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DEVELOPMENT OF VAGINAL IBUPROFEN MICROPARTICLES: A DoE-BASED OPTIMIZATION STUDY

VAJİNAL İBUPROFEN MİKROPARTİKÜLLERİNİN GELİŞTİRİLMESİ: DoE TABANLI BİR OPTİMİZASYON ÇALIŞMASI

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ABSTRACT

Objective: *This study aims to formulate and optimize hydroxypropyl methylcellulose (HPMC)-based microparticles for the vaginal delivery of ibuprofen using a full factorial design approach, aiming for sustained drug release, enhanced local effect, and reduced systemic exposure.*
Material and Method: *Ibuprofen-loaded HPMC microparticles were prepared via the simple desolvation method using dichloromethane (DCM) as solvent and liquid paraffin as the continuous phase. The HPMC:DCM ratio and volume of paraffin were selected as independent variables, while particle size and drug loading efficiency were evaluated as responses. Particle characterization was performed using Zetasizer, SEM, and DSC. In vitro drug release was assessed under simulated vaginal conditions (pH 4.5)*
Result and Discussion: *Particle sizes ranged from 1.09 to 10.23 µm with polydispersity indices below 0.5, indicating acceptable uniformity. Drug loading efficiency was between 66.47% and 89.23%, increasing with higher HPMC concentrations. In vitro release studies demonstrated sustained ibuprofen release, reaching approximately 88% over 180 minutes. ANOVA confirmed that the HPMC:DCM ratio significantly affected both particle size and drug entrapment ($p < 0.0001$). The optimized HPMC-based microparticles provide a promising vaginal drug delivery system for ibuprofen, offering controlled release, high drug loading, and potential for improved therapeutic efficacy with reduced systemic side effects.*
Keywords: *Factorial design, microparticle, ibuprofen, vaginal drug delivery*

ÖZ

Amaç: *Bu çalışma, sürekli ilaç salınımı, geliştirilmiş lokal etki ve azaltılmış sistemik maruziyet hedefleyen tam faktöriyel tasarım yaklaşımı kullanarak ibuprofenin vajinal taşıma için hidroksipropil metilselüloz (HPMC) bazlı mikropartikülleri formüle etmeyi ve optimize etmeyi amaçlamaktadır.*
Gereç ve Yöntem: *İbuprofen yüklü HPMC mikropartikülleri, çözücü olarak diklorometan (DCM) ve sürekli faz olarak sıvı parafin kullanılarak basit desolvasyon yöntemi ile hazırlanmıştır. HPMC:DCM oranı ve parafin hacmi bağımsız değişkenler olarak seçilirken, partikül boyutu ve ilaç*

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yükleme verimliliği bağımlı değişkenler olarak değerlendirilmiştir. Partikül karakterizasyonu Zetasizer, SEM ve DSC kullanılarak gerçekleştirilmiştir. İn vitro ilaç salınımı simüle edilmiş vajinal koşullar altında (pH 4,5) değerlendirilmiştir.

Sonuç ve Tartışma: *Partikül boyutları 1.09 ila 10.23 µm arasında değişmiş ve polidispersite indeksleri 0.5'in altında olup kabul edilebilir bir tekdüzelik olduğunu göstermektedir. İlaç yükleme verimliliği %66.47 ile %89.23 arasında ve daha yüksek HPMC konsantrasyonlarıyla yükleme verimliliği artmaktadır. İn vitro ilaç salım çalışmaları, 180 dakika boyunca yaklaşık %88'e ulaşan sürekli ibuprofen salımını göstermiş ve ANOVA, HPMC:DCM oranının hem parçacık boyutunu hem de ilaç tutulmasını önemli ölçüde etkilediğini doğrulamıştır ($p < 0,0001$). Optimize edilmiş HPMC tabanlı mikropartiküller, kontrollü salım, yüksek ilaç yüklemesi ve azaltılmış sistemik yan etkilerle iyileştirilmiş terapötik etkinlik potansiyeli sunan ibuprofen için umut verici bir vajinal ilaç verme sistemi sağlamaktadır.*

Anahtar Kelimeler: *Faktöriyel tasarım, mikropartikül, ibuprofen, vajinal ilaç taşıma*

