https://doi.org/10.33472/AFJBS.6.6.2024.5328-5338

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

A Comprehensive Study on the Mucoadhesive Gastroretentive Microspheres for Prolonged Therapeutic Effects of Pregabalin

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Article Info

Volume 6, Issue 6, June 2024

Received: 17 April 2024

Accepted: 20 May 2024

Published: 11 June 2024

doi: 10.33472/AFJBS.6.6.2024.5328-5338

ABSTRACT:

This study aimed to fabricate mucoadhesive gastroretentive microspheres of pregabalin and evaluate the performance of the mucoadhesive microsphere formulations (PMF1 to PMF6) focusing on their percentage yield, drug loading & entrapment efficiency, drug release profiles, mucoadhesive properties, particle characteristics, and fitting to mathematical models. The *in-vitro* drug release tests revealed that PMF6 had the most controlled and sustained release, reaching 92.32% cumulative release over 12 hours, making it ideal for extended therapeutic effects. Mucoadhesion tests showed that PMF6 retained the highest adhesion at 10 hours, indicating superior mucoadhesive properties. Particle size analysis confirmed that PMF6 had an average size of 340 µm, contributing to its consistent performance. Additionally, PMF6 demonstrated the highest drug loading and entrapment efficiency, ensuring effective encapsulation and delivery of pregabalin. The release data best fit the Korsmeyer–Peppas model for all formulations, suggesting a combination of Fickian diffusion and non-Fickian transport mechanisms. In conclusion, PMF6 emerged as the optimal formulation, combining strong mucoadhesion, high drug entrapment efficiency, and a controlled release profile. These findings highlighted the potential of PMF6 as a promising formulation for sustained drug delivery applications, providing a foundation for further optimization and development in pharmaceutical gastroretentive formulations.

Keywords: Microspheres, Mucoadhesion, Gastroretentive, Mucoadhesive microspheres, Pregabalin

1. INTRODUCTION

The benefits of mucoadhesive microspheres include improved oral drug absorption features because of their close interaction with the mucus layer, extended gastrointestinal tract (GI) retention, and occasionally their specific targeting of the gastric absorption location (Chowdary and Rao, 2004, Kaurav et al., 2012). The observable fact is better known as "bioadhesion or mucoadhesion" if the bioadhesive primarily acts on the mucous membrane that contains the mucous layer (Kaurav et al., 2012). One can acquire mucoadhesion by non-specific or specific contact with surface ligands at the mucosa's surface. Over the past twenty years, mucoadhesive drug delivery systems have received a lot of attention due to their ability to improve oral drug bioavailability through systemic delivery, which involves keeping a formulation in closer contact with the absorption site, or localised drug release, which involves keeping a dosage form at the site of action (Kaurav et al., 2012, Patil and Sawant, 2008). Numerous studies in the literature have shown the effectiveness of mucoadhesive microspheres or microparticles in enhancing drug absorption over an extended period of time and enabling controlled release action to improve patient compliance (Patil and Sawant, 2008, Kumari et al., 2014, Rahaman and Mukherjee, 2020).

Anticonvulsant and neuropathic pain reliever pregabalin is used to treat a variety of ailments, including fibromyalgia, generalised anxiety disorder, and epilepsy. It functions by attaching itself to the central nervous system's voltage-gated calcium channel alpha-2-delta subunit, which prevents the release of excitatory neurotransmitters and lowers neuronal excitability. Due to its short half-life and efficacy in treating chronic pain, it is a great option for formulations with sustained release, such as mucoadhesive microspheres (Federico et al., 2020, Evoy et al., 2021). The rationale for selecting pregabalin for the fabrication of mucoadhesive microspheres lies in the need to enhance its bioavailability and prolong its therapeutic effect. Traditional oral administration of pregabalin requires multiple daily doses due to its short half-life, leading to potential fluctuations in plasma drug levels and increased side effects (Evoy et al., 2021, Freynhagen et al., 2021).

