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**ORIGINAL ARTICLE / ÖZGÜN MAKALE**

# DEVELOPMENT AND CHARACTERIZATION OF AN OCULAR *IN SITU* GEL FORMULATION CONTAINING INDOMETHACIN

## *İNDOMETAZİN İÇEREN OKÜLER İN SİTU JEL FORMÜLASYONU GELİŞTİRİLMESİ VE KARAKTERİZASYONU*

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## ABSTRACT

**Objective:** *This study aims to formulate in-situ gel formulations for extended duration of indomethacin (INDO) on the corneal surface which will improve the ocular bioavailability for sufficial treatment of ocular inflammatory disorders.*
**Material and Method:** *Formulations were prepared by cold method. Briefly polymers were dissolved in cold ultrapure water and INDO was added to the solutions. A modified UV method was used. DSC, FT-IR and $^{1}$H-NMR analyses were used for the determination of structural properties of INDO and excipients. The formulations were characterized through measurements of gelation temperature and gelation time, determination of pH, rheological assessments, and in vitro drug release experiments conducted in PBS (pH 7.4) at 34±2°C.*
**Result and Discussion:** *According to the gelation temperature and gelation time analyses optimum formulation which contained %17 (w/w) Poloxamer 407 (P407) was selected for further studies. Evidence of drug–polymer compatibility was obtained through DSC, FT-IR, and ¹H-NMR studies. INDO was loaded to the formulation at 0.1% (w/w). pH of the formulation was 5.29±0.00 and considering the ocular tolerability no adjustment was required. The rheological analyses revealed the gel transition point at 34±2°C. In vitro release analyses revealed that even after 6 hours only 30% of the INDO was released from the formulations showing the extended release of the active agent with the help of transition of the eye drops to the solidified gel structure. These results support the notion that ocular bioavailability will be enhanced with P407 based in-situ gels considering extended retention time of INDO on the corneal surface.*
**Keywords:** *Indomethacin, in situ gel, ocular inflammation, poloxamer 407*

## ÖZ

**Amaç:** *Bu çalışma, oküler inflamatuar hastalıkların etkin tedavisi için kornea yüzeyinde İndometazin'in (INDO) kalış süresini uzatarak oküler biyoyararlanımını artıracak in-situ jel formülasyonları hazırlamayı amaçlamaktadır.*
**Gereç ve Yöntem:** *Formülasyonlar, soğukta hazırlama yöntemi ile hazırlanmıştır. Bu yöntemde kısaca polimerler soğutulmuş distile suda çözündürülerek INDO eklenmiş ve homojen hale*

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*getirilmiştir. Analitik çalışmalarda düzenlenmiş bir UV yöntemi kullanılmıştır. INDO ve yardımcı maddelerin yapısal özelliklerinin belirlenmesi adına DSC, FT-IR ve ¹H-NMR analizleri kullanılmıştır. Formülasyonların karakteristik özellikleri; jelleşme sıcaklığı ve jelleşme süresi, pH, reolojik analizler ve in vitro salım çalışmaları (pH 7.4 PBS, 34 ± 2°C) ile değerlendirilmiştir.*

**Sonuç ve Tartışma:** *Jelleşme sıcaklığı ve jelleşme süresi analizlerine göre, %17 (a/a) Poloksamer 407 (P407) içeren optimal formülasyon daha sonraki çalışmalar için seçilmiştir. Etkin madde-polimer geçimliliği DSC, FT-IR ve ¹H-NMR analizleri ile doğrulanmıştır. INDO, formülasyona %0.1 (a/a) oranında yüklenmiştir. Formülasyonun pH değeri 5.29 ± 0.00 olarak belirlenmiş ve oküler tolerans göz önünde bulundurularak herhangi bir pH ayarlamasına gerek duyulmamıştır. Reolojik analizler, jelleşme noktasının 34 ± 2°C olduğunu ortaya koymuştur. In vitro salım analizleri, 6 saat sonunda INDO'nun yalnızca %30'unun salındığını göstermiştir. Bu durum, göz damlasının jel yapıya dönüşmesi sayesinde etkin maddenin uzamış salımını ortaya koymaktadır. Bu sonuçlar, INDO'nun kornea yüzeyinde uzamış kalış süresi dikkate alındığında, P407 bazlı in situ jellerle oküler biyoyararlanımın artırılacağı düşüncesini desteklemektedir.*