INTRODUCTION

Ibuprofen is a widely used member of the nonsteroidal anti-inflammatory drug (NSAID) class, known for its analgesic, antipyretic, and anti-inflammatory properties. Chemically defined as 2-[4-(2-methylpropyl) phenyl] propanoic acid, ibuprofen exerts its pharmacological effects by inhibiting cyclooxygenase (COX) enzymes, resulting in decreased prostaglandin synthesis. This mechanism relieves pain, fever, and inflammation, making ibuprofen a preferred treatment for conditions such as headache, musculoskeletal pain, dysmenorrhea, and arthritis. However, long-term use or high doses can lead to adverse effects, including gastrointestinal disturbances, renal dysfunction, and increased cardiovascular risks [1,2]. Consequently, improved drug delivery systems are essential to optimize its therapeutic profile and reduce these disadvantages. When administered orally, ibuprofen is rapidly absorbed, reaching peak plasma concentrations within 1 to 2 hours. Its bioavailability ranges from 80% to 100%, ensuring efficient gastrointestinal absorption. The drug exhibits high plasma protein binding, predominantly to albumin, with binding rates between 90% and 99%, which influences its pharmacokinetic behavior. Hepatic metabolism via the cytochrome P450 enzyme system produces metabolites that are primarily eliminated via renal excretion. The elimination half-life of ibuprofen is generally 2 to 4 hours, but extended-release formulations may extend this period [3,4].

Despite its rapid analgesic onset, the short half-life of ibuprofen necessitates frequent dosing, potentially compromising patient compliance and increasing the likelihood of adverse gastrointestinal effects. Controlled-release systems and microencapsulation technologies offer promising strategies to address these limitations, improving both therapeutic efficacy and safety [5].

Microparticles are advanced drug delivery vehicles designed for controlled and targeted release of active pharmaceutical ingredients. They are particles typically used for biological, pharmaceutical, and industrial applications ranging from 1 to 1000 µm [6]. Microparticles can be composed of biocompatible natural or synthetic polymers that provide improved drug stability, sustained release profiles, and improved therapeutic outcomes. Microparticles enable site-specific drug delivery while minimizing systemic exposure and associated adverse effects. Sustained release mechanisms extend the therapeutic window of ibuprofen, facilitating effective treatment with reduced dosing frequencies. This not only improves patient compliance but also optimizes therapeutic outcomes. Additionally, microparticles increase the solubility and bioavailability of poorly soluble drugs such as ibuprofen. Uniform distribution of the active pharmaceutical ingredients within the polymeric matrix contributes to improved dissolution profiles [7]. Additionally, microparticle systems can respond to environmental stimuli such as pH or enzymatic activity to regulate drug release. This versatility allows them to be applied in a variety of routes of administration, including oral, topical, transdermal, intravenous, inhalation, and vaginal. As a result, microparticles offer a robust and adaptable platform for pharmaceutical innovation by balancing increased efficacy with minimized side effects [8].

This study is the preparation of Ibuprofen-loaded HPMC microparticles suitable for vaginal application. In this way, high concentrations of ibuprofen can be delivered to the vaginal area. In addition, when taken orally, ibuprofen is metabolized in the liver and its bioavailability decreases. However, vaginal application can increase local effects while reducing systemic side effects. On the

other hand, HPMC is a bio-adhesive polymer, so it can adhere well to the vaginal mucosa in gel form and provide long-term effects [9-11].

MATERIAL AND METHOD

Materials

HPMC K100M, ibuprofen, dichloromethane (DCM), liquid paraffin, monobasic phosphate and dibasic phosphate were supplied by Sigma-Aldrich, USA. All chemicals used were at least pharmaceutical grade.

Methods

Preparation of HPMC-Ibuprofen Microparticles

In this study, microparticles containing 5% ibuprofen in the formulation were prepared using the simple desolvation method. Hydroxypropyl methylcellulose (HPMC) was first dissolved in dichloromethane under continuous stirring. The solution was then subjected to magnetic stirring for 2 hours, during which liquid paraffin was gradually added dropwise. As a result, microparticles were formed, which were subsequently collected through filtration. To ensure the removal of any residual impurities, the obtained particles were washed multiple times (2–3 cycles) with n-hexane. Finally, the purified microparticles were dried in an oven at 30°C to obtain the final product [12,13].

Optimization of HPMC-IBU Loaded Microparticles

In this study, the optimization of HPMC-IBU microparticles was carried out using a full factorial experimental design. This approach facilitates the systematic evaluation of all factors and their respective levels, thereby enhancing formulation optimization and process improvement in pharmaceutical development. Through this method, the effects of active ingredients, excipients, and manufacturing parameters on the final drug formulation can be thoroughly analyzed. Identifying the interactions between components is particularly crucial for optimizing bioavailability, dissolution profile, and stability. Testing all possible combinations allows the selection of the most suitable formulation, thereby increasing efficacy and safety while minimizing unnecessary costs and time losses. Additionally, the ability to detect experimental errors more effectively and support the best formulation with scientific data provides an advantage in regulatory approval processes. Consequently, full factorial design serves as a powerful tool in pharmaceutical development by accelerating the process while ensuring reliability and reproducibility [14,15].