Mucoadhesive microspheres can adhere to the mucosal lining of the gastrointestinal tract, providing a controlled and sustained release of pregabalin. This not only ensures a more consistent plasma concentration but also enhances patient compliance by reducing the frequency of dosing. Moreover, the mucoadhesive property of these microspheres ensures prolonged residence time at the site of absorption, thereby improving the overall bioavailability of pregabalin. This approach addresses the limitations of conventional formulations, offering a more efficient and patient-friendly method of drug delivery, especially for chronic conditions requiring long-term medication (Freynhagen et al., 2021, Cao et al., 2023). Therefore, this present study aimed to fabricate and develop gastroretentive mucoadhesive microspheres of pregabalin for sustained release of the drug for better and superior therapeutic effects.

2. MATERIAL AND METHODS

Drugs and chemicals

Pregabalin was obtained as a gift sample from M/s M Sea Pharmaceuticals Pvt. Ltd., Paonta Shahib, Himachal Pradesh, India. Poly (Vinyl Pyrrolidone) (PVP) and Poly (Acrylic Acid) (PAA) were obtained from M/s S.D Fine Chemicals, Mumbai, India. Dichloromethane and Polyvinyl alcohol were obtained from M/s Loba Chem, Mumbai, India. All other supplementary chemicals were utilized in the study of analytical grades and used as obtained.

Drug-excipients compatibility study

FT-IR spectroscopic analysis was performed on a Shimadzu IR Affinity-I instrument (Shimadzu, Tokyo, Japan) and measurements of spectra were performed using KBr pellets. Interaction studies between drug and various mucoadhesive polymers were analysed by comparing the FT-IR spectra.

Preparation of mucoadhesive microspheres

The fabrication of mucoadhesive microspheres incorporating the drug pregabalin was carried out using the interpolymer complexation and solvent diffusion method. This method leverages the ability of polymers to interact and form complexes in a suitable solvent mixture, leading to the formation of microspheres with desired mucoadhesive properties. To begin, a precise amount of polyacrylic acid (PAA) was dissolved in a mixture of ethanol and water, prepared in a specific ratio to optimize the solubility and interaction of the polymers. Polyvinylpyrrolidone (PVP) was then added to the solution, allowing it to dissolve completely and form an interpolymer complex with PAA. The choice of solvent mixture and the ratio of ethanol to water is critical as it influences the solubility and the rate of solvent diffusion, which in turn affects the size and morphology of the microspheres. Pregabalin, the drug intended for incorporation, was then dissolved in the polymer solution. The addition of the drug at this stage ensures that it is evenly distributed within the polymer matrix, facilitating efficient encapsulation during microsphere formation. Once the polymers and pregabalin were fully dissolved and mixed, span 80 (sorbitan monooleate) was added as a surfactant. The surfactant plays a crucial role in stabilizing the formed microspheres, preventing coalescence, and ensuring uniform size distribution. The solution was then subjected to high-speed stirring to facilitate the formation of microspheres through solvent diffusion. The mixture was then slowly added to a larger volume of water, which acts as a non-solvent for the polymers, inducing phase separation and leading to the formation of microspheres. The process parameters such as stirring speed, the concentration of the surfactant, and the ratio of solvent to non-solvent were carefully optimized to achieve the desired size and mucoadhesive properties of the microspheres. After the formation of microspheres, the suspension was allowed to settle, and the microspheres were collected by filtration. They were then washed with distilled water to remove any residual surfactant or unreacted polymers and dried under vacuum to obtain the final mucoadhesive microspheres with encapsulated pregabalin (Chun et al., 2005).