**Anahtar Kelimeler:** *İndometazin, in-situ jel, oküler inflamasyon, poloksamer 407*

## INTRODUCTION

The eye is a sophisticated organ distinguished by its specialized anatomy and physiology. Structurally, it is composed of two primary regions: the anterior and posterior segments. The anterior segment comprises the aqueous humor, conjunctiva, cornea, iris, ciliary body, and lens, while the posterior segment consists of the choroid, optic nerve, retinal pigment epithelium, sclera, vitreous humor, and neural retina [1]. Postoperative inflammation may arise due to multiple causes such as pre-existing uveitis, residual lens or foreign material, intraocular lens (IOL) irritation, immune reactions, or infection. Factors like extended surgery duration or toxic responses to surgical substances (e.g., irrigating fluids or IOL coatings) can disrupt the blood-aqueous barrier, increasing inflammatory response after the procedure [2]. Corticosteroids are commonly used to manage postoperative ocular inflammation however may cause side effects such as elevated intraocular pressure (IOP), increased infection risk, and delayed corneal healing. As an alternative in routine cases, non-steroidal anti-inflammatory drugs (NSAIDs) can be used. NSAIDs reduce inflammation by inhibiting cyclooxygenase (COX) and lowering prostaglandin production. Numerous controlled studies have confirmed their safety and effectiveness in treating postoperative inflammation, pain, and related complications [3]. Indomethacin (INDO) is a well-established NSAID that functions as a prostaglandin synthesis inhibitor. It has been widely used for decades in the management of postoperative inflammation [4]. Multiple studies have demonstrated that 0.1% INDO is both safe and effective for managing postoperative inflammation and pain [5–7].

Conventional ocular drug delivery has predominantly relied on eye drops due to their ease of use and patient compliance; however, their bioavailability remains critically low (1–10%) owing to rapid precorneal clearance, limited absorption area, and enzymatic degradation [8]. To overcome these limitations, there are various formulation strategies have emerged in the literature aiming to improve ocular drug bioavailability. In addition, alternative formulations such as ointments and suspensions were developed to enhance ocular retention, yet issues like blurred vision and inconsistent dosing limited their widespread use [8,9]. In recent years, advanced delivery systems (including nanoparticles, hydrogels, and implantable devices) have emerged, offering improved residence time, sustained release, and enhanced therapeutic efficacy [9].

Various strategies have been developed to enhance therapeutic efficacy in ocular drug delivery. Among these, the use of penetration enhancers that facilitate drug transport across the corneal epithelium holds significant importance. Penetration enhancers such as surfactants, calcium chelators, and cyclodextrins improve drug absorption by transiently disrupting the intercellular junctions of epithelial cells [10]. Moreover, to ensure adequate residence time of the drug on the ocular surface, the development of mucoadhesive carrier systems is also essential. Mucoadhesive nanosystems formulated using biopolymers such as chitosan, hyaluronic acid, and hydroxypropyl methylcellulose (HPMC) exhibit enhanced adhesion to the ocular surface, thereby improving therapeutic efficacy [11,12]. Additionally, positively charged cationic polymers interact electrostatically with the negatively charged

mucosal surface, thereby prolonging the residence time and enhancing bioavailability [13].

In this study, *in-situ* gel formulations containing INDO were developed. *In-situ* gels are basically polymer-based colloidal systems that remain as liquids or solutions before administration, and subsequently transform into a gel once administered, forming an *in-situ* gel at the site of action [14]. Typically, *in-situ* gel systems fall into two groups based on their triggering mechanism: those activated by pH changes and those responsive to temperature variations [15]. Polymeric *in-situ* gel formulations have several advantages, such as enhanced patient compliance, prolonged drug localization at the target site, and reduced dosing frequency and lower therapeutic doses therefore minimized local and systemic adverse effects. These systems enable localized and sustained drug delivery, making them highly suitable for long-term therapeutic applications [16].

The aim of this study is to prolong the residence time of INDO on the cornea unlike conventional eye drops, thereby enhancing its therapeutic efficacy in the treatment of postoperative inflammation. *In vitro* drug release profiles and kinetic modeling analyses were performed using the DDSolver software to evaluate the sustained release behavior of INDO.

## MATERIAL AND METHOD

INDO was kindly gifted by Deva, Turkey. Poloxamer 407 (P407) was purchased from Sigma, (Germany). Ultrapure water (UPW) was sourced from the MilliQ Millipore purification system (MilliQ Millipore, France). All other reagents used in the study were of analytical grade.

### Analytical Method Development

A modified UV method was used for the determination of INDO with Shimadzu UV-160 UV-Vis-NIR Spectrophotometer (Japan) [17] . UV detection was performed at 240 nm. An accurate amount of INDO was dissolved in methanol to prepare a stock solution, which was then diluted to six different concentrations ranging from 5 to 17.5 µg/ml for validation studies. It should be noted that the phosphate buffer without INDO exhibited no measurable absorbance when measured against methanol. The analytical methods were validated following the recommendations of the ICH [18].

