


## Emulsion Formulations of Indomethacine and Xylometazoline Hydrochloride for Intranasal Delivery

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### Abstract

Nasal administration has many advantages over parenteral and oral administration. Some drugs are ineffective when administered orally due to absorption and first pass metabolism. Therefore, if the aqueous solubility problem can be overcome, the intranasal route will be an alternative method for administration. In this study, emulsion formulation was proposed as a new approach in order to increase the duration of the indomethacin-xylometazoline hydrochloride combination in the nose. The pH value of F1 and F2 emulsions were determined 9.4 and as 5.6 respectively. The particle size of F1 and F2 formulations were found to be 136.8±24 nm and 269.5±66 nm respectively.

Formulation of o/w emulsion IND and XYL may be considered as an alternative to iv and po administration. This administration of drugs may be delivery to achieve rapid onset of its pharmacological effect.

**Keywords:** Emulsion, Indomethacine, xylometazoline hydrochloride, intranasal delivery

### Öz

Nazal yolla ilaç uygulamanın, parenteral ve oral uygulamaya nazaran birçok avantajı vardır. Bazı ilaçlar emilim ve ilk geçiş metabolizması nedeniyle ağızdan uygulandığında etkisizdir. Bu nedenle, sulu çözünürlük probleminin üstesinden gelinirse, burun içi yol uygulama için alternatif bir yöntem olacaktır. Bu çalışmada, indometazin-ksilometazolin hidroklorür kombinasyonunun burunda kalma süresinin uzatmak amacıyla emülsiyon formülasyonu yeni bir yaklaşım olarak önerilmiştir. F1 ve F2 emülsiyonlarının pH değeri sırasıyla 9,4 ve 5,6 olarak *belirlenmiştir*. F1 ve F2 formülasyonlarının partikül boyutunun sırasıyla 136.8 ± 24 nm ve 269.5 ± 66 nm olduğu *bulunmuştur*.

İndometazin-ksilometazolin içeren y/s emülsiyon formülasyonu, iv ve po uygulamasına bir alternatif olarak düşünülebilir. Bu ilaç uygulaması, farmakolojik etkisinin hızlı başlangıcını sağlamak için verilebilir.

**Anahtar Kelimeler:** Emülsiyon, indometazin, ksilometazolin hidroklorür, intranasal uygulama

## 1. Introduction

Emulsion refers to a mixture that includes two or more liquid phases. Emulsions can be categorized as water-in-oil emulsions (with water droplets as a dispersed phase in the flow of oil as the continuous phase), oil-in-water emulsions (with oil droplets in the flow of water), and more complex configurations of emulsions such as water-in-oil-in-water emulsions.

Nasal route; systemically effective drugs have also been the route of administration with advantages such as easily accessible, large surface area, thin membrane feature and excess vascularity, and elimination of hepatic first passage.

The nasal cavity is mainly used for treatment of local diseases of the upper respiratory tract such as nasal congestion, nasal infections and nasal allergic diseases e.g. allergic rhinitis.

Hydrophobic drugs with low molecular weight applied nasally are used for the treatment of nasal mucosa and sinus. (Matsuyama et al. (2006), Mitra et al. (2000), Shekade et al. (2020))

Indomethacin (IND), a lipophilic model drug in this study, is an anti-inflammatory and analgesic antipyretic drug used in experiments. It produces erosions and ulcers in the gastrointestinal tract. An alternative route of administration for IND would allow blood drug concentrations to be maintained in the therapeutic range while avoiding gastric irritation. Huang et al. (1995) showed that IND solutions could easily pass through the nasal mucosa in rats and enter the systemic circulation. In this study, nasal absorption was close to that obtained after per oral (po) dosing (Karasulu et al (2008)).

Xylometazoline HCl (XYL) is applied topically to relieve nasal congestion associated with acute or chronic rhinitis, common cold, sinusitis, hay fever or other

allergies. It causes vasoconstriction in the nasal submucosa, which is manifested as a collapse of the venous sinusoids. Xylometazoline HCl action is characterized by a fast onset with an effect obtained after 5–10 minutes and lasting for 6–8 *hours*. The efficacy of xylometazoline HCl as a topical nasal decongestant is well proven. (Graf et al. (2018))

It is usual for surgery to result in inflammation, causing postoperative pain and edema. Possible pain and inflammation are also common problems, especially after rhinoplasty, and the active ingredient of indomethacin, which is a non-steroidal anti-inflammatory group, has been included in the formulation as both analgesic and anti-inflammatory. Edema is the most uncomfortable situation in patients who have undergone nasal surgery, especially in the postoperative period, and xylometazoline was added as a decongestant to prevent edema.