For this purpose, in this study, the HPMC:DCM ratio (1:15, 1:20, 1:25, and 1:30) and liquid paraffin volume (30, 40, 50, and 60) were considered as independent variables, while the percentage of ibuprofen loaded into the formulation and particle size were taken as dependent variables.

Characterization of HPMC-IBU Loaded Microparticles

The size distribution and polydispersity indexes of the prepared microparticles were determined using the Malvern Zetasizer. The morphological characteristics of optimized HPMC-IBU microparticles were evaluated in its swollen state upon contact with water using scanning electron microscopy (SEM) (Carl Zeiss Microscope, 2.00 kV, Germany) [16].

Differential Scanning Calorimetry (DSC) analysis was conducted to assess potential physicochemical interactions between the components used in the formulation of HPMC-IBU microparticles [17].

The drug entrapment efficiency was determined using a direct UV-Vis spectroscopic method. Briefly, ibuprofen-loaded HPMC microparticles were extracted using methanol, and the amount of encapsulated ibuprofen was quantified at 272 nm using the following calibration equation:

$$y = 907.94x - 13.217 \quad (R^2 = 0.9992, \text{ range: } 0–1000 \text{ ppm}). \qquad \text{(Equation 1)}$$

Entrapment efficiencies were calculated based on Equation (1). The UV-Vis method was fully

developed and validated in compliance with the ICH Q2(R1) guidelines for analytical method validation. The method demonstrated high specificity, excellent linearity (R^2 = 0.9992, >0.995), remarkable precision (RSD% = 0.415% ± 0.020%, <2%), and exceptional accuracy (recovery rate = 100.79% ± 0.13%, within 98.0%–102.0%). Additionally, the limit of detection (LOD) and limit of quantification (LOQ) were determined as 0.5 ppb and 2 ppb, respectively [18].

The release rate of ibuprofen contained in HPMC microparticles was determined using the dialysis membrane diffusion method. For this purpose, 2 grams of HPMC-IBU microparticles were accurately weighed and enclosed in dialysis bags. These bags were then immersed in a beaker containing phosphate buffer at pH 4.5, and the setup was maintained in a water bath at 37 ± 0.5°C equipped with both a heater and a magnetic stirrer to simulate physiological conditions. At predetermined intervals (10, 30, 60, 90, 120, and 150 minutes), aliquots were withdrawn, centrifuged to remove any particulate matter at 3000 rpm for 5 minutes at room temperature, and the supernatant was analyzed for ibuprofen concentration using a validated UV-Vis spectrophotometric technique. To ensure the reliability and reproducibility of the results, all measurements were carried out in triplicate [19,20].

Statistical Analysis

To ensure the robustness and reproducibility of the data, all experimental analyses were performed in triplicate. The results were expressed as mean values along with their corresponding standard deviations (mean ± SD). Comparative statistical analyses between sample groups were carried out using Student's t-test and one-way ANOVA, where applicable. Statistical significance was defined as a p-value less than 0.05 [21].

RESULT AND DISCUSSION

Optimization of HPMC-IBU Loaded Microparticles

The results obtained by experimentally determining the determined independent variables according to the dependent variables are shown in Table 1.

The particle sizes of the prepared HPMC-IBU microparticles were measured to be in the range of 1.09–10.23 µm. This size range is considered suitable for pharmaceutical applications, particularly for drug delivery systems via mucosal routes. Micron-sized particles offer advantages in terms of both controlled drug release potential and effective interaction with the gastrointestinal mucosal surface. Moreover, the relatively narrow particle size distribution and the fact that most particles are below 10 µm support the homogeneity of the system and indicate good reproducibility of the formulation. Therefore, the obtained particle sizes can be considered appropriate for the intended drug delivery and release characteristics [22, 23]. These results are consistent with previous studies using HPMC or similar hydrophilic polymers for microparticulate delivery. For example, Pham et al. (2023) reported particle sizes between 2–12 µm for HPMC-based mucoadhesive microparticles containing ibuprofen. Similarly, Kruk et al. (2023) observed particle sizes ranging from 3–8 µm in HPMC-alginate systems. Compared to these studies, the optimized formulation in this study (1.73 µm) demonstrates finer and more uniform particle formation, likely due to the higher HPMC content and optimized solvent/non-solvent interaction [10,12].