### Characterization Studies of INDO

### Differential Scanning Calorimetry Analyses

The physical state of INDO was characterized by Differential scanning calorimetry (DSC) using Shimadzu DSC-60 instrument (Japan). Aluminum cells with ~4 mg samples were analyzed under the nitrogen atmosphere (50 ml/min) with a heating rate of 10°C/min within a temperature range of 30-300°C.

### Fourier Transform Infrared Spectrophotometry Analyses

Fourier transform infrared (FT-IR) analysis of the selected formulation was performed using a Shimadzu IR Prestige-21 (Japan) instrument, covering a spectral range of 4000 to 500 cm-1.

### Proton Nuclear Magnetic Resonance Analyses

$^{1}$H-NMR analyses were conducted on a Bruker UltraShield™ CPMAS NMR instrument (Germany), with samples prepared by dissolving both the formulation and ingredients in deuterated chloroform.

### Preparation of *In-Situ* Gel Formulations

Thermoresponsive *in-situ* gels based on P407 were prepared using the cold dispersion method [19]. For blank formulations, P407 was dissolved in UPW at three different concentrations (12%, 15%, and 17% w/w, respectively) by continuous stirring at 200 rpm in an ice bath with a magnetic stirrer. The INDO-loaded formulations were obtained following the same procedure, with 0.1% (w/w) INDO added gradually to the mixture during the stirring process. The composition and details of the prepared formulations are presented in Table 1.

**Table 1.** The compositions of *in-situ* gel formulations

| Code | P407 (%, w/w) | INDO (%, w/w) | UPW (%, w/w) |
|---|---|---|---|
| **IND-12** | 12 | 0.1 | 87.9 |
| **IND-15** | 15 | 0.1 | 84.9 |
| **IND-17** | 17 | 0.1 | 82.9 |

### Physiochemical Characterization of *In Situ* Gel Formulations

#### Gelation Temperature and Gelation Time

Gelation temperature and gelation time were determined as follows: approximately 5 ml of the formulation was transferred into a sealed tube with an inserted thermometer probe and placed in a water bath. The temperature of the bath was increased at a rate of 5°C per minute, and the time was recorded. The temperature at which gelation was first visually observed was noted as the gelation temperature, and the corresponding time was recorded as the gelation time.

#### pH Analyses

pH value of freshly prepared formulations was determined by WTW Profi Lab (pH 597, Wilhelm, Germany) at 25 ± 1°C in triplicate.

#### Rheological Analyses

Rheological analyses of the selected formulation were performed using a Brookfield Rheometer (Brookfield Engineering Laboratories, USA) at three different temperatures: 25 ± 2°C, 30 ± 2°C, and 35 ± 2°C. Rheological measurements were conducted using a CP-51 spindle, with approximately 10 mg of each sample. Shear rates ranging from 0 to 400 $s^{-1}$ were applied in 5-second intervals, and all measurements were performed in triplicate.

#### *In Vitro* Drug Release Studies

*In vitro* release studies were conducted using the dialysis membrane method, as described by Moreno-Bautista and Tam [20]. Cellulose-based dialysis membranes (molecular weight cut-off value of 14 kDa) were pre-soaked in phosphate buffer (pH 7.4), which served as the release medium, one day prior to the experiment for 24 hours. The lower ends of the soaked membranes were tightly sealed, and approximately 50 mg of the prepared formulation, containing 50 µg of INDO, was introduced into each membrane to maintain sink conditions of INDO [21], followed by the addition of 1 ml of release medium. The openings were then securely closed. Membranes containing pure INDO (1 mg) were prepared similarly and used as reference samples. The release medium was maintained at 34 ± 2°C to simulate ocular surface temperature. Samples were collected at 15, 30, 45, 60, 120, 240, and 360 minutes. At predetermined time intervals, 5 ml samples were withdrawn and analyzed using a UV spectrophotometer. To maintain a constant volume of the release medium, 5 ml of freshly prepared buffer was added after each sampling, as described by Başaran [22].

*In vitro* dissolution data were subjected to kinetic modeling using the DDSolver software. This program was employed to reduce computational time, minimize potential calculation errors, and accurately identify the most appropriate drug release model [23]. The DDSolver software was utilized to evaluate drug release kinetics by fitting the data to various models, including zero order, first order, Higuchi, Korsmeyer–Peppas, Hixson-Crowell, Baker–Lonsdale, and Hopfenberg.

