle size, in vitro release of drugs, mucoadhesion test of microspheres. With different polymer ratios, five formulations were created. The range of encapsulation efficiency was 82.95% to 97.75%. Formulation 5 (Gabapentin: Ethyl Cellulose: HPMC, 1:2:3) exhibited optimal drug release characteristics, sustaining release for 16 hours in simulated gastric fluid (0.1N HCl), following first-order kinetics. Microspheres showed strong mucoadhesive properties, potentially prolong the medication's half-life in the stomach, increasing its bioavailability and therapeutic effectiveness. This research uses HPMC and EC polymers to develop and evaluate sustained-release mucoadhesive microspheres of gabapentin. Formulation 5 is the optimal formulation, demonstrating sustained drug release and excellent mucoadhesive properties. These microspheres hold promise for the oral sustained release of Gabapentin, potentially improving the treatment of epilepsy and neuropathic pain.

Keywords: Muco-adhesive, gabapentin, gastro-retentive, Hydroxypropyl Methylcellulose (HPMC), microspheres, solvent evaporation method.

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INTRODUCTION

Mucoadhesion is the process of a natural or synthetic polymer adhering to the mucosal layer. The development of pharmaceutical delivery systems shows interest in prolonging the dosage form's residence duration in the gastrointestinal tract. This allows for more intimate contact with the absorption surface, which improves the bioavailability of pharmaceuticals(Rhushikesh and Suresh, 2020). Epilepsy and neuropathic pain are two of the most prevalent neurological condition affecting millions of people worldwide (Cano *et al.*, 2021). The severity of these conditions necessitating effective treatments like gabapentin to improve quality of life. Its oral bioavailability is limited due to poor solubility and permeability. To overcome this challenge, Microencapsulation of gabapentin in a sustained-release formulation could improve its oral bioavailability, reduce dosing frequency, and enhance patient compliance (Kim *et al.*, 2024). This project aims to develop and validate gabapentin microspheres as a new dosage form to improve gabapentin's bioavailability and therapeutic efficacy for neuropathic pain and epilepsy patients, thereby improving their quality of life.

Gabapentin is available in various formulations, including capsules, tablets and oral solution. These conventional drug delivery systems offer ease of usability and adaptability in formulation, but they have drawbacks such as patient non-adherence because of frequent dosing, unpleasant consequences resulting from inconsistent plasma drug concentrations, incompetence to maintain optimal drug levels in plasma for therapeutic efficacy, and excessive dosing (Bouchard *et al.*, 2022). To address these limitations, altering actual drug delivery systems (DDSs) to design prolonged release (PR) or controlled release (CR) DDS is essential. Developing limited absorption window drugs in Gastroretentive dosage forms enables prolonged absorption phases and simultaneous enhancement of bioavailability (Rimawi *et al.*, 2019). Mucoadhesive systems, which utilize bio adhesive polymers adhering to the epithelial surface in the stomach, can target delivery devices within the lumen to optimize drug absorption in a localized technique. These innovative formulations and drug delivery systems can significantly optimize patient adherence and therapeutic results (Waqar *et al.*, 2024).

The neuroprotective drug gabapentin (GBP), also known as 1-aminomethyl cyclohexane acetic acid, has antiepileptic qualities (Yu *et al.*, 2019). Although Its structure is similar to that of GABA, it does not bind to GABA receptors or affect GABA production or uptake. In order to function, gabapentin must have a strong affinity

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for binding sites across the brain that correspond to voltage-gated calcium channels, particularly alpha-2-delta-1. This binding affinity appears to inhibit the release of excitatory neurotransmitters in the presynaptic area that are involved in epileptogenesis (Yasaei *et al.*, 2022). Given its short half-life (5-7 hours) and limited bioavailability (60%) of gabapentin, typical immediate-release solid dosage formulations require three daily doses (Agró *et al.*, 2020). Mucoadhesive Gastroretentive microspheres can provide the sustained release of drug by reducing dosing frequency and increasing gastric retention time of drug by virtue of slower release rate that avoid saturation of carrier mediated transport of conventional dosages (Mandal *et al.*, 2016).