Table 1. Formulation composition table for the pregabalin loaded mucoadhesive microspheres

Formulation	PAA (mg)	PVP (mg)	Ethanol (ml)	Span 80 (mg)	Pregabalin (mg)
PMF1	100	50	10:90	2	25
PMF2	150	75	15:85	3	25
PMF3	200	100	20:80	4	25
PMF4	250	125	25:75	5	25
PMF5	300	150	30:70	6	25
PMF6	350	175	35:65	7	25

Characterizations of the mucoadhesive microspheres

Percentage Yield

The prepared microspheres of all batches were accurately weighed. The measured weight of the prepared microspheres was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which gave the total percentage yield of microspheres. It was calculated using the following equation:

% Yield = actual weight of product/total weight of excipients and drug × 100

Micromeritics Studies

The prepared microspheres were characterized by their micromeritics properties such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose (Lachman et al., 1986, Martin et al., 2011). These properties are essential to understand the flowability and compressibility of the microspheres, which are critical for subsequent processing and handling.

Particle Size Determination

The particle size of the microspheres was determined using the optical microscopy method (Kalyankar et al., 2010). Approximately 100 microspheres were counted for particle size using a calibrated optical microscope. This method provided an average particle size, which is crucial for ensuring uniformity in drug delivery.

Morphological Study using SEM

The morphological study was carried out using a Scanning Electron Microscope (SEM). Microspheres were scanned and examined under an Electron Microscope Hitachi SU 1500, Japan, connected with Fine coat, JEOL JFC-1100E Ion sputter. The sample was loaded on a copper sample holder and sputter-coated with carbon followed by gold. This analysis provided detailed images of the surface morphology of the microspheres, highlighting their shape and surface characteristics.

Drug Loading and Drug Entrapment

Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH 1.2) repeatedly. The extract was transferred to a 100 mL volumetric flask, and the volume was made up using 0.1N HCl (pH 1.2). The solution was filtered, and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 242 nm against an appropriate blank. The amount of drug loaded and entrapped in the microspheres was calculated using the following formulas (Satish K and Kiran K, 2010, Kavitha et al., 2011):

$$\%\ Drug\ loading\ = \frac{Weight\ of\ the\ drug\ loaded\ in\ the\ microspheres}{Total\ weight\ of\ the\ microspheres} \times 100$$

$$\%\ Drug\ entrapment\ = \frac{Amount\ of\ drug\ actually\ present}{Theoretical\ drug\ load\ expected} \times 100$$

***In-vitro* Wash-off Test for Mucoadhesion**

The mucoadhesive property of the microspheres was evaluated by an *in-vitro* adhesion testing method known as the wash-off method (Kalyankar et al., 2010). A 1-cm by 1-cm piece of rat stomach mucosa was tied onto a glass slide (3-inch by 1-inch) using thread. About 100 microspheres were spread onto the wet, rinsed tissue specimen, and the prepared slide was hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up-and-down movement in the test fluid (400 mL) at 37 ± 0.5°C contained in a 1000 mL vessel of the machine. At the end of 1 hour and at hourly intervals up to 10 hours, the machine was stopped, and the number of microspheres still adhering to the tissue was counted. The test was performed in simulated gastric fluid (pH 1.2).

***In-vitro* Release Study**

The drug release study was performed for microspheres containing a quantity equivalent to 15 mg of pregabalin using a USP dissolution apparatus Type I in 900 mL of 0.1 N HCl acid dissolution media (pH 1.2) at 100 rpm and 37 ± 0.5°C (Satish K and Kiran K, 2010). Five millilitres of the sample were withdrawn at predetermined time intervals for 12 hours, and the same volume of fresh medium was replaced to maintain sink conditions. Withdrawn samples were filtered through a 0.45 µm membrane filter, diluted suitably, and assayed

spectrophotometrically at 242 nm. The cumulative % drug release was calculated using a standard calibration curve.

Release Kinetics

To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. By comparing the R^2-values obtained, the best-fit model was selected, providing insight into the drug release mechanism from the microspheres (Satish K and Kiran K, 2010).