The aim of this study is the preparation and quality control studies of an emulsion formulation containing indomethacin-xylometazoline that can be applied intranasally.

## 2. Material and Methods

### Materials

IND and XYL HCl were kindly supplied by Deva Pharmaceutical Fac. (Istanbul, Turkey) and Berko Pharmaceutical Fac. (Istanbul, Turkey) respectively. The emulsifying agents; polyoxyethylene 20 sorbitan monooleate (Tween 80) and sorbitan monooleate (Span 80) were purchased from E. Merck. Co (Schuchardt, Germany). Ethyl alcohol was used as a cosurfactant and purchased from E. Merck. Co (Schuchardt, Germany). Methanol and acetonitrile were obtained from Carlo Erba. Sodium acetate

and acetic acid were purchased from Merck. Water was purified by a Milli-Q Water Purification System (Direct-Q 8 UV). The black seed oil as an oily phase was purchased from Zade Vital Pharmaceuticals (Konya, Turkey). All chemicals were used as analytical grade.

### Preparation and characterization of intranasal emulsions

Two different type of oil-in-water (F1-O/W and F2-O/W) emulsions of black seed oil were prepared using different ratio emulsifying agents (Table 1).

Ethyl alcohol was added as cosurfactant. Isotonic phosphate buffer and sodium carbonate solution were used as the aqueous phase of emulsions. IND and XYL were incorporated into the oil phases and water phase of emulsions respectively and they were stirred with magnetic stirrer at 1000 rpm for 5 min. All emulsions were stable and neutral pH during the time course of the experiments.

**Table 1.** The composition (%), particle size distribution, viscosity and final drug loading of water in two different oil emulsion (O/W). Each value represents the mean $\pm$ SD (n=3)

	F1	F2
Black seed oil	21.4	22
Tween 80	20.6	22.5
Span 80	3.6	2.5
Ethyl Alcohol	8.5	8.5
Isotonic Phosphate Buffer	-	42.5
Sodium carbonate solution (2.5 %)	40	-
Distilled water	14	-
IND	0.3	0.15
XYL	0.1	0.1

For the characterization studies, the droplet size distribution and average droplet size of emulsions were measured using Zetasizer 3000 HSA (Malvern, UK). The viscosity of emulsions were measured on a Brookfield viscometer, model DV-II+PRO spindle ULA, I equipment with Rheocalc V1.1 software,

Brookfield Engineering Laboratories Inc. (Massachusetts, USA).

### Preparation of nasal indomethacin solution

For permeation studies, IND and XYL were solved with isotonic phosphate buffer: ethanol (3:2) and isotonic phosphate buffer respectively (IND-Sol and XYL-Sol). All solutions was freshly prepared daily.

### Drug content studies

#### Preparation of stock solutions

Stock solutions of indomethazin and xylometazoline were prepared by dissolving 10 mg of each compound in 10 mL methanol. These solutions were stored at 4 °C and were stable for at least three weeks. Working standard solutions were prepared by diluting the stock solution (5.0, 10.0, 20.0, 50.0 and 100.0  $\mu$ g/mL for xylometazoline, 1.0, 5.0, 10.0, 25.0 and 50.0  $\mu$ g/mL for indomethazin).

### Equipment and Chromatographic Conditions

Shimadzu HPLC system has been employed to apply the method. System consists of a degasser unit (DGU-20A SR), a quaternary pump (LC-20AT), an auto injector (SIL-20AC HT), column oven (CTO-10AS VP) and communications bus module (CBM-20A). The system was equipped with a PDA detector (SPD-M20A).

