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Research Article

Asymmetric Membrane Floating Microspheres for Enhanced Anti-Inflammatory and Sustained Release of Ibuprofen

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Abstract

Poorly water-soluble drugs like ibuprofen present challenges related to limited absorption and gastrointestinal (GI) side effects. This work aims at preparing asymmetric membrane floating microspheres (AMFM) with the purpose of enhancing the solubility, gastric retention, and therapeutic efficiency of ibuprofen, thereby decreasing its adverse effects. Ibuprofen-AMFM were prepared by a phase inversion technique, which resulted in the formation of microspheres containing a porous inner layer and a non-porous outer membrane as evidenced by scanning electron microscopy. This special structure allowed the microspheres to float in gastric fluid for up to 12 hours, thereby increasing the gastric residence time. The microspheres showed high drug loading of 89.52 ± 1.23% and process yield 74.23 ± 0.65%. *In vitro* drug release studies indicated that the drug release gets extended up to a period of 12 hours through Fickian diffusion and Higuchi kinetics. *In vivo* anti-inflammatory studies also demonstrated increased efficacy of ibuprofen-AMFM, with an increase in inflammation inhibition of about 85.34%, compared to 60.92% with pure ibuprofen. All the above observations indicated that ibuprofen-AMFM was one of the most efficient ways to improve drug bioavailability and patient compliance, hence being a prospective delivery system for poorly soluble drugs.

Keywords: *Ibuprofen; Asymmetric Membrane; Floating; Kinetics; Phase Inversion*

Abbreviations

AMFM: Asymmetric Membrane Floating Microspheres; GI: Gastrointestinal (GI); NSAID: Nonsteroidal Anti-Inflammatory Drug

Introduction

Ibuprofen belongs to the nonsteroidal anti-inflammatory drug (NSAID) family of drugs [1]. It is widely used both clinically and non-clinically because of its analgesic, antipyretic, and anti-inflammatory action [2]. Like so many drugs that have poor aqueous solubility, it presents limited bioavailability and, thus, therapeutic use. Because of its poor solubility in water, the absorption rate in the GI tract may be poor, hence leading to less-than-ideal amounts in general circulation [3]. In addition, traditional ibuprofen preparations are often linked with GI irritation, including nausea, gastric ulcers, and even bleeding in extreme conditions, which all negatively affects patient compliance [4,5]. These disadvantages have also drawn a lot of attention to the improvement of the solubility and GI retention of ibuprofen.

Approaches including solid dispersions, micronization, and surfactants have been adopted during the past few years to enhance the bioavailability of such poorly soluble drugs like ibuprofen [6-8]. However, most of these techniques are far from being satisfactory for solving the dual problems of drug solubility and GI-side effects. The floating drug delivery systems, on the other hand, have been one of the most promising developments for remaining in the stomach for considerable periods, thus improving the window of opportunity regarding drug absorption [9,10]. By using a floating mechanism, these systems can minimize early gastric emptying, a common problem with traditional oral systems, improving drug retention and reducing erratic therapeutic levels. Indeed, this has been particularly promising in the case of NSAIDs, whose drug levels are required to remain within a particular therapeutic range for continuous anti-inflammatory and analgesic action, without spiking into harmful levels that might give rise to GI irritation.

Among different floating drug delivery systems, the asymmetric membrane floating systems show importance due to their unique structure [11]. These systems are designed in such a way that they contain a porous internal membrane providing for the gradual release of the encapsulated drug and an outer denser, non-porous membrane which supports buoyancy at the gastric site. The inner structure provides for a time-released drug effect, while floating capability prolongs the stay in the gastric environment; both its solubility and absorption are improved [12]. Moreover, a sustained release pattern of asymmetric membrane floating systems can reduce the dosing frequency, with a possible favorable influence on patient compliance, especially for chronic conditions requiring long-term NSAID therapy. The interest in new drug delivery systems and the use of asymmetric membrane floating systems technology raise an interest in how such a delivery system would affect the delivery of ibuprofen.