Statistical analysis

All the results were presented in this work as mean ± SD (Standard Deviation) for n = 3 or 6 where necessary. GraphPad Prism Software Version 7 was used for the statistical analysis of the raw data employing one way ANOVA followed by Dunnett's test as *post hoc*.

3. RESULTS AND DISCUSSION

Drug-excipients compatibility study

The FTIR analysis was conducted to assess the compatibility between the pregabalin and the selected excipients. The FTIR spectra of the pure drug, individual excipients, and their physical mixtures were thoroughly compared. The results indicated no significant shifts or changes in the characteristic absorption peaks of the drug and excipients in their mixtures compared to their pure forms. This suggests that there were no detectable interactions or incompatibilities between the pregabalin, and the excipients used in the formulation. Therefore, the selected excipients are compatible with the drug, ensuring the stability and integrity of the final product.

Characterizations of the mucoadhesive microspheres

Percentage Yield

The practical yield of mucoadhesive microspheres for various formulations was evaluated and compared against the theoretical weights. The percentage yield for each formulation was calculated, showing values between 66.58% and 73.63%. PMF3 exhibited the highest yield at 73.63%, suggesting an efficient formulation process with minimal losses. Conversely, PMF4 had the lowest yield at 66.58%, indicating potential issues such as material loss during processing or incomplete recovery of microspheres. The relatively consistent yielded across the other formulations, ranging from 70.50% to 72.25%, suggested a stable and reproducible process. These results are crucial for optimizing the formulation parameters to maximize yield and ensure cost-effective production (Table 2).

Table 2. Practical yield of the mucoadhesive microspheres

Formulation Code	Theoretical Weight (mg)	Practical Yield (mg)	%Yield
PMF1	1200	867	72.25
PMF2	1400	987	70.50
PMF3	1600	1178	73.63
PMF4	1200	799	66.58
PMF5	1600	1130	70.63
PMF6	1700	1200	70.59

Micromeritics Studies

The micromeritic properties of mucoadhesive microspheres were assessed for six different formulations, focusing on bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. Bulk density ranged from 0.4724 g/cm³ (PMF1) to 0.6466 g/cm³ (PMF6), indicating variation in particle packing. Tapped density values were higher, ranging from

0.5424 g/cm³ to 0.7434 g/cm³, reflecting the potential for densification under mechanical stress. The compressibility index, a measure of powder flowability, ranged from 11.03% (PMF4) to 15.42% (PMF3). Formulations with a compressibility index below 15% generally indicate good flow properties. Hausner's ratio, another indicator of flow characteristics, ranged from 1.116 (PMF4) to 1.182 (PMF3). Values below 1.25 are typically considered acceptable, suggesting all formulations exhibit good flowability. The angle of repose, which assesses the ease of powder flow, ranged from 20.56° (PMF1) to 26.04° (PMF6). Angles below 30° generally indicate excellent flow properties (Table 3). Overall, the micromeritic properties suggested that all formulations possess good flowability and packing characteristics, essential for consistent dosing and manufacturability. The slight variations in density and flow parameters among formulations can guide further optimization to enhance processing efficiency and product quality.

Table 3. Micromeritic properties of the mucoadhesive microspheres

Formulation Code	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
PMF1	0.4724 ± 0.006	0.5424 ± 0.010	12.90 ± 1.13	1.148 ± 0.012	20.56±0.32
PMF2	0.5284 ± 0.009	0.6112 ± 0.005	13.56 ± 1.09	1.155 ± 0.0031	23.11±0.35
PMF3	0.5532 ± 0.016	0.6541 ± 0.009	15.42 ± 1.14	1.182 ± 0.002	25.42 ±0.24
PMF4	0.5111 ± 0.010	0.5744 ± 0.006	11.03 ± 1.16	1.116 ± 0.003	22.16±0.91
PMF5	0.5716 ± 0.014	0.6481 ± 0.002	11.80 ± 1.07	1.134 ± 0.004	23.53±0.99
PMF6	0.6466 ± 0.012	0.7434 ± 0.013	13.00 ± 1.13	1.150 ± 0.006	26.04±0.79