## RESULT AND DISCUSSION

### Characterization Studies of INDO

#### Differential Scanning Calorimetry Analyses

The DSC thermograms of INDO, P407, and their physical mixture are presented in Figure 1.

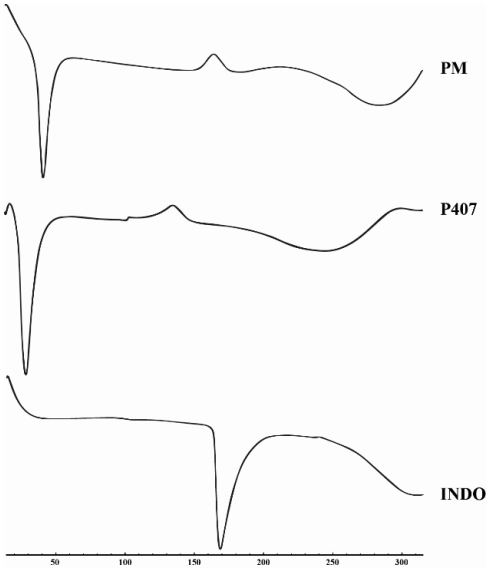


**Figure 1.** DSC thermogram of INDO, P407 and PM (physical mixture of INDO and P407)

The DSC thermogram of INDO revealed a melting point in the range of 158–162°C, which is consistent with values reported in the literature [24]. P407 displayed a melting transition at ~55–60°C. In the physical mixture, the characteristic INDO melting peak became significantly broadened and less intense. This behavior can be attributed to the partial dissolution of indomethacin within the molten P407 phase and possible amorphization, rather than any chemical interaction or degradation [7].

**Fourier Transform Infrared Spectrophotometry Analyses**

FT-IR spectra of INDO, P407, physical mixture and the formulations are given at Figure 2.

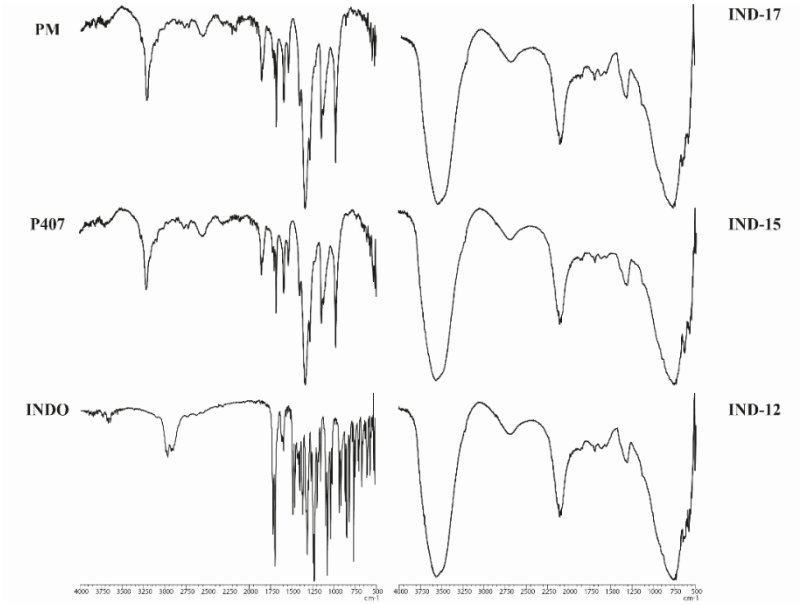


**Figure 2.** FT-IR chromatograms of INDO, P407, PM (physical mixture of INDO and P407), and formulations

Upon analysis of the FT-IR spectra of IND, characteristic aromatic C–H stretching bands were detected within the 3200–3000 $cm^{-1}$ region, followed by aliphatic C–H stretching vibrations in the 3000–

2800 $cm^{-1}$ range. Additionally, C=O stretching vibrations were observed between 1800 and 1600 $cm^{-1}$, while symmetric aromatic O–H stretching appeared in the 1200–1000 $cm^{-1}$ region. The obtained spectral data align well with previously published reports [25,26]. Although the FT-IR spectra did not show significant differences, the observed peak variations between the physical mixture [7].

**Proton Nuclear Magnetic Resonance Analyses**

$^1$H-NMR spectroscopy is a well-established technique employed to elucidate the structural features of both small and large molecules. $^1$H-NMR analysis offers valuable information regarding chemical shift values and spin-spin coupling patterns, while also enabling the evaluation of intra- and intermolecular proton interactions in a quantitative manner [27].