The drug loading capacity of the prepared HPMC microparticles was determined to be in the range of 66.47–89.23%. These values are considered relatively high for microparticulate systems, indicating good compatibility between the polymeric matrix and ibuprofen, as well as efficient incorporation of the drug into the carrier. A high loading capacity not only enhances the therapeutic efficacy of the dosage form but also allows for the development of more compact formulations with reduced excipient use, potentially improving patient compliance. Moreover, this range suggests that the production process was well-controlled and that formulation parameters were optimized to achieve a stable interaction with the active compound [24]. These results highlight the promising potential of the system in terms of therapeutic performance and formulation efficiency [25]. In comparison, Kruk et al. (2023) reported entrapment efficiencies of 58–75% for HPMC-alginate microparticles loaded with posaconazole, while Guerreiro et al. (2021) achieved approximately 70–80% for konjac glucomannan-based microparticles [10,25]. The higher loading capacity observed in the present study may be

attributed to the optimized HPMC concentration and the hydrophobic nature of ibuprofen, which favors retention within the polymer matrix during the desolvation process.

Table 1. The dependent and independent variables of formulations

	Factor 1	Factor 2	Response 1	Response 2	
Code	**A:HPMC:DCM**	**B:Volume of liquid paraffin**	**Particle Size**	**Entrapment Efficiency**	**PDI**
	Ratio	ml	µm	%	
F1	1:15	40	2.41	89.23	0.405±0.006
F2	1:15	50	1.09	88.36	0.372±0.002
F3	1:15	60	1.32	89.12	0.231±0.002
F4	1:15	30	1.73	89.06	0.434±0.001
F5	1:20	60	4.01	79.33	0.287±0.005
F6	1:20	30	3.68	80.78	0.198±0.005
F7	1:20	50	3.32	81.14	0.245±0.003
F8	1:20	40	3.65	80.33	0.407±0.001
F9	1:25	40	5.84	73.56	0.289±0.006
F10	1:25	60	7.17	74.02	0.302±0.008
F11	1:25	50	6.67	74.45	0.217±0.004
F12	1:25	30	5.01	75.30	0.416±0.007
F13	1:30	40	8.22	67.82	0.309±0.001
F14	1:30	50	10.23	67.24	0.357±0.005
F15	1:30	30	8.99	68.22	0.415±0.003
F16	1:30	60	9.52	66.47	0.207±0.003

The PDI values of the prepared microparticles being below 0.5 indicate that the system possesses an acceptable level of homogeneity. The polydispersity index (PDI) is a critical parameter reflecting the distribution of particle sizes, and values below 0.5 suggest that the formulation underwent a well-controlled production process with minimal size variation among particles. This characteristic is favorable for both the physical stability and reproducibility of the drug delivery system. Moreover, a homogeneous particle size distribution contributes to a more predictable and controlled drug release profile, thereby enhancing the overall performance of the formulation. Therefore, the obtained PDI values support the pharmaceutical suitability and reliability of the microparticle system [26]. This aligns with the findings of Muhaimin et al. (2021), who achieved narrow size distributions using process analytical technology during encapsulation [22].

In-vitro Evaluations of HPMC-IBU Microparticles

The results of DSC analysis and SEM image of the optimized HPMC-IBU microparticle are presented in Figures 1 and 2, respectively.