Particle Size Determination

The average particle size of mucoadhesive microspheres was evaluated for six different formulations. The particle sizes ranged from 240 μm (PMF2) to 353 μm (PMF3), with standard deviations indicating the consistency of each formulation. PMF2 had the smallest average particle size at 240 μm, suggesting a potentially faster dissolution rate due to the larger surface area-to-volume ratio. In contrast, PMF3 had the largest average particle size at 353 μm, which may result in a slower release rate, benefiting sustained-release applications (Table 4). The relatively narrow standard deviations across all formulations indicate uniformity in particle size distribution, which is crucial for consistent drug release and bioavailability. The variations in particle size across the formulations can influence the drug release kinetics and mucoadhesive properties. Smaller particles typically offer larger surface areas for drug release but may also lead to faster clearance from the mucosal site. Larger particles, on the other hand, might adhere better but release the drug more slowly. These insights can guide further optimization of particle size to balance release rate and mucoadhesion for the desired therapeutic effect.

Table 4. Average particle size of the mucoadhesive microspheres

Formulation code	Average particle size (μm)
PMF1	280±4.92
PMF2	240±6.76

PMF3	353±6.35
PMF4	275±6.27
PMF5	347±7.11
PMF6	340±7.31

**Data presented as Mean ± SD*

Morphological Study using SEM

The scanning electron microscopy (SEM) images revealed detailed insights into the morphology of the mucoadhesive microspheres (Figure 1). This photograph in Figure 1 (left) showed a collection of spherical microspheres with smooth surfaces, indicating uniform particle formation and good sphericity. The consistency in shape and size suggested a controlled manufacturing process, essential for ensuring reproducibility and uniform drug release. A closer view of a single microsphere (Right) revealed a slightly rough surface texture. This roughness could enhance mucoadhesion by increasing the surface area for interaction with the mucosal tissue. The detailed surface topology indicated potential for better adhesion and prolonged residence time at the site of application. In inference, these SEM images suggested that the microspheres have a desirable morphology for mucoadhesive applications, combining uniformity in shape with surface characteristics that favour effective mucoadhesion.