The $^1$H-NMR spectra of the INDO and P407 were presented in Figure 3.

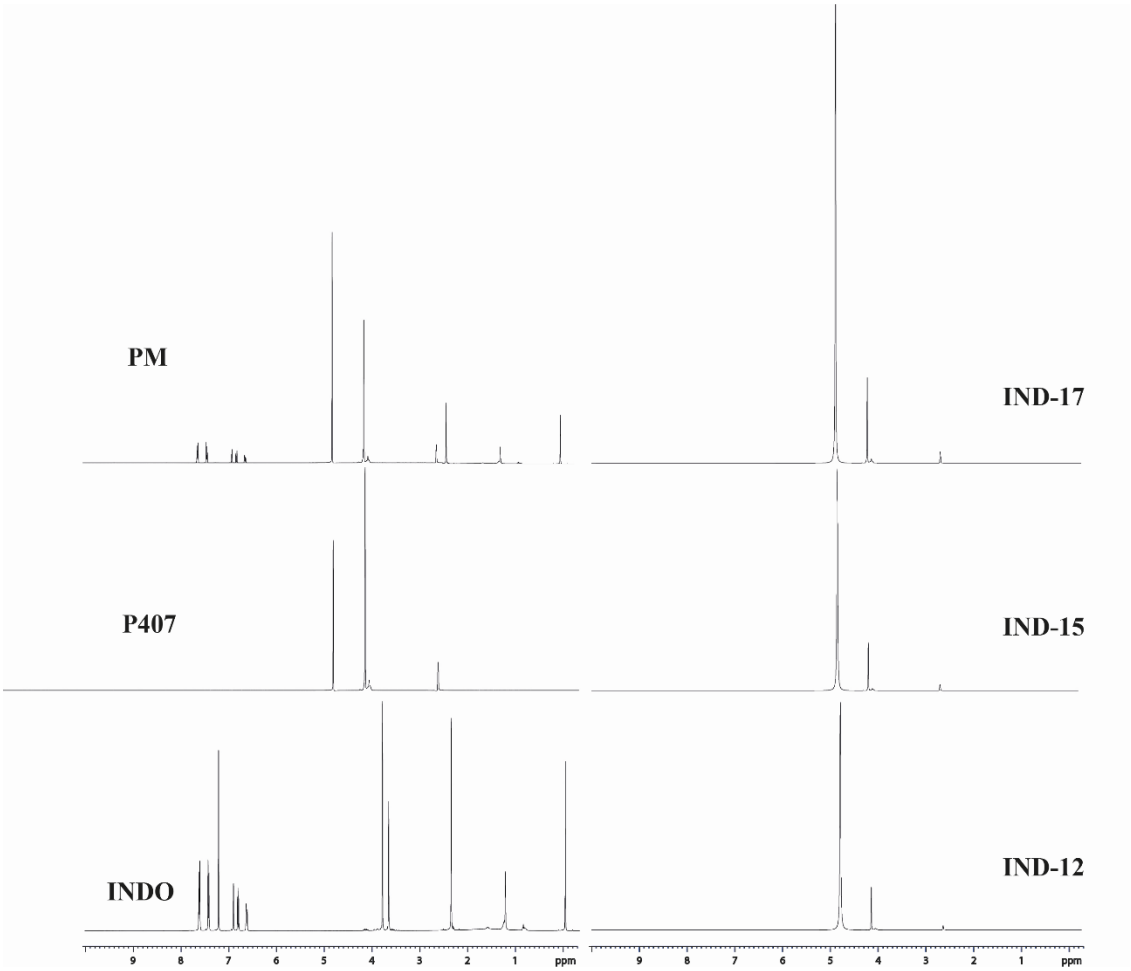


**Figure 3.** $^1$H NMR spectra of INDO, P407, PM (physical mixture of INDO and P407) and the formulations

Characteristic peaks of INDO were identified at 2.22 ppm and within the range of 3.67–3.74 ppm, as well as at 7.67 ppm, 6.94 ppm, 6.91 ppm, and 6.74 ppm, which are attributed to the protons of the benzene ring structure of INDO [28].

**Physiochemical Characterization of *In Situ* Gel Formulations**

**Gelation Temperature and Gelation Time**

Gelation temperature and time values of 3 formulations were given in Table 2.