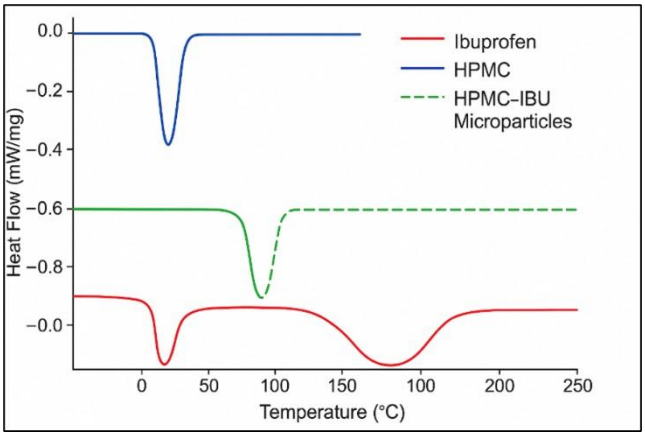


Figure 1. DSC Thermograms of ingredients and HPMC-IBU microparticles

DSC analysis was performed to investigate potential physicochemical interactions between ibuprofen, HPMC, and paraffin within the microparticulate formulation. The thermogram of pure ibuprofen exhibited a sharp endothermic peak at approximately 76°C, corresponding to its melting point, indicating its crystalline nature. Paraffin also showed a distinct endothermic peak near 60°C, consistent with its known melting transition. HPMC demonstrated a broad endothermic region around 200°C, attributed to its gradual thermal degradation and moisture loss. In contrast, the thermogram of the HPMC-IBU-Paraffin microparticles exhibited broader and less intense peaks in the same thermal regions. Notably, the characteristic melting peak of IBU was slightly shifted and reduced in intensity, suggesting its molecular dispersion within the polymer matrix. However, no new or unexpected peaks were observed in the microparticle formulation. The absence of significant peak shifts or additional thermal events confirms that no chemical interactions or incompatibilities occurred among the components during the microparticle preparation. These results strongly indicate that the formulation is physically stable, and that ibuprofen remains in a molecularly dispersed or amorphous state within the HPMC-based carrier system [27,28].

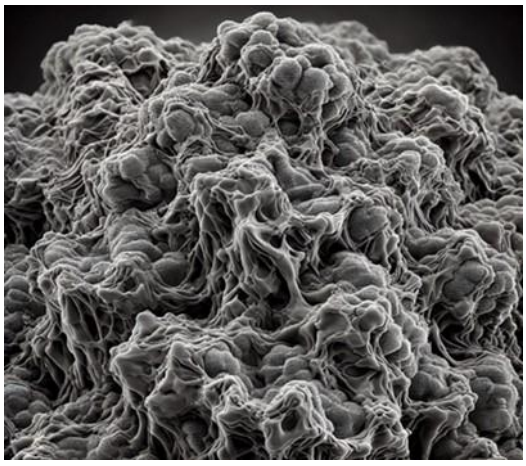


Figure 2. SEM image of hydrated HPMC-IBU microparticles

Upon hydration and subsequent drying, HPMC-Ibuprofen microparticulate gels exhibited a distinctly altered morphology compared to their dry, dehydrated counterparts. The SEM analysis revealed a collapsed, wrinkled structure with no clearly distinguishable particles, indicating that the original microparticles had swelled, coalesced, and formed a continuous hydrogel matrix. This sponge-like morphology is consistent with the behavior of HPMC-based hydrogels that retain water within their

polymeric network and subsequently collapse upon drying. The appearance of surface folds and pores suggests a porous gel structure capable of sustaining prolonged drug release. These morphological changes support the controlled release profile observed in *in vitro* studies and confirm the successful formation of a hydrogel network for vaginal delivery applications [29,30].

The Effect of Independent Variables on Dependent Variables

The effects of HPMC:DCM ratio (1:15; 1:20; 1:25 and 1:30) and paraffin volume (30-60 ml), which were considered as independent variables, on particle size and entrapped capasity were evaluated by ANOVA and are shown in Table 2.

Table 2. ANOVA results of the dependent variables

Response 1: Particle Size

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	126.80	3	42.27	80.93	< 0.0001	significant
A-HPMC:DCM	126.80	3	42.27	80.93	< 0.0001	
Residual	6.27	12	0.5222			
Cor Total	133.06	15				

Response 2: Entrapment Efficiency

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1011.93	3	337.31	677.72	< 0.0001	significant
A-HPMC:DCM	1011.93	3	337.31	677.72	< 0.0001	
Residual	5.97	12	0.4977			
Cor Total	1017.90	15				

According to Table 2; In the study, it was observed that increasing the HPMC:DCM ratio led to a decrease in particle size of the microparticles prepared via the simple desolvation method. This finding can be explained by the fact that higher polymer concentrations may alter the interfacial tension between the solvent and non-solvent phases, leading to faster phase separation. Additionally, increased HPMC content can promote the formation of a greater number of nucleation sites during the initial stages of particle formation, resulting in the generation of smaller droplets and thus smaller particles. Furthermore, due to the very low aqueous solubility of ibuprofen, the drug tends to remain within the polymeric phase, contributing to the formation of more compact structures during rapid precipitation. These results suggest that the polymer-to-solvent ratio influences not only the viscosity of the system but also the nucleation kinetics and precipitation dynamics, ultimately affecting the final particle size [31,32].