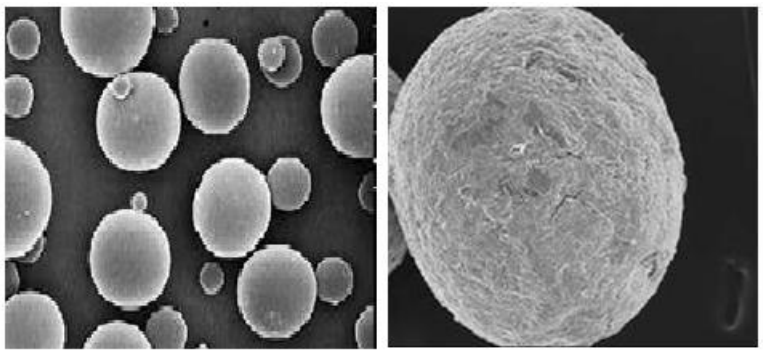

Figure 1. SEM photographs of the mucoadhesive microspheres

Drug Loading and Drug Entrapment

The evaluation of drug loading and drug entrapment efficiency in mucoadhesive microspheres provided critical insights into the formulation's effectiveness in encapsulating and delivering the drug. The results for formulations PMF1 through PMF6 indicated varying degrees of drug loading and entrapment. PMF1 showed a drug loading of 40.74% with an entrapment efficiency of 80.32%. This balance indicated a substantial amount of drug within the microspheres but suggests potential for improvement in entrapment efficiency. PMF2 had a lower drug loading of 29.16% but a higher entrapment efficiency of 84.74%, suggesting that while the amount of drug per unit weight was less, a higher proportion of the drug was successfully encapsulated. PMF3 displayed the lowest drug loading at 24.19% but the highest entrapment efficiency at 92.51%, indicating excellent encapsulation efficiency despite the lower drug content. PMF4 presented a high drug loading of 41.71% with an entrapment efficiency of 81.26%, similar to PMF1, indicating a good balance between drug content and encapsulation. PMF5 showed moderate drug loading at 31.97% and an entrapment efficiency of 85.37%, suggesting a decent balance between the amount of drug loaded and the efficiency of entrapment. PMF6 had the lowest drug loading at 23.76% but the highest entrapment efficiency at 93.58%, indicating it was the most efficient in encapsulating the drug within the microspheres (Table 5). Overall, PMF6 demonstrated to be the best for its high drug entrapment efficiency, making it the most effective in ensuring that the maximum amount of drug is encapsulated. However, the lower

drug loading suggested that it might require higher doses to achieve the desired therapeutic effect. Formulations like PMF1 and PMF4 offered a good balance of high drug loading and reasonable entrapment efficiency, which could be more practical for delivering higher drug doses efficiently.

Table 5. Drug loading and drug entrapment of the mucoadhesive microspheres

Formulation Code	**% Drug Loading**	**%Drug Entrapment**
PMF1	40.74±1.11	80.32 ±1.18
PMF2	29.16±1.02	84.74±1.19
PMF3	24.19 ±1.04	92.51±1.27
PMF4	41.71 ±1.13	81.26 ±1.31
PMF5	31.97±1.10	85.37 ±1.11
PMF6	23.76 ±1.02	93.58 ±1.23

***In-vitro* wash-off test for mucoadhesion**

The *in-vitro* wash-off test evaluated the mucoadhesive properties of various microsphere formulations by measuring the percentage of microspheres adhered to stomach mucosa over time in 0.1N HCl (pH 1.2). The results for formulations PMF1 through PMF6 showed varying degrees of adhesion over a 10-hour period. PMF1 started with 78.34% adhesion at 1 hour, decreasing to 16.43% at 10 hours. This indicated a moderate initial adhesion with significant loss over time. PMF2 showed a slightly higher initial adhesion of 81.65%, dropping to 19.51% by 10 hours, suggesting better performance than PMF1 but still considerable wash-off. PMF3 demonstrated an even stronger initial adhesion of 83.54%, maintaining 22.66% adhesion at 10 hours, indicating good mucoadhesive properties throughout the test period. PMF4 started at 80.34% and retains 20.81% after 10 hours, reflecting a similar pattern to PMF2, with moderate adhesion. PMF5 exhibited the highest initial adhesion among the first five formulations at 84.63%, with 23.91% remaining at 10 hours, showcasing strong and lasting mucoadhesion. PMF6 outperformed all other formulations, starting at 86.66% adhesion and retaining 25.58% after 10 hours, indicating superior mucoadhesive strength and duration (Table 6). Overall, the results highlighted PMF6 as the most effective formulation in terms of mucoadhesion, maintaining the highest percentage of adhered microspheres over the test period. This suggested that PMF6 could provide prolonged drug delivery at the mucosal site, enhancing therapeutic efficacy.

Table 6. *In–vitro* wash-off test for the mucoadhesive microspheres in 0.1n HCL (pH 1.2)

	Percentage of microspheres adhered to stomach mucosa					
Formulation Codes	**Time (Hours)**					
	1	**2**	**4**	**6**	**8**	**10**
PMF1	78.34±1.16	73.34±1.04	59.67±1.01	36.91±1.01	22.46±1.01	16.43±0.98
PMF2	81.65±1.10	75.64±1.08	61.87±1.09	39.87±1.02	25.67±1.01	19.51±0.99
PMF3	83.54±1.14	77.45±1.02	66.98±1.04	42.77±1.02	29.25±1.01	22.66±0.99
PMF4	80.34±1.12	74.91±1.06	65.55±1.09	39.69±0.98	26.68±1.01	20.81±1.00
PMF5	84.63±1.09	77.80±1.06	69.44±1.05	41.88±1.02	28.81±1.00	23.91±1.01