The mucoadhesive microspheres containing olanzapine demonstrated a prolonged release action, resulting in enhanced treatment efficacy and patient compliance (Deshmukh and Mohite, 2017). When furosemide was formulated into Gastroretentive mucoadhesive microspheres, it was discovered that as mucoadhesive polymer increases, it leads to decreased medication release. This may be explained by the microspheres' increased mucoadhesive polymer content, which causes them to swell more when hydrated. This lengthens the diffusional channel, which slows the release of the medicine (Kumar and Nanda, 2016). Because of characteristics including high entrapment efficiency and swelling index, pioglitazone HCl microspheres are utilized to reduce adverse effects, lower dosage frequency, and increase patient compliance (Nagarajan and Katakam, 2016). High swelling index pioglitazone microspheres were synthesized with sodium carboxy methyl cellulose, HPMC, sodium alginate, Carbopol 934 P, and cellulose acetate butyrate polymers. The capability of a polymer to swell before the drug is released is swelling index which determines the rate and mechanism of drug release from the polymer matrix (Gebre-Mariam *et al.*, 2015).

The objective of the formulation of gabapentin microspheres for mucoadhesive drug delivery is to increase its residence time in the stomach, enhancing absorption and efficacy. This formulation aims to control drug release by adhering to gastric mucosa lining, thus reducing dosing frequency and enhancing patient compliance (Gaur *et al.*, 2014). The absorption of gabapentin in the stomach shows saturation kinetics due to less absorption time, demanding a longer and better formulation without exceeding saturation, aiming to increase absorption and bioavailability.

MATERIALS AND METHODS

Materials

Gabapentin was handed down from Horizon Pharmaceuticals, Pakistan. Ethyl cellulose was purchased from Dow Chemical Company, Washington. Hydroxypropyl methylcellulose K100 (HPMC) was attained from Zeon Health®. Acetone and PVA (Sigma-Aldrich) were purchased from local market. Tween 80 (Sigma Chemical Company, Germany) was purchased from local market. Double Distilled water was obtained from lab distillatory machine. All the chemicals employed were of research grade.

Table 1: Formulation of gabapentin microspheres

Formulation code	Drug: Polymer	Ratio
F1	Gabapentin: EC: HPMC	1:1:1
F2	Gabapentin: EC: HPMC	1:2:1
F3	Gabapentin: EC: HPMC	1:1:2
F4	Gabapentin: HPMC	1:2
F5	Gabapentin: EC: HPMC	1:2:3
F6	Gabapentin: EC	1:2

Pre-Formulation Studies

Crystallinity

Gabapentin's crystalline structure was investigated by microscopy, using scanning electron microscope operating at 15 kv (Biswas and Siddique, 2024). The shape and surface characteristic of the gabapentin was observed.

Particle size

Particle size analysis of gabapentin powder was performed using the sieving method (Samani *et al.*, 2020). The drug powder was sieved through a series of meshes with decreasing aperture sizes, measuring the mass retained on each sieve. Results showed a particle size distribution of 90% between 150-250 µm, 5% below 150 µm, and 5% above 250 µm. This indicates a relatively uniform particle size, suitable for pharmaceutical applications. The sieving method provided a simple and effective way to determine the particle size distribution of gabapentin powder.

Melting point

The determination of gabapentin's melting point is a crucial aspect of its characterization, as it provides valuable information about its thermal stability and purity. In this experiment, we employed a precise and reliable method to determine the melting point of gabapentin, yielding a value of 162-167°C. This result is consistent with previously reported values, confirming the accuracy of our experimental procedure.

Flow properties

Angle of repose

The precise weighted microcapsules were taken in funnel utilizing the fixed funnel method. Mixtures were freely permitted to pour onto the surface through the funnel. After measuring the cone diameter of the microcapsules, the angle of repose was calculated using the formula.

$$\tan \theta = h/r \qquad \text{Eq 1}$$

θ represents angle of repose, h represents Height, r represents Radius of base pile

Table 2: Micromeritics of gabapentin microspheres

Formulation code	Compressibility index %	Hausner ratio	Angle of repose
F1	12.5	1.17	23.44
F2	10.54	1.14	20.6
F3	11.17	1.12	24.5
F4	10.78	1.15	25.8
F5	12.71	1.18	21.9
F6	8.74	1.05	19.4