In the study, the increase in ibuprofen loading percentage with rising polymer concentration can be attributed to the enhanced drug-carrying capacity provided by higher polymer content. Elevated polymer concentrations create more space within the matrix for the incorporation of the active substance, allowing for more efficient entrapment of the drug during the microparticle formation process. This is particularly beneficial for poorly water-soluble drugs like ibuprofen, as the polymer-rich environment facilitates greater drug encapsulation. Additionally, higher polymer content may improve the solubility of ibuprofen within the polymeric matrix, promoting the retention of a larger amount of the drug inside the microparticles. Furthermore, the denser structure formed by the increased polymer phase may contribute to a more controlled drug release profile. Therefore, the increase in polymer concentration enhances both the drug loading capacity and the overall efficiency of the formulation, thereby improving the drug delivery potential of the microparticles [33,34].

3D surface graphics according to ANOVA values are shown in Figure 3. In the optimization, interaction graphs were drawn and shown in Figure 4.

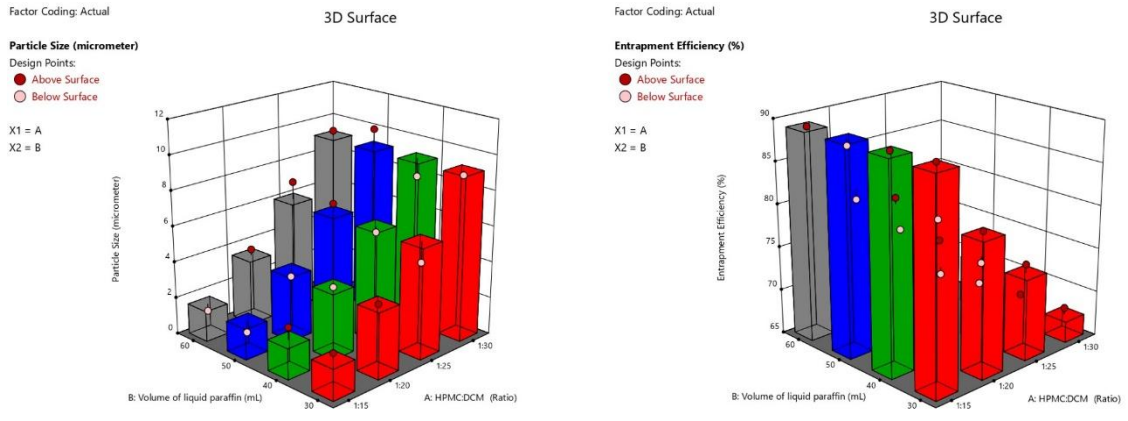


Figure 3. 3D-Surface graphs of variables

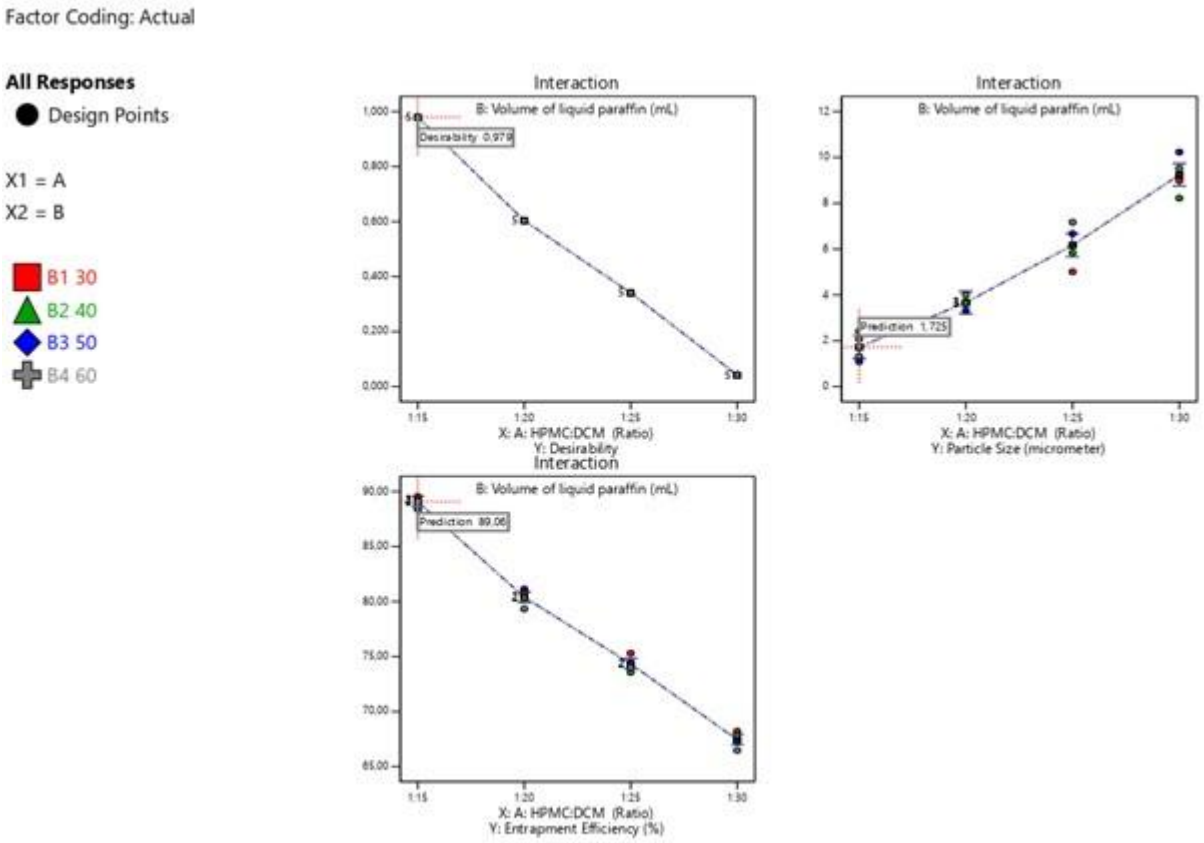


Figure 4. Interaction of variables

According to the evaluations based on ANOVA, the optimized HPMC-IBU microparticle formulation was identified as the one prepared with an HPMC:DCM ratio of 1:15, a paraffin volume of 30 ml, a particle size of 1.73 µm, and a drug loading capacity of 89.06%.

In Vitro IBU Release Studies

The release rate of the active substance from microparticles is a critical parameter in terms of therapeutic efficacy, safety, and patient compliance. A controlled and sustained release profile allows

the drug to maintain its therapeutic concentration at the target site for an extended period, thereby reducing dosing frequency and improving adherence to treatment. Moreover, the prevention of sharp peak concentrations helps minimize systemic side effects. Slow and controlled release is particularly advantageous for drugs associated with irritation or toxicity. Since the release rate reflects the structural characteristics of the polymer used in the formulation, it serves as an important indicator of the formulation's overall success. In local delivery systems (e.g., vaginal administration), targeted release can limit systemic absorption and provide more effective and safer treatment. Therefore, in microparticle-based drug delivery systems, the release rate plays a fundamental role both in pharmaceutical development and in optimizing therapeutic outcomes [35,36]. The ibuprofen release profiles from the optimized three HPMC-IBU microparticle formulations are illustrated in Figure 5.