PMF6	86.66±1.15	79.72±1.09	73.65±1.04	46.81±1.03	34.91±1.02	25.58±1.02

**Data presented as Mean ± SD (n = 3)*

In-vitro Release Study

The *in-vitro* drug release study of the mucoadhesive microspheres formulations (PMF1 to PMF6) in 0.1 N HCl (pH 1.2) demonstrated varying release profiles over a 12-hour period. Initially, all formulations showed no drug release at the zero-hour mark. At 1 hour, PMF6 exhibited the highest initial release of 12.73%, while PMF2 had the lowest at 8.02%. By 2 hours, PMF6 continued to release the most drug (22.39%), suggesting a rapid initial release phase. As the study proceeded, PMF3 consistently released a significant amount of the drug, achieving 31.45% at 3 hours and 51.84% at 5 hours. PMF6, however, showed the highest cumulative release at nearly every interval, reaching 62.33% at 6 hours and 72.99% at 8 hours, indicating a sustained release pattern. At the 12-hour mark, PMF6 had the highest total drug release at 92.32%, followed closely by PMF3 at 91.22%. PMF1 and PMF5 also performed well, with releases of 90.11% and 90.64%, respectively. Throughout the study, PMF6 demonstrated the most consistent and sustained drug release profile, making it the most effective formulation in terms of prolonged drug delivery.

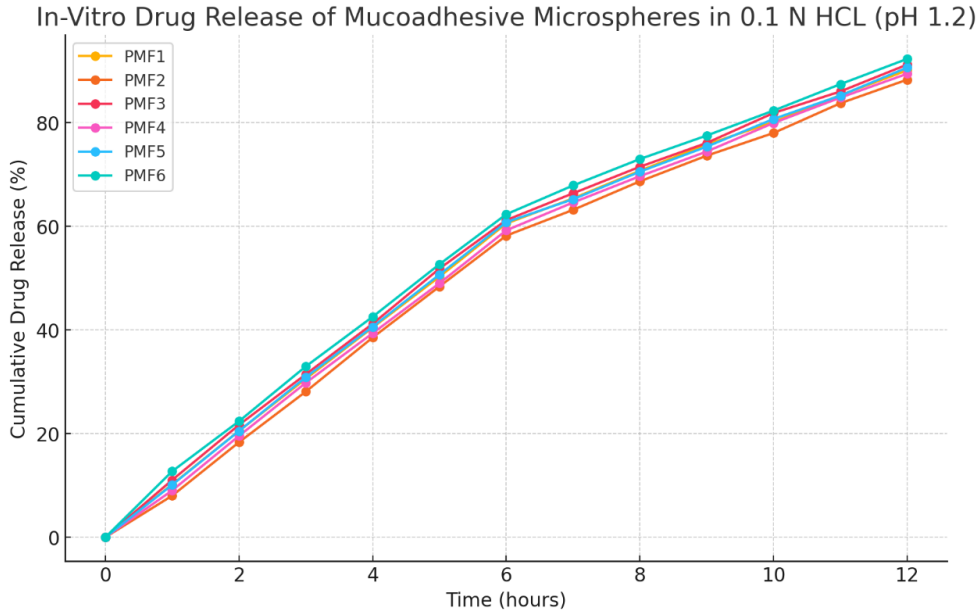

Figure 2. In–vitro drug release for the Mucoadhesive Microspheres in 0.1 N HCL (pH 1.2)