This work describes the development of ibuprofen-asymmetric membrane floating microspheres (AMFM) and evaluates the suitability of these forms in improving bioavailability, prolonging gastric retention, and exerting prolonged anti-inflammatory action. Some serious drawbacks with conventional ibuprofen therapy include poor aqueous solubility and GI irritation. To be able to avoid these would establish ibuprofen-AMFMs as substantial progress in the oral delivery of poorly soluble drugs. The microspheres will be evaluated for their drug loading, yield, *in vitro* buoyancy, and drug release profiles, other than for their anti-inflammatory activity *in vivo*. The ultimate objective of this study is the assessment whether AMFM can provide a more efficient and patient-friendly ibuprofen delivery system, besides the possible extension of this technology to other drugs characterized by poor water solubility.

Materials and Methods

Ibuprofen was a generous gift from the National Pharmaceutical Industry (NPI), Rusayl, Muscat, Oman. Tween 20, acetone, isopropanol, sodium dihydrogen phosphate, disodium hydrogen phosphate, ethylcellulose (EC, 50 cps), polyvinyl alcohol (PVA) was procured from Chemistry for Life, Muscat. All chemicals were of analytical grade, and the use of double-distilled water was ensured throughout the experiments.

Preparation of ibuprofen-asymmetric membrane floating microspheres (Ibuprofen-AMFM)

Ibuprofen-AMFM were prepared by the phase inversion technique. First, the polymer solution was prepared by dissolving 20% w/v EC in a mixture of 50% v/v acetone and 30% v/v ethanol in a 3:1 ratio. Ibuprofen was then added to the above polymer solution with continuous stirring on a magnetic stirrer to get a homogenous dispersion of Ibuprofen. A separate surfactant solution was prepared by dissolving PVA in deionized water. Microspheres were formed by gradually dropping the polymer-drug solution into the PVA solution under constant magnetic stirring at room temperature. Because of phase inversion, upon contact with the aqueous phase, asymmetric membrane microspheres were formed. Stirring was continued for a period of 3 hours to allow the organic solvent to evaporate completely and harden the microspheres. The spheres were then filtered off, washed repeatedly with deionized water to remove residual PVA, and air-dried at room temperature. The product obtained was stored in a desiccator until further use.

Loading efficiency and process yield

The loading efficiency and process yield of the ibuprofen-AMFM were assessed after the preparation of the microspheres. Process yield was determined by comparing the total mass of the collected dried microspheres against the total weight of starting material, which is the sum of the polymer and drug, used in formulation as described by equation 1:

$$Percentage\ Yield = \frac{Actual\ Weight\ of\ Microspheres}{Theoretical\ Weight\ of\ Drug+Polymer} * 100 \quad \text{Eq1}$$

For the determination of drug loading efficiency, a 10 mg of dried microspheres was dissolved in ethanol to extract the ibuprofen. The solution was filtered using a 0.1-µm syringe filter to remove the undissolved particles, and the content of ibuprofen was analyzed by fiber optics at 264 nm. Loading efficiency was determined by equation 2:

$$Drug\ Loading\ (\%) = \frac{Amouont\ of\ Drug\ in\ Microspheres}{Weight\ of\ Microspheres} * 100 \quad \text{Eq 2}$$

All measurements for each sample were made in triplicate and the average reported to ensure accuracy. Both the process yield and loading efficiency results serve as useful indicators of the effectiveness of the microsphere preparation process and the amount of ibuprofen the formulation had successfully encapsulated.

In vitro buoyancy test

The *in vitro* buoyancy of Ibuprofen-AMFM was tested for floating capacity and time. A 100 mg of dried microspheres was dispersed in 900 mL of 0.1N hydrochloric acid solution (pH 1.2) kept at 37°C ± 0.5°C, mimicking the gastric condition. Thereafter, the solution was transferred to a USP Type II dissolution apparatus with the paddle rotation at 100 rpm. Floating microspheres on the surface of the medium were considered buoyant, and all those that sank were counted as nonbuoyant. The duration of floating as floating time was noted and the percentage of floating microspheres calculated at regular intervals (1, 3, 6, 12h). The buoyancy percent was calculated using Equation 3:

$$Floating\ \% = \frac{Number\ of\ floating\ microspheres}{Total\ Number\ of\ microspheres} * 100 \quad \text{Eq 3}$$

The test was conducted in triplicate, and the results were averaged to ensure accuracy and reproducibility. The *in vitro* buoyancy test results indicated the ability of the microspheres to remain buoyant for prolonged periods, which is essential for enhancing gastric retention and sustained drug release.