**Table 2.** Gelation temperature and time values of the prepared formulations

| Code | Gelation temperature (°C) | Gelation time (sec) |
|---|---|---|
| **IND-12** | 40 ± 2 | 1-2 |
| **IND-15** | 35 ± 2 | 1-2 |
| **IND-17** | 34 ± 2 | 1-2 |

A thermoresponsive ocular *in situ* gel is ideally designed to remain liquid at room temperature and to gel upon reaching the temperature of the corneal surface [29]. Among individuals aged 21–60 years, the cornea demonstrated the lowest ocular surface temperature, with an average value of 34.79 ± 0.68°C [30]. Hence, considering both the gelation temperature and gelation time, IND-17 was identified as the optimal formulation for subsequent studies.

**pH Value**

The pH value of the selected IND-17 formulation was observed to be 5.29±0.00. The pH value of the formulation falls within the acceptable physiological range of 3.5 to 9.0, which helps minimize the risk of eye irritation, lacrimation, and discomfort [31]. This is in alignment with previously reported literature, which emphasizes the importance of maintaining pH levels close to that of natural tears to ensure ocular tolerance [32].

**Rheological Analyses**

The rheological analyses of the selected IND-17 formulation conducted at 25 ± 2°C, 30 ± 2°C, and 35 ± 2°C are presented in Figure 4 and viscosity values are given in Table 3.

**Table 3.** Gelation temperature and time values of the prepared formulations

| Shear rate (1/sec) | Viscosity (mPas) (25°C) | Viscosity (mPas) (30°C) | Viscosity (mPas) (35°C) |
|---|---|---|---|
| **1.92** | 13359.24 | 15430.44 | 16155.36 |
| **44.47** | 3380.46 | 2535.34 | 3443.06 |
| **88.90** | 1308.48 | 1813.98 | 2174.09 |
| **133.36** | 1086.89 | 1359.73 | 1481.98 |
| **177.79** | 792.92 | 1092.64 | 1005.40 |
| **222.22** | 538.65 | 678.52 | 799.92 |
| **266.69** | 463.75 | 532.36 | 683.69 |
| **311.12** | 352.78 | 444.24 | 589.25 |
| **355.55** | 330.51 | 421.29 | 523.45 |
| **400.13** | 291.70 | 312.39 | 477.05 |

The rheological evaluation of the formulation at different temperatures demonstrated clear temperature-dependent gelation behavior. At 25°C, the formulation exhibited high initial viscosity with rapid shear-thinning under increasing shear rate, indicating a fluid-like behavior. Upon heating to 30°C, the system began to show increased structural integrity, consistent with the onset of gelation and at 35°C, a more stable viscosity profile and higher shear resistance were observed, suggesting that the formulation had transitioned into a well-formed gel network. Throughout all cases, pseudoplastic flow behavior was maintained, as expected for polymer-based gel systems [33–35].