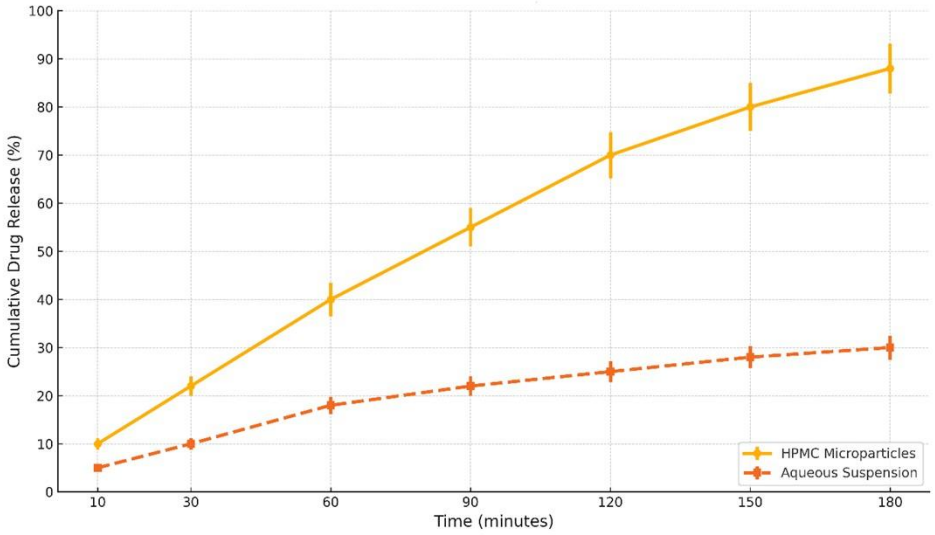


Figure 5. IBU releases from HPMC-IBU microparticles and IBU aqueous suspension

The comparative *in vitro* release profiles of ibuprofen from HPMC microparticles and aqueous suspension at pH 4.5 demonstrate a distinct difference in drug release kinetics over time. The HPMC-based microparticles exhibited a controlled release suitable for vaginal administration and progressively increasing release, reaching approximately 88% cumulative release at 180 minutes. In contrast, the aqueous suspension showed a much slower release rate, with only about 30% release at the same time point. This substantial difference is attributed to the gel-forming and swelling nature of HPMC, which creates a hydrated matrix upon contact with the release medium. This matrix acts as a diffusion barrier, enabling controlled drug release over time. The slower initial release observed in the microparticles is advantageous for prolonging drug availability and minimizing burst effects, while the consistent increase indicates stable diffusion through the polymer network. Meanwhile, the aqueous suspension presents a faster initial dissolution but rapidly reaches a plateau, likely due to ibuprofen's limited solubility in acidic environments such as pH 4.5. These findings confirm that HPMC-based microparticulate systems provide a more desirable controlled release profile for vaginal delivery of ibuprofen compared to conventional aqueous suspensions [12,37]. Pham et al. (2023) observed ~80% release at 180 min using similar HPMC-IBU microparticles for oral mucosal application, while Amante et al. (2023) achieved up to 70% release over 4 hours using alginate-pectin microparticles. Thus, the formulation developed in this study demonstrates superior release kinetics, suitable for vaginal application where prolonged local effect is desirable [12,29].

The release mechanism of ibuprofen (IBU) from the optimized HPMC-IBU microparticle-containing gel was evaluated using Python programming on the Google Colab platform. Among the evaluated kinetic models, the highest coefficient of determination ($R^2 = 0.9977$) was obtained with the Korsmeyer-Peppas model. This suggests that the drug release likely follows a non-Fickian diffusion or

a polymer matrix-controlled mechanism. Such behavior is frequently observed in hydrophilic polymers like HPMC, where water uptake causes the polymer matrix to swell. As a result, the drug molecules are released through a combination of diffusion and relaxation of the polymer chains. On the other hand, an aqueous suspension of ibuprofen initially contains undissolved crystalline drug particles. Because ibuprofen has very low solubility at pH 4.5, the dissolution rate in the early stage is inherently slow, resulting in less than 10% release within the first 30 min. In contrast, in the HPMC microparticle system, ibuprofen is molecularly dispersed within a hydrated polymer matrix, facilitating rapid surface diffusion after initial wetting; hence the slightly higher early release (~10%) observed in Figure 5. However, as the polymer swells, gel layer formation slows further diffusion, providing a more gradual, controlled release profile thereafter. Therefore, the microparticles do not exhibit a true "immediate release," but instead show a short initial diffusion phase followed by sustained release; This is also supported by the Korsmeyer-Peppas kinetic fit ($R^2 = 0.9977$, $n \approx 0.58$). Regarding overall extent of release, the aqueous suspension achieved only approximately 30% drug release after 180 minutes due to ibuprofen's low solubility and tendency to precipitate at acidic vaginal pH, while the microparticle formulation achieved approximately 88% due to polymer-assisted solubility and dispersion.

Conclusion

In this study, ibuprofen-loaded HPMC microparticles were successfully formulated using a simple desolvation method and optimized via full factorial design. The findings demonstrated that the HPMC:DCM ratio significantly influences both particle size and drug entrapment efficiency. Higher polymer concentrations resulted in smaller particles and enhanced drug loading, attributed to increased nucleation and improved polymer–drug compatibility. The optimized formulation exhibited a controlled release suitable for vaginal administration profile suitable for vaginal delivery, with over 88% ibuprofen release within 180 minutes. The particle size, polydispersity index, entrapment efficiency, and release behavior collectively confirm that the developed microparticulate system offers an effective and reliable platform for localized ibuprofen delivery. This approach may improve patient compliance by reducing dosing frequency and minimizing systemic adverse effects, highlighting the formulation's potential for further development in vaginal drug delivery applications.

AUTHOR CONTRIBUTION

Concept: E.D.Ö.; Design: E.D.Ö., T.Ç.; Control: T.Ç.; Sources: E.D.Ö., T.Ç.; Materials: E.D.Ö.; Data Collection and/or Processing: E.D.Ö., T.Ç.; Analysis and/or Interpretation: E.D.Ö., T.Ç.; Literature Review: E.D.Ö.; Manuscript Writing: E.D.Ö., T.Ç.; Critical Review: E.D.Ö., T.Ç.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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