Scanning electron microscopy (SEM) analysis

SEM (JSM-6510LA, Jeol, Japan) was used to investigate the morphology and surface features of the Ibuprofen-AMFM. The dried samples of the microspheres were mounted on aluminum stubs, and to enhance the conductivity, a thin layer of gold was coated using a sputter coater for about 30 seconds. Then, the samples were observed under SEM at an accelerating voltage of 15 kV. High-resolution images were captured to observe the structural feature, especially focusing on the outer non-porous layer and the inner porous membrane, important for the buoyancy and sustained release properties of microspheres. SEM pictures gave a detailed visual confirmation of the structure of the microspheres, confirming that the phase inversion technique adopted during their preparation was effectively employed.

In vitro drug release and kinetics study

In the present study, the *in vitro* drug release profile of Ibuprofen-AMFM was performed by a USP Type II dissolution apparatus. 100 mg of microspheres were exposed to 900 mL of 0.1N HCl solution, pH 1.2, at 37°C ± 0.5°C to simulate gastric condition. The stirring paddle was kept at 100 rpm. At specific time intervals of 1, 2, 4, 6, 8, 10, and 12h, 5-mL aliquots were withdrawn and replaced by an equivalent volume of fresh dissolution medium to maintain the sink condition. The withdrawn samples were filtered using a 0.45-µm membrane

filter and assayed for ibuprofen content by UV spectrophotometry at 264 nm. Results are expressed as a percentage of cumulative drug release related to the total amount of encapsulated drug.

To study the drug release kinetics, the release data were fitted to various mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, to determine the release mechanism. The correlation coefficient (R^2) values were calculated for each model, and the model with the highest R^2 value was considered to best describe the drug release kinetics. Additionally, the Korsmeyer-Peppas equation was used to determine the release exponent (n), which provided insight into the drug release mechanism, whether it was Fickian diffusion ($n \leq 0.5$), non-Fickian transport ($0.5 < n < 1$), or case II transport ($n = 1$). The experiments were conducted in triplicate to ensure reproducibility and accuracy of the results.

Anti-inflammatory effect of ibuprofen-asymmetric membrane floating microspheres (Ibuprofen-AMFM)

Male Sprague-Dawley rats weighing 180 - 220g were used for this test with permission from the University of Al Qadisiyah's Animal Care Committee, Iraq. The Guide for the Care and Use of Laboratory Animals, published by the Association for Laboratory Animal Sciences at the University of Al Qadisiyah in Iraq, was followed in conducting this study. Every sacrifice was carried out using an appropriate anesthetic protocol, with every step taken to reduce the suffering of the animals. The animals were given a week to become acclimated before the experiment began. The animals were kept in a 12-hour light/dark cycle with standard laboratory conditions (temperature ~24 - 26°C, relative humidity 60 - 70%). During this time, food and water were available to the rats at all times. The animals were fasted for six hours prior to the commencement of the experiment. The research was carried out in two stages:

1. Acute anti-inflammatory activity: Three groups of twenty-one (21) male Sprague-Dawley rats were randomly assigned to the experiment (7 rats each). By intradermal injection, 0.1 mL of carrageenan in 1% normal saline solution was used to cause acute inflammation. The plantar surface of the rat's right hind paw served as the injection site. The following was the course of treatment taken:

a. Group 1: Treated with normal saline (10 mL/kg p.o.)
b. Group 2: Received ibuprofen, 15 mg/kg orally.
c. Group 3: Received Ibuprofen-AMFM, 15 mg/kg orally.

One hour prior to the introduction of carrageenan (a phlogistic agent), all samples were administered. The acute inflammatory reaction phase (edema in the right hind paw volume) was measured with a plethysmometer prior to (zero) and at predetermined intervals (0.5, 1, and 3h) following carrageenan injection. The paw edema inhibition percentage was computed using the following equation (8).

2. Chronic anti-inflammatory activity: Twenty-one (21) male Sprague Dawley rats were randomly assigned to three groups, each consisting of seven rats, in a manner similar to acute-inflammatory studies. By injecting 2 percent formalin (0.01 mL) subcutaneously beneath the plantar surface of the rat's right hind paw, the chronic inflammation phase was brought on. This was carried out, on the first and third days of the experiment. The following was the course of treatment was taken:

a. Group 1: Treated with formalin (10 mL/kg p.o.)
b. Group 2: Received ibuprofen, 15 mg/kg orally.
c. Group 3: Received Ibuprofen-AMFM, 15 mg/kg orally.