Release Kinetics

The drug release data from the mucoadhesive microspheres (PMF1 to PMF6) were analysed using various mathematical models to determine the best fit for each formulation (Table 7). The models evaluated included Korsmeyer–Peppas, Higuchi, Hixson–Crowell, First-order, and Zero-order kinetics. All formulations (PMF1 to PMF6) exhibited exceptionally high correlation coefficients ($R^2 > 0.9994$) when fitted to the Korsmeyer–Peppas model. The release exponent (n) values ranged from 0.79 to 0.83, indicating a combination of Fickian diffusion and non-Fickian (anomalous) transport mechanisms. Specifically, PMF1 and PMF5 showed the highest R^2 values (0.9998), suggesting an almost perfect fit to this model. The Higuchi model also showed high R^2 values (0.9969 to 0.9983), indicating a good fit, though slightly less than the Korsmeyer–Peppas model. This suggested that drug release was primarily diffusion-controlled, consistent with the mechanism described by the Higuchi equation. The

Hixson–Crowell model exhibited slightly lower R^2 values (0.9923 to 0.9952) compared to the Higuchi model, suggesting that changes in surface area and particle diameter influenced the drug release but were not the predominant mechanisms. Both the first-order and zero-order models showed the lowest R^2 values among the evaluated models (0.9848 to 0.9931). This indicated that neither purely concentration-dependent release (first-order) nor constant release rate (zero-order) accurately described the release kinetics for these formulations. The best fit model for all formulations (PMF1 to PMF6) was the Korsmeyer–Peppas model, as indicated by the highest correlation coefficients (R^2) and the release exponent (n) values. This model suggested that the drug release from the mucoadhesive microspheres followed a combination of Fickian diffusion and non-Fickian transport mechanisms.

Table 7. Model fitting release profile of the mucoadhesive microspheres

Formulation code	**Mathematical Models (Kinetics)**						**Best Fit Model**
	Korsmeyer–Peppas		**Higuchi**	**Hixson–Crowell**	**First order**	**Zero order**	
	R^2	**n**	**R^2**	**R^2**	**R^2**	**R^2**	
PMF1	0.9998	0.8	0.9975	0.9941	0.9913	0.9867	Korsmeyer–Peppas
PMF2	0.9994	0.83	0.9969	0.9923	0.9911	0.9848	Korsmeyer–Peppas
PMF3	0.9996	0.81	0.9978	0.9943	0.9924	0.9873	Korsmeyer–Peppas
PMF4	0.9995	0.79	0.9971	0.9937	0.9917	0.9861	Korsmeyer–Peppas
PMF5	0.9998	0.8	0.998	0.9948	0.9929	0.9879	Korsmeyer–Peppas
PMF6	0.9997	0.82	0.9983	0.9952	0.9931	0.9884	Korsmeyer–Peppas

4. CONCLUSIONS

The study clearly and successfully fabricated the gastroretentive mucoadhesive microspheres for prolong pregabalin drug release. The comprehensive evaluation of pregabalin loaded mucoadhesive microspheres across various formulations (PMF1 to PMF6) revealed significant insights into their drug release profiles, mucoadhesive properties, and particle characteristics. The *in-vitro* drug release studies indicated that PMF6 exhibited the most controlled and sustained release profile, reaching 92.32% cumulative release over 12 hours, making it ideal for prolonged therapeutic effects. The mucoadhesion tests showed that PMF6 also had the highest retention, maintaining 25.58% adhesion at 10 hours. The particle size analysis confirmed uniformity, with PMF6 having an average size of 340 μm, contributing to its consistent performance. The drug loading and entrapment efficiency were highest in PMF6, ensuring effective encapsulation and delivery. Model fitting analyses identified the Korsmeyer–Peppas model as the best fit for all formulations, indicating a combination of Fickian diffusion and non-Fickian transport mechanisms. Overall, PMF6 emerged as the optimal formulation, combining strong mucoadhesion, high drug entrapment, and a controlled release profile, making it highly suitable for sustained drug delivery applications.

DECLARATION OF INTEREST

The authors declare that there is not any conflict of interest in this manuscript.

FUNDINGS

None

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