Table 3: Data for different aspects of mucoadhesive microcapsules of Gabapentin

Formulations	Yield (%)	Mean particle diameter (µm)	Encapsulation efficiency (%)	Swelling ratio (X±S.D.)
F1	89.25	752.21	90.88	0.634±.0055
F2	92.83	744.52	94.62	0.664±.0066
F3	82.95	783.87	87.66	0.588±.004
F4	86.33	763.64	88.36	0.599±.0033
F5	95.5	756.46	95.18	0.697±.0252
F6	97.75	754.96	97.72	0.767±.0019

Table 0: Drug release kinetics

Release models	Release coefficients	F1	F2	F3	F4	F5	F6
Zero-order (F=k0*t)	k0	13.733	14.467	13.254	12.853	11.374	12.446
	Rsqr	0.9365	0.9170	0.8779	0.8405	0.9841	0.9227
	AIC	37.916	40.937	41.251	41.423	28.749	38.014
	MSC	2.4242	2.1555	1.7700	1.5022	3.8097	2.2273
First-order (F=100*[1-Exp(-k1*t)])	k1	0.280	0.310	0.274	0.261	0.189	0.236
	Rsqr	0.9743	0.9556	0.9819	0.9822	0.9645	0.9903
	AIC	32.501	37.177	29.815	28.276	33.576	25.589
	MSC	3.3267	2.7820	3.6760	3.6935	3.0052	4.2981
Higuchi (F=kH*t^0.5)	kH	32.604	34.252	31.703	30.959	26.434	29.573
	Rsqr	0.9346	0.8976	0.9328	0.9696	0.8624	0.9269
	AIC	38.098	42.194	37.674	31.473	41.707	37.685
	MSC	2.3937	1.9460	2.3661	3.1606	1.6499	2.2822
Korsmeyer-Peppas (F=kKP*t^n)	kKP	22.878	23.284	24.262	25.874	13.866	20.948
	Rsqr	0.9943	0.9573	0.9664	0.9892	0.9875	0.9820
	AIC	24.104	37.610	34.174	25.928	27.989	29.931
	MSC	4.7261	2.7100	2.9494	4.0847	3.9363	3.9545
	n	0.719	0.738	0.666	0.612	0.892	0.813