Ten days of treatment were required. An ankle joint was measured directly with a vernier caliper to determine the linear cross-section (LCS). All groups had their LCS differences computed between the first and tenth day. Calculation of percentage of ibuprofen anti-inflammatory effect was by the following Eq.

At the conclusion of the chronic inflammation experiment, the rats were put under anesthesia and their heart blood was extracted directly for the measurement of TNF-α, hs-CRP, fibrinogen, WBC count, IL-6 (pro-inflammatory), and IL-10 (anti-inflammatory).

Results and Discussion

Loading efficiency and process yield

The process yield and loading efficiency of the Ibuprofen-AMFM were determined in order to find out how effective the formulation process was. Process yield was calculated by comparing the total mass of the dried microspheres against theoretical mass of polymer and drug used and was determined to be 89.52 ± 1.23%. This high yield is indicative of the efficiency of the phase inversion technique in the preparation of the microspheres where there is no or minimal loss of material in the process. In pharmaceutical applications, such efficiency suggests scalability with optimal costs and material use.

The drug loading efficiency, as determined by dissolving a sample of the microspheres in ethanol and quantitatively assaying the ibuprofen content using UV spectrophotometry, was 74.23 ± 0.65%. This indicated that a high amount of ibuprofen was encapsulated within the microspheres, thus showing good interaction between the drug and the polymer matrix and a minimum loss of the drug during preparation. A high drug loading is important to realize the intended dose of the microspheres for the period of sustained release.

Both the high process yield and loading efficiency confirm the success of the formulation technique and the capability of microspheres for efficient drug delivery. The results also confirmed the appropriateness of the use of PVA as a polymer and of the phase inversion method in order to formulate a stable and effective delivery system for poorly soluble drugs like ibuprofen.

In vitro buoyancy studies

The *in vitro* buoyancy test showed that the ibuprofen-AFMF presented excellent buoyancy. Under the simulated conditions of simulated gastric fluid (0.1 N HCl, pH 1.2) at 37°C, it was found that the prepared microspheres could float for more than 12 hours, which only pointed towards the feasibility of the ibuprofen-AFMF for a prolonged gastric retention. The floating percentage of microspheres was determined at every interval, and the percentage buoyancy calculated to be 96.76 ± 1.43% also did not vary much during this whole observation period. This long floating time is attributed to the special design of the microspheres, which enhances the air-trapping capacity and also provide more stability to the floating property.

The buoyancy of the microspheres is very important in sustaining the release of ibuprofen within the stomach, enhancing thereby the drug absorption and its therapeutic efficacy. *In vitro* buoyancy results corroborated the principle of the floating delivery system, confirming that the phase inversion technique used in the formulation was able to produce microspheres with appropriate structural properties. These results indicate that the prepared Ibuprofen-AMFM formulation could be able to delay the gastric residence time of the drug, with a possible improvement in its bioavailability and patient compliance, particularly for poorly soluble and absorbed drugs in the gastro-intestinal tract.

Scanning electron microscopy (SEM) analysis

The SEM analysis of the Ibuprofen-AMFM showed that the structural characteristics are important for their performance in sustained drug release and buoyancy. The asymmetric membrane structure was represented with a non-porous outer surface (Figure 1) and a porous inner layer (Figure 2). While the outer nonporous membrane acts like a barrier and regulates the rate of drug release, the inner porous membrane allows Fickian diffusion of the drug through the matrix. The two-layer structure is integrally related with the prolonged gastric retention and sustained release of the microspheres.

The smooth and continuous non-porous outer layer probably plays a role in preventing the drug from releasing early into the acidic environment of the stomach. This external membrane enhances the stability of the microsphere, ensuring they remain intact in gastric fluids floating for as long as 12h, confirmed by buoyancy studies. On the other hand, the sponge-like appearance of the porous layer enables sustained release of ibuprofen because of the potential gradient across the microspheres core. The porous matrix supports the sustained drug release over extended periods, which is quite helpful in preventing fluctuating therapeutic levels in the bloodstream.

The SEM images confirmed the suitability of the phase inversion technique during microsphere preparation. The well-defined porous and nonporous surface basically demonstrated that the fabrication was able to achieve the desired morphology. This kind of unique architecture is directly responsible for the Higuchi release kinetics observed in the drug release studies, wherein the drug release will be controlled by diffusion through the porous membrane. This design further improves the floating capability of the microspheres, which is of high importance in extending residence time in the stomach and, therefore, enhances the bioavailability of the drug.