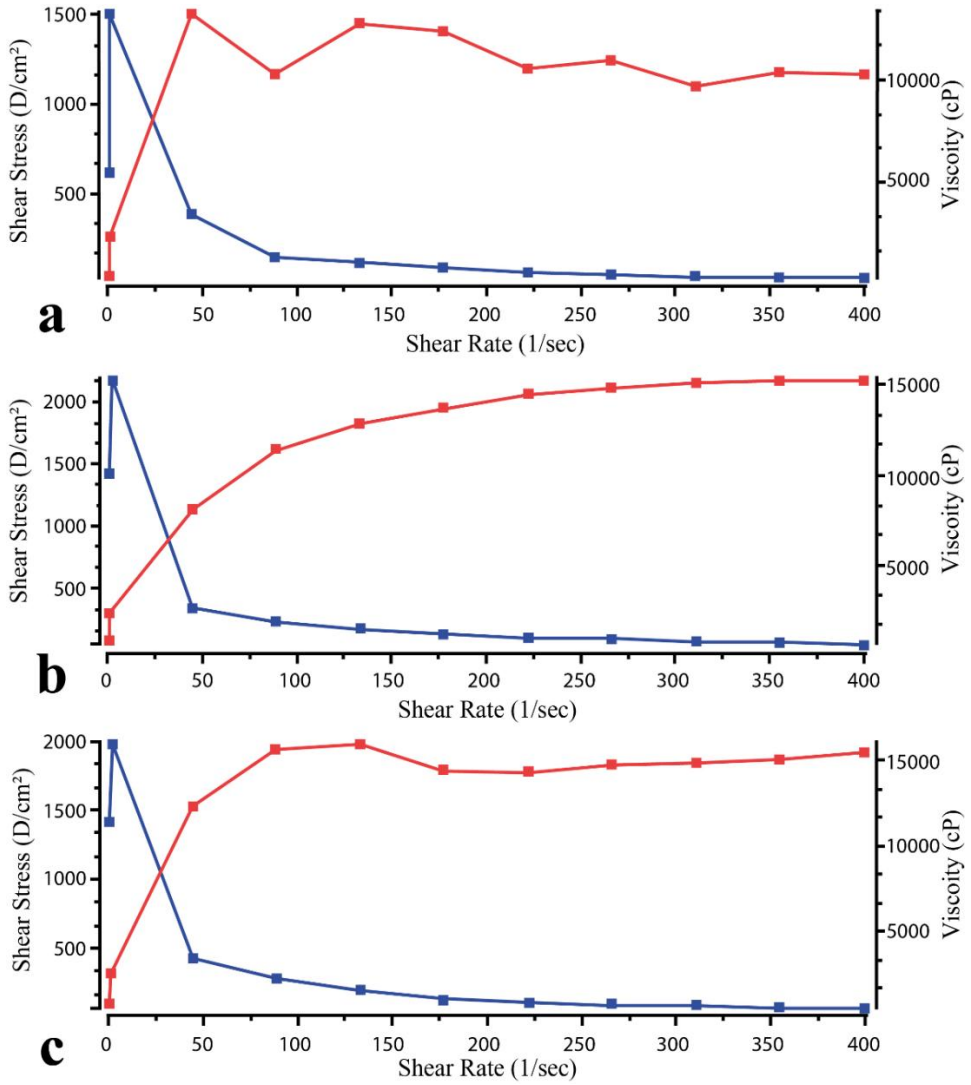


**Figure 4.** Rheological analyzes of IND-17 at 25°C (a), 30°C (b) and 35°C (c)

### *In Vitro* Drug Release Analyses

*In vitro* release rates and *in vitro* release profiles of IND-17 and pure INDO are given in Table 4 and Figure 5, respectively.

**Table 4.** *In vitro* cumulative release rates of IND-17 and pure INDO

| Time (min) | IND-17 | | INDO | |
|---|---|---|---|---|
| | Cumulative release (%) | Standard error (%) | Cumulative release (%) | Standard error (%) |
| **15** | 0.18 | 0.18 | 35.37 | 2.60 |
| **30** | 2.33 | 0.36 | 53.81 | 5.70 |
| **45** | 5.96 | 0.62 | 63.09 | 6.10 |
| **60** | 7.05 | 0.53 | 64.01 | 5.47 |
| **120** | 16.68 | 0.81 | 74.59 | 4.71 |
| **240** | 28.71 | 0.94 | 80.25 | 3.12 |
| **360** | 36.70 | 0.84 | 81.87 | 3.46 |