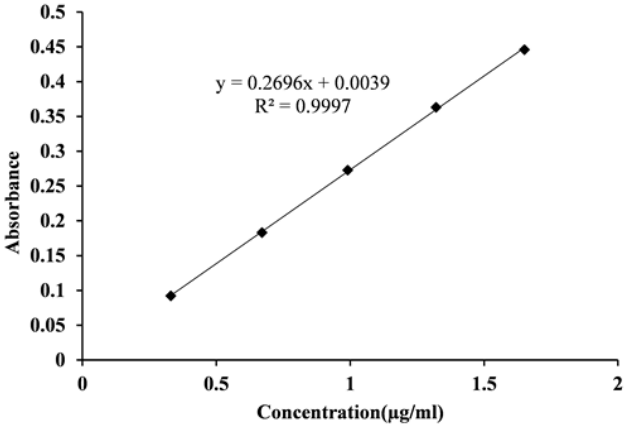

Fig. 1: Standard Curve of Gabapentin in Phosphate buffer

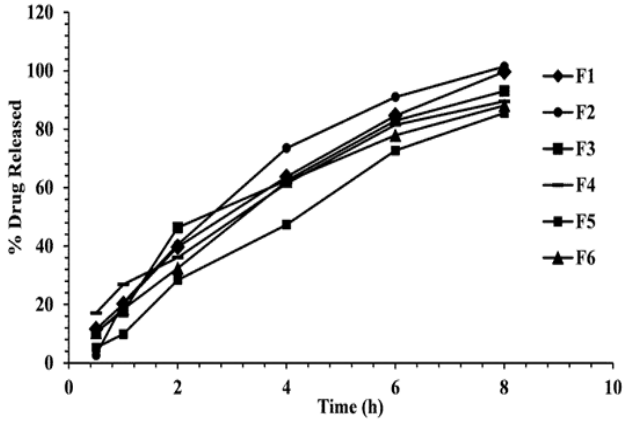

Fig. 2: Dissolution profile of F1 to F6

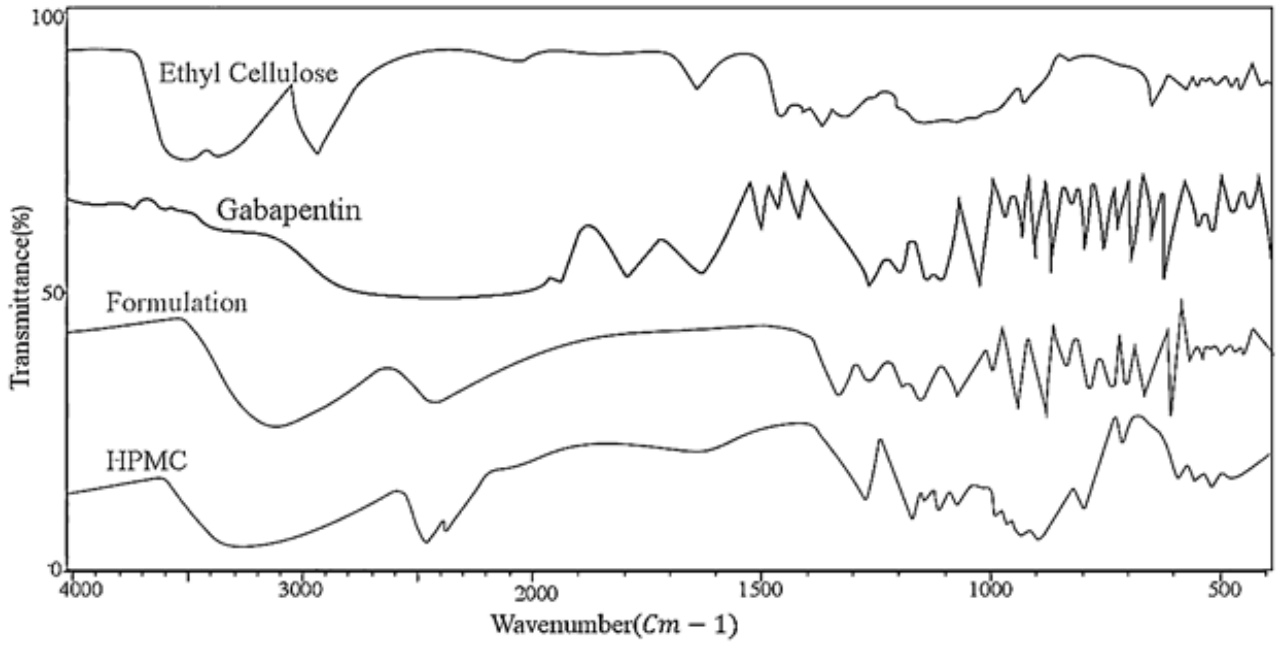

Fig. 3: FTIR scan of drug, polymers and Formulation (F6)