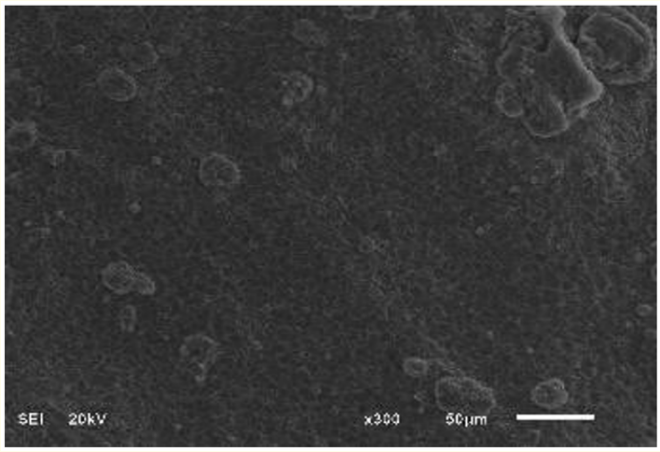

Figure 1: *SEM of outer nonporous layer of the asymmetric membrane.*

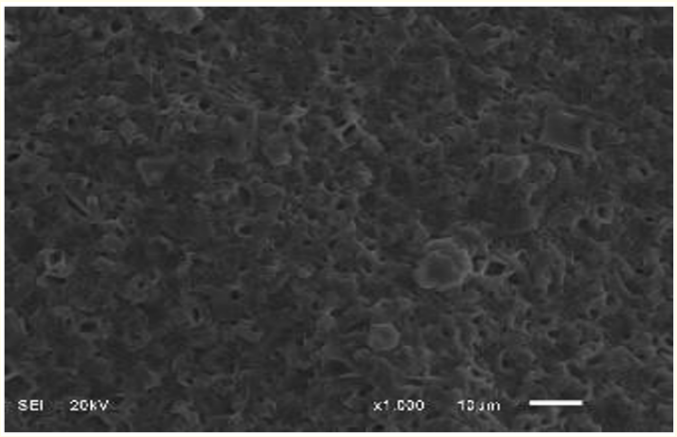

Figure 2: *SEM of inner porous layer of the asymmetric membrane.*

In vitro drug release and kinetics study

The *in vitro* drug release study of Ibuprofen-AMFM showed a sustained release profile, very important for the improvement of its therapeutic efficacy. Conducted under simulated gastric environment conditions, 0.1N HCl, pH 1.2 at 37°C, the microspheres released ibuprofen over a period of 12 hours in a three-stage process: starting with a rapid release in the initial hours, followed by a slow and sustained release phase. On the other hand, in 12h, approximately 95.65 ± 1.32% of the drug was released from the microspheres, while only 48.65 ± 2.46% of the pure ibuprofen was released, displaying the efficacy of the AMFM system in prolonging drug availability (Figure 3).

The burst release observed in the *in-vitro* drug release study is quite a common phenomenon in sustained-release formulations, which might be ascribed to various reasons. Generally, a rapid or burst release of the drug is viewed during the initial phase of drug release, and that in this case was within 1 - 2 hours. This initial burst can be explained by the presence of ibuprofen particles that are loosely associated with or adsorbed onto the outer surface of the microspheres, where the polymer matrix has not yet fully encapsulated the drug. These surface-bound drug molecules are easily dissolved and rapidly released upon exposure to the dissolution medium.

Further, the phase inversion technique used in preparing the microspheres supports this phenomenon, as some ibuprofen may remain near the surface during the formation of the polymer membrane. Additionally, the porosity of the inner layer may initially allow for a quicker diffusion of drug molecules which are trapped closer to the surface of the pores. This leads to the burst effect. While a burst release is often desirable to achieve a therapeutic concentration of the drug rapidly, it must be followed by a slower, sustained release to maintain drug levels over longer period. This was observed in our study, where the burst release was followed by a sustained release phase that aligns with Higuchi kinetics, ensuring that after the initial release, the remaining drug is released at a sustained rate over the 12-hour period. Controlling burst release through formulation adjustments, such as altering the polymer concentration or surface properties, could further improve the delivery system for even more consistent therapeutic outcomes.