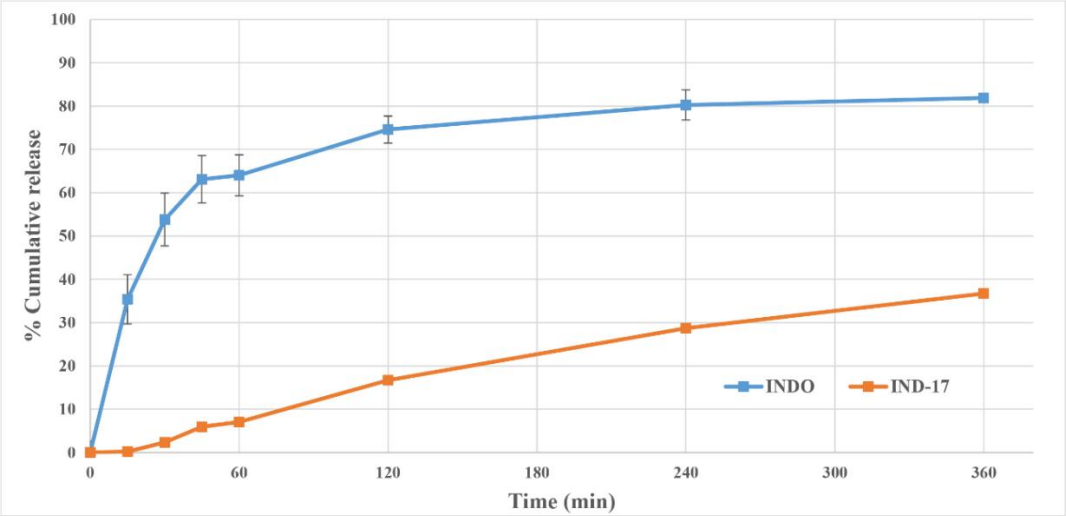


**Figure 5.** *In vitro* dissolution profile of pure INDO and IND-17 (Mean ± SE, n=3)

Upon evaluation of the *in vitro* release data, it was observed that pure INDO exhibited a release of 81.9% at the end of 6 hours, whereas the *in-situ* gelling systems resulted in a significantly lower release of 36.7% within the same time frame. This indicates that the *in-situ* gel formulation effectively prolonged the release of the active compound. The sustained release profile is attributed to the increased ocular residence time provided by the gelling system, suggesting its potential advantage in enhancing therapeutic efficacy and reducing dosing frequency. The observed *in vitro* release behavior is supported by related literature on P407-based *in-situ* gels. In their 2020 study, Nagai et al. reported that a thermoresponsive P407 gel formulation incorporating indomethacin nanocrystals exhibited markedly reduced drug release at physiological temperature. This effect was attributed to the increased viscosity of the gel and the prolonged precorneal residence time [36]. Furthermore, extensive literature reviews emphasize the thermoresponsive and mucoadhesive characteristics of P407-based hydrogels, both of which play a crucial role in reducing ocular surface drainage and maintaining prolonged drug availability [37].

The kinetic modeling outcomes for INDO release from the in-situ gel are summarized in Table 3. After obtaining the release profiles, the data were analyzed with DDSolver software considering four main criteria: coefficient of determination ($R^2$), adjusted $R^2$, Akaike Information Criterion (AIC), and Model Selection Criterion (MSC). The model demonstrating the highest $R^2$, adjusted $R^2$, and MSC, along with the lowest AIC, was selected as the best fit [38]. Based on these parameters, the release of INDO from the in-situ gel followed first-order kinetics.

**Table 5.** Kinetic results for various models

| Kinetic model | Evaluation criteria | | | |
|---|---|---|---|---|
| | $R^2$ | $R^2$ adjusted | AIC | MSC |
| **Zero order** | 0.9776 | 0.9776 | 29.26 | 3.43 |
| **First order** | 0.9899 | 0.9899 | 22.93 | 4.22 |
| **Higuchi** | 0.8642 | 0.8642 | 43.68 | 1.63 |
| **Korsmeyer-Peppas** | 0.3788 | 0.2752 | 57.85 | -0.14 |
| **Hixson-Crowell** | 0.9873 | 0.9873 | 24.73 | 4.00 |
| **Baker-Lonsdale** | 0.7338 | 0.7338 | 49.07 | 0.96 |
| **Hopfenberg** | 0.9873 | 0.9852 | 26.73 | 3.75 |

Table 5 shows that the dissolution data was fitted best to the first order kinetics and drug release of INDO was dependent on concentration remaining in the gel formulation. Among the limited studies in the literature where first-order kinetics predominates in P407-based systems, one notable example is the release of Cortex Moutan extract from a P407/carboxymethyl cellulose composite hydrogel. In this study, DDSolver evaluations in this case revealed a superior correlation with the first-order kinetic model [39]. In a different study with P407-based *in-situ* gel formulations, kinetic analyses of clorhexidine and doxycycline release demonstrated distinct first-order kinetic behavior. The results showed that the release rate is proportional to the residual drug concentration, confirming the direct validity of the first-order model [40].

The goal of this study was to extend release time of INDO on the corneal surface and improve the ocular bioavailability by developing *in-situ* formulations. Characterization studies have confirmed INDO's thermal characteristics, FT-IR spectra, $^{1}$H NMR spectra and *in vitro* dissolution studies were consistent with the data obtained from former studies. Optimum P407 percentage for the *in-situ* gel formulation has been determined as 17% (w/w) considering surface characteristics of the eye. Considering *in vitro* release studies data, *in-situ* gel formulation's release properties are longer then pure INDO as expected, showing the extended release duration on the corneal surface could reduce dosing frequency which will enhance the patients compliance. In view of the study's outcomes, further studies including *in vivo* studies will also highlight the real potential of the formulations.

## AUTHOR CONTRIBUTONS

Concept: Ö.B.C., K.Y., E.A., E.B.; Design: Ö.B.C., K.Y., E.A., E.B.; Control: Ö.B.C., K.Y., E.A., E.B.; Sources: Ö.B.C., K.Y., E.A., E.B.; Materials: Ö.B.C., K.Y., E.A., E.B.; Data Collection and/or Processing: Ö.B.C., K.Y., E.A., E.B.; Analysis and/or Interpretation: Ö.B.C., K.Y., E.A., E.B.; Literature Review: Ö.B.C., K.Y., E.A., E.B.; Manuscript Writing: Ö.B.C., K.Y., E.A., E.B.; Critical Review: Ö.B.C., K.Y., E.A., E.B.; 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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