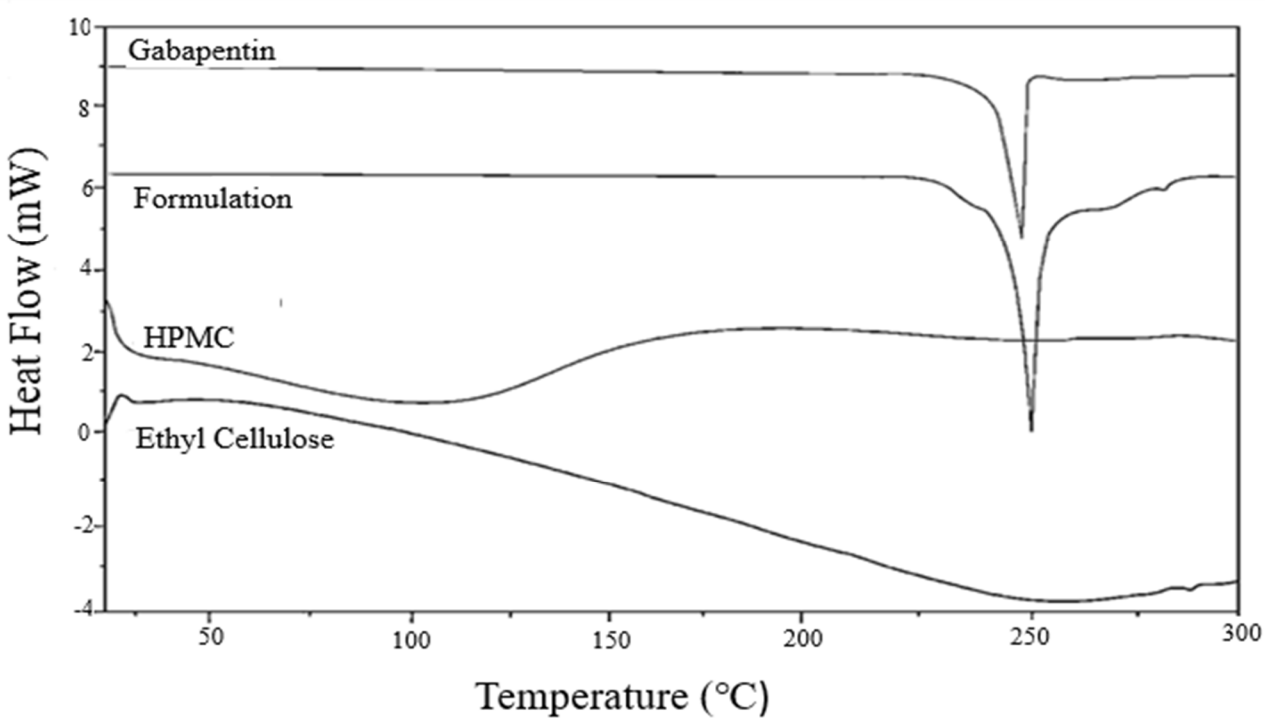

Fig. 4: DSC Scan of drug, polymer and Formulation (F6)

Compressibility index

The formula that was applied to determine it.

Ci = (Vo – Vt) / Vo x 100 Eq 2

Where Vo corresponds volume before tapping and Vt as volume after tapping

Hausnner's ratio

The formula that was applied to determine it.

Hausnner,s ratio =V / Vt Eq 3

Where Vo is the volume before tapping and Vt is the volume after tapping

Hygroscopicity

The hygroscopicity of gabapentin powder was determined by using the gravimetric method (Tereshchenko, 2019). The drug powder was exposed to varying humidity levels and the mass change was measured over time. Results showed that gabapentin powder exhibited low

hygroscopicity, with a moisture uptake of 0.5% at 60% RH and 1.2% at 80% RH. These findings confirm the powder's stability and ease of processing, supporting its use in pharmaceutical applications. The gravimetric method proved to be a reliable and accurate technique for assessing hygroscopicity.

Preparation of microspheres

The gabapentin microspheres were prepared by the solvent evaporation technique (Ahangaran, 2023). The summary of all prepared formulations is shown in Table 1. Firstly, in a beaker 0.5% w/v of PVA solution was prepared by dissolving 0.5g PVA in 100 ml distilled water. In another beaker different ratios (1:1, 1:2 and 1:3) of the drug: polymer solution was prepared. The polymers like, ethyl cellulose and Hydroxypropyl Methylcellulose (HPMC) were used. The batches were designated as F1, F2, F3, F4, F5 and F6. The polymers used alone or in combination along with known quantity of gabapentin were dissolved in 20 mL of acetone using a magnetic stirrer. The above process continued until complete mixing of the drug and polymer in acetone took place. The resulting solution was taken in a syringe and added drop wise into the beaker containing a solution of PVA (0.5% w/v) which is under stirring at 900 rpm using mechanical stirrer. Along with 0.2% w/v of Tween 80 was added which was used as a surfactant. The stirring was continued until acetone was evaporated in about 2 to 3 h. After the solvent completely evaporated, the microspheres solidified into distinct particles. The microspheres were separated by filtration using Whatman filter paper and washed three times with distilled water and dried in a desiccator at 45°C. Then the obtained microspheres were collected and performed further studies.

Post-Formulation Studies

Determination of drug content

Precisely weighed 100 mg microcapsules were broken up into a powder using a pestle and mortar, which was then combined with 100 milliliters of 0.1 N hydrochloric acid. The solution was filtered after 24 hours, and the amount of drug in the filtrate was measured using a UV-visible spectrophotometer (Sarita and Muzaffar, 2013).

Encapsulation efficiency

The entrapment efficiency was measured in order to evaluate the amount of gabapentin that was successfully encapsulated within the microspheres. To enable the disintegration and the release of the medicine that was encapsulated, precisely weighed microspheres were incubated for a predetermined amount of time in a suitable buffer solution. Based on the initial amount added in relation to the total weight of all formulation components, the theoretical amount of drug present was calculated. Calculation was performed using Microsoft excel.