The release data were fitted to various kinetic models to elucidate the mechanism by which the drugs were released. The best fit obtained was from the Higuchi model; hence, the release mechanism is dominated by Fickian diffusion as reflected by the release exponent ($n \leq 0.5$). This, therefore, shows that the release of the drug from the microspheres is diffusion-controlled through the polymer matrix. This corroborates the structural properties of the microspheres by the fact that SEM analysis confirmed the porous inner layer, which provides for controlled diffusion. These results point out the possibility of prolonged release of the Ibuprofen-AMFM formulation of poorly water-soluble drugs such as ibuprofen, leading to improved bioavailability with minimal gastrointestinal adverse effects.

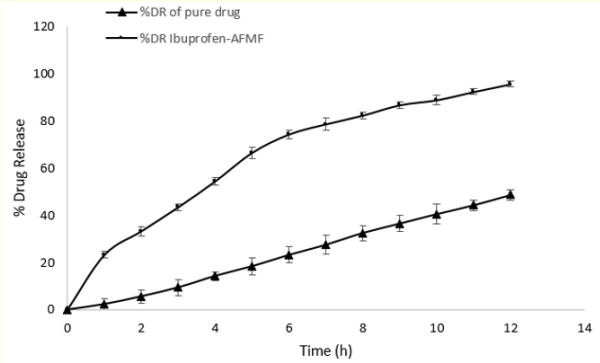

Figure 3: *Cumulative drug release profile of the pure ibuprofen and the ibuprofen-AFMF.*

Anti-inflammatory effect of ibuprofen-asymmetric membrane floating microspheres (Ibuprofen-AMFM)

The anti-inflammatory effect of Ibuprofen-AMFM was evaluated in both acute and chronic inflammation models using male Sprague-Dawley rats. The acute model, induced by carrageenan, demonstrated that Ibuprofen-AMFM showed a significantly higher inhibition of paw edema (62.68%) compared to pure ibuprofen (49.27%) after 3 hours, indicating enhanced anti-inflammatory activity (Table 1). This could be attributed to the sustained release and prolonged gastric retention of the AMFM, ensuring a more consistent therapeutic effect. Statistical analysis of the data showed a significant difference between the groups ($p < 0.05$), confirming the superior efficacy of the AMFM formulation.

Time (h)		Groups	
	G1 (Control)	G2 (ibuprofen)	G3 (ibuprofen-AFMF)
0	0.353 ± 0.032	0.312 ± 0.014	0.299 ± 0.024
1	0.642 ± 0.034	0.398 ± 0.021	0.421 ± 0.021
2	0.772 ± 0.342	0.397 ± 0.025	0.398 ± 0.023
3	0.895 ± 0.054	0.454 ± 0.041	0.334 ± 0.018
% inhibition (3rd h)		49.27	62.68

Table 1: *Effects of ibuprofen and ibuprofen-AMFNP on inflammatory markers, acute model.*

In the chronic inflammation model induced by formalin, Ibuprofen-AMFM further demonstrated superior anti-inflammatory effects. After 10 days of treatment, rats administered with Ibuprofen-AMFM showed a significant reduction in inflammation markers, including hs-CRP, TNF-α, and IL-6, along with an increased IL-10 level compared to pure ibuprofen. Notably, Ibuprofen-AMFM reduced TNF-α levels by 20%, whereas pure ibuprofen reduced it by 30%, further highlighting its enhanced anti-inflammatory potential (Table 2).

Parameter		Groups	
	G1 (Control)	G2 (ibuprofen)	G3 (ibuprofen-AFMF)
hs-CRP (ng/ml)	303.12 ± 14.50	532 ± 12.4	415.00 ± 14.61
Fibrinogen (mg/dl)	84.00 ± 3.50	234.22 ± 12.23	200.7 ± 14.01
TNF-α (pg/ml)	17.25 ± 0.32	30.21 ± 1.21	20.22 ± 0.38
IL-6 (pg/ml)	26.31 ± 2.51	130 ± 13.22	101.00 ± 19.40
IL-10 (pg/ml)	82.38 ± 1820	251.11 ± 20.54	502.48 ± 10.21
WBCs count (× 10^3/mL)	2.54 ± 0.45	7.80 ± 0.22	7.348 ± 0.43

Table 2: *Effects of ibuprofen and ibuprofen-AMFNP on inflammatory markers, chronic model.*

Additionally, Ibuprofen-AMFM exhibited an 85.34% reduction in inflammation, significantly outperforming the 60.92% reduction seen with pure ibuprofen. These results demonstrate that the AMFM formulation offers a sustained release profile that enhances the drug's bioavailability and anti-inflammatory effect, as confirmed by statistical analysis also (Table 3).

Parameter		Groups	
	G1 (Control)	G2 (ibuprofen)	G3 (ibuprofen-AFMF)
Day 1 (initial)	2.43 ± 0.56	3.13 ± 0.20	3.86 ± 0.07
Day 10	6.32 ± 0.43	4.65 ± 0.23	4.43 ± 0.62
Mean difference	3.89	1.52	0.57
% of the anti-inflammatory effect	-	60.92	85.34

Table 3: *Percentage anti- inflammatory effect between ibuprofen and ibuprofen-AMFM.*

Conclusion

The study successfully developed and characterized Ibuprofen-AMFM for the enhanced anti-inflammatory and sustained release of ibuprofen. The results demonstrated that ibuprofen-AMFM improved the solubility, gastric retention, and bioavailability of ibuprofen compared to its pure form. The SEM analysis confirmed the unique asymmetric structure of the microspheres, with a non-porous outer surface and a porous inner layer, which facilitated both prolonged buoyancy and sustained drug release. The *in vitro* drug release study showed a significant sustained release over 12 hours, with the microspheres following Fickian diffusion and Higuchi kinetics. Furthermore, the *in vivo* anti-inflammatory studies in rats revealed that the AMFM formulation exhibited superior efficacy in both acute and chronic inflammation models compared to the pure drug. This enhanced effect can be attributed to the controlled and extended release of ibuprofen, leading to a more consistent therapeutic profile. Therefore, the AMFM system holds promise for improving the therapeutic outcomes and patient compliance associated with poorly water-soluble drugs like ibuprofen.

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Conflict of Interest

The authors declare no conflict of interest.

Bibliography

1. Upadhyay AR., *et al*. "Ibuprofen-based advanced therapeutics: breaking the inflammatory link in cancer, neurodegeneration, and diseases". *Drug Metabolism Reviews* 53.1 (2021): 100-121.
2. Collins D., *et al*. "Ibuprofen for acute pain relief in the emergency department". *BMJ Evidence-Based Medicine* 3 (2020): bmjebm-2019-111312.
3. Amirinejad M., *et al*. "Preparation, characterization and improved release profile of ibuprofen-phospholipid association". *Journal of Drug Delivery Science and Technology* 60 (2020): 101951.
4. Mahmood S., *et al*. "Ibuprofen-loaded chitosan-lipid nanoconjugate hydrogel with gum Arabic: Green synthesis, characterisation, *in vitro* kinetics mechanistic release study and PGE2 production test". *Gels* 7.4 (2021): 254.
5. Gaur P., *et al*. "Development of ibuprofen nanoliposome for transdermal delivery: Physical characterization, *in vitro/in vivo* studies, and anti-inflammatory activity". *Artificial Cells, Nanomedicine, and Biotechnology* 44.1 (2016): 370-375.
6. Chaudhari SP., *et al*. "Application of surfactants in solid dispersion technology for improving solubility of poorly water soluble drugs". *Journal of Drug Delivery Science and Technology* 41 (2017): 68-77.
7. Abuzar S., *et al*. "Enhancing the solubility and bioavailability of poorly water-soluble drugs using supercritical antisolvent (SAS) process". *International Journal of Pharmaceutics* 538.1-2 (2018): 1-13.
8. Bhalani DV., *et al*. "Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics". *Biomedicines* 10.9 (2022): 2055.
9. Yashavanth G., *et al*. "Floating drug delivery system: A review". *International Journal of Advanced Research* 10.11 (2022): 161-167.

10. Thakur S., *et al*. "Floating drug delivery system". *Journal of Drug Delivery and Therapeutics* 11.3S (2021): 125-130.

11. Guo C., *et al*. "Asymmetric polymersomes, from the formation of asymmetric membranes to the application on drug delivery". *Journal of Controlled Release* 338 (2021): 422-224.

12. Samuel B., *et al*. "Phase transited asymmetric membrane floating nanoparticles: a means for better management of poorly water-soluble drugs". *DARU Journal of Pharmaceutical Sciences* 29.2 (2021): 241-253.

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