Contents uniformity

The contents uniformity of gabapentin mucoadhesives microspheres was evaluated to ensure consistent drug delivery. Microspheres from different formulations were analyzed, and the percentage yield was calculated to be 86.6%.

In vitro dissolution study

In in-vitro drug release studies, USP type I (Basket type) dissolution test apparatus was used. Sufficient amount of microspheres, equivalent to 100 mg gabapentin, from each batch were added to 900 ml of dissolution medium having 1.2 pH and was stirred at 100 rpm at 37 ± 0.5°C. A 10 ml quantity was withdrawn from the dissolution medium at pre-determined intervals of 0.5-hour, 1st hour, 2nd hour, 4th hour, 6th hour, and 8th hour. After every withdrawal, the volume taken out was supplanted with an equivalent volume (10 ml) of new disintegration medium to keep up with sink conditions. The collected samples were filtered, appropriately diluted, and then analyzed for gabapentin content by measuring absorbance at 277 nm using a UV spectrophotometer. The drug release percentage was plotted against time. Each experiment was repeated three times, and the average percentage of release was calculated for each batch.

Drug release kinetics

To comprehend the release mechanism and kinetics, the drug release data from the in-vitro dissolution study were analyzed using a variety of mathematical models, including zero order, first order, Higuchi's, and Korsmeyer-Peppa's. The correlation coefficient (R^2), Akaike Information Criterion (AIC), and Model Selection Criterion (MSC) values for the linear curves were determined using regression analysis. The approval criteria were MSC > 3.5, AIC ≤50, and $R^2 \geq 0.95$. All of the analyses were done with DDSolver (Elmas *et al.*, 2020, Hussain *et al.*, 2020).

Compatibility studies

FT-IR studies

A Fourier-transform infrared (FTIR) spectrometer such as the Avatar System 320 was utilized to ascertain the chemical composition of microsphere formulation. A small quantity of the sample was blended with potassium bromide using a mortar and pestle. This amalgam was then compressed into a pellet and positioned within the FTIR spectrophotometer for analysis across a frequency range spanning from 500 to 4000 cm^-1 (Hv and Bhattacharyya, 2021).

Differential Scanning Calorimetry

DSC studies were conducted to investigate the interactions between Gabapentin and two polymers, ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC). The samples were accurately weighed and placed in aluminum crucibles, which were then sealed

tightly. Nitrogen gas was continuously passed through the system at a rate of 60 mL/min to maintain an inert atmosphere. Heating was carried out from 30°C to 230°C at a rate of 10°C/min (Dewangan *et al.*, 2021).

Ex vivo wash off test

The adhesive properties of the microspheres were examined using the wash-off technique, an ex vivo assessment method for adhesion. Freshly harvested sections of gastric mucosa were adhered to glass slides using cyanoacrylate glue, and two such slides were connected with appropriate support. About 50 microspheres were dispersed onto each dampened tissue sample, which was promptly attached to the arm of a USP tablet disintegration test apparatus. The tissue underwent a slow, rhythmic movement in the test solution at 37°C within a 1 L vessel of the apparatus. This evaluation was conducted under simulated gastric (pH 0.1 N HCl, pH 1.2) and intestinal (phosphate buffer, pH 6.8) conditions. At intervals of 30 minutes, 1 hour, and subsequently every hour up to 12 hours, the apparatus was paused, and the remaining microspheres adhered to the tissue were counted (Djekic and Martinovic, 2020).

RESULTS

The evaluation of gabapentin microspheres revealed favorable flow properties, with compressibility index values ranging from 8.74% (F6) to 12.71% (F5), indicating good flowability and suitability for further processing. The Hausner ratio, which measures powder cohesion, ranged between 1.05 (F6) and 1.18 (F5), confirming excellent flow characteristics, while the angle of repose values varied from 19.4° (F6) to 25.8° (F4), indicating smooth powder flow and minimal chances of aggregation during handling. The content uniformity of the formulations was excellent, with encapsulation efficiency ranging from 82.95% (F3) to 97.75% (F6), and formulation F6 achieving a high encapsulation efficiency of 97.72%**,** reflecting effective drug entrapment within the microspheres. Additionally, the percentage yield was high across all formulations, with values ranging from 82.95% (F3) to 97.75% (F6), and formulation (F6) demonstrating a high yield of 97.75%**,** indicating minimal material loss during the production process. Solubility analysis of gabapentin showed a strong linear correlation between absorbance and concentration, with a correlation coefficient of 0.998, indicating consistent release from the microspheres. The in vitro dissolution studies demonstrated that formulations sustained drug release for up to 16 hours, following first-order kinetics with an R^2 value of 0.9227. The drug release mechanism, as determined by the Korsmeyer-Peppas model, had an n value of 0.813, indicating a combination of diffusion and polymer relaxation as the primary mechanisms of drug release. Compatibility studies using FT-IR and DSC confirmed the stability of gabapentin within the microspheres, with no observable chemical interactions between the drug and the polymers (ethyl cellulose and HPMC). The FT-IR spectra showed no significant shifts in the characteristic peaks of gabapentin, while the DSC thermograms revealed no change in the drug's melting point (250°C), confirming the preservation of its thermal and chemical integrity throughout the formulation process.

DISCUSSION

The results indicate that the gabapentin microspheres possess excellent flow properties, crucial for large-scale pharmaceutical production. The low compressibility index and Hausner ratio values suggest that the microspheres can be easily processed, allowing for efficient handling and uniform filling during tablet or capsule production, minimizing the risk of flow-related issues such as segregation or inconsistent dosing (Shetty *et al.*, 2019) . The high encapsulation efficiency observed, particularly in formulation F6, indicates that the solvent evaporation method used in the preparation of the microspheres was highly effective in entrapping gabapentin, ensuring consistent drug loading within the particles (Ganju *et al.*, 2024) . This uniformity in drug content is critical for achieving predictable and reliable therapeutic outcomes, particularly in sustained-release formulations where precise dosing over extended periods is required. The excellent percentage yield further supports the scalability of this formulation process, as it reflects minimal material loss, making it economically viable for mass production. The solubility analysis highlights the improved solubility and consistent release profile of gabapentin in its microsphere form, which is vital for enhancing the bioavailability of the drug, particularly given its poor solubility and limited absorption in conventional dosage forms.

The *In Vitro* dissolution studies provide strong evidence for the sustained-release capabilities of the microspheres, which demonstrated controlled drug release over a 16-hour period. The release profile, governed by first-order kinetics, suggests that the rate of drug release is concentration-dependent, while the Korsmeyer-Peppas model confirms that the release mechanism involves both drug diffusion through the polymer matrix and relaxation of the polymer chains. This combination of mechanisms is ideal for ensuring a prolonged therapeutic effect, reducing the frequency of dosing and improving patient compliance, which is particularly important for managing chronic conditions such as neuropathic pain and epilepsy, where consistent plasma drug levels are essential for effective treatment (Gharat *et al.*, 2024) . The compatibility studies using FT-IR and DSC confirm that the encapsulation process did not alter the chemical or thermal properties of gabapentin, ensuring that the drug remains stable throughout the formulation and storage processes. The absence of chemical interactions between gabapentin and the polymers (ethyl cellulose and HPMC)

suggests that the formulation is stable and unlikely to undergo degradation, making it suitable for long-term use in sustained-release drug delivery systems. These findings indicate that the developed microspheres, particularly formulation F6, represent a promising approach for the oral sustained delivery of gabapentin, offering potential improvements in therapeutic efficacy, patient compliance, and overall treatment outcomes.

CONCLUSION

It is inferred that, sustained-release mucoadhesive microspheres of Gabapentin were successfully formulated and evaluated by using Hydroxypropyl Methylcellulose (HPMC) and Ethyl Cellulose (EC). Among the formulations that were formulated, Formulation 6 (Gabapentin: EC: HPMC, 1:2:3) exhibits the best drug release properties in simulated stomach fluid, demonstrating sustained release for up to 16 hours. High drug loading capabilities were shown by capsules, showing encapsulation efficiency ranged from 82.95% to 97.75%. In vitro, every microsphere exhibited remarkable mucoadhesive properties, indicating an extended residence time in the stomach. These results imply possible improvements in therapeutic efficacy and drug bioavailability in the treatment of neuropathic pain and epilepsy. As a result, the formulated microspheres show a viable method for the prolonged release of gabapentin orally, leading to an improvement in its therapeutic use.

Conflict of Interest

The authors declare that they have no conflict of interest.

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