The chromatographic separation was performed on a ACE 5 C18 column (250 x 4.6 mm, 5  $\mu$ m). The mobile phase consisted of 10 mM sodium acetate buffer pH 3, acetonitrile and methanol (40:50:10 – v:v). The flow rate was 1 mL/min. The wavelengths of the detection were at 220 nm for indomethazin and 230 nm for xylometazoline. The column oven temperature was 25 °C and the injection volume was 20  $\mu$ L. The elution times for indomethazin and xylometazoline were

approximately 10.5 and 4.2 min, respectively (Pai et al. (2017))

### In vitro permeation studies

The permeation studies were carried out by vertical diffusion cell method ( $0.34 \text{ cm}^2$ ) thermostatted at  $37^\circ\text{C}$  in water bath (Variomag, Germany). The apparatus consisted of mixed cellulose ester membrane (Millipore) on to glass diffusion cell between donor and receptor compartments. The receptor solution was 5 mL of isotonic phosphate buffer: ethanol (3:2). The receptor solutions were magnetically stirred at 600 rpm throughout experiment. The donor compartment was 0.5 mL of F1 emulsion or F2 emulsion or IND solution or XYL solution. The aliquots withdrawn at various intervals for 24 hours were immediately analysed for drug concentration with HPLC and refilled with the same volume of fresh receptor solution. Three replicates of each experiment were performed. Sink conditions were maintained in the receptor compartment during in vitro permeation studies.

### Data treatment

The permeation of IND and XYL from nasal preparations was investigated. The cumulative amount-time profiles were plotted. The effective permeability coefficients and flux values at steady state were calculated (Karasulu et al. (2008)).

## 3. Research Findings

The characteristics of F1 and F2 emulsions such as particle size, pH, conductivity, viscosity, measurements and final drug loading were given in Table 2.

**Table 2.** The composition (%), particle size distribution, viscosity and final drug loading of water in two different oil emulsion (O/W). Each value indicates the mean  $\pm$  SD (n=3).

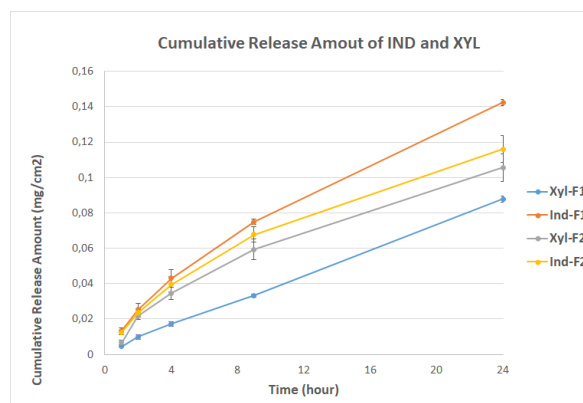
	F1	F2
Particle size (nm) $\pm$ SD	136.8 $\pm$ 24	269.5 $\pm$ 66
pH	9.4	5.6

Conductivity ( $\mu\text{Scm}^{-1}$ )	4.9	2.2
Drug loading (mg/mL)for IND $\pm$ SD	1.0 $\pm$ 0.04	1.1 $\pm$ 0.11
Drug loading (mg/mL) for XYL $\pm$ SD	2.8 $\pm$ 0.11	1.7 $\pm$ 0.14
Viscosity (cp) $\pm$ SD	204.6 $\pm$ 5	192.2 $\pm$ 14

**Table 3.** Flux and Peff IND&XYL Through cellulose ester membrane from F1 and F2 formulations

	Peff (cm/s)	J ( $\text{cm}^2/\text{s}$ )
F1-XYL	1.5E-03 $\pm$ 3.52E-04	2.4E-03 $\pm$ 5.86E-04
F1-IND	3.3E-03 $\pm$ 9.20E-04	5.3E-03 $\pm$ 1.53E-03
F2-XYL	2.4E-03 $\pm$ 6.41E-04	2.2E-03 $\pm$ 4.89E-04
F2-IND	2.9E-03 $\pm$ 8.42E-04	2.7E-03 $\pm$ 6.67E-04

**Fig. 1.** In vitro permeation profiles of IND&XYL into isotonic phosphate buffer-ethanol (3:2) (pH 7.4) at  $37^\circ\text{C}$  from nasal formulations using cellulose ester membrane. Each points represents the means of three assignments  $\pm$  SD.



## 4. Results

### Particle size

The particle size of F1 and F2 formulations were found to be  $136.8\pm 24 \text{ nm}$  and  $269.5\pm 66 \text{ nm}$  respectively. The size range of macroemulsions is usually  $0.1\text{--}5 \mu\text{m}$ . Polydispersity index determines the homogeneity of the emulsion. For a

homogeneous emulsion it should be  $<1$  (Danaei et al. (2018)). It was found to be 0.3 for F1 and 0.5 for F2 respectively.

### pH

The pH value of F1 and F2 emulsions were determined 9.4 and as 5.6 respectively. The nasal mucosal pH is  $\approx 5.5-6.5$  which approximating the normal pH range of nasal fluids (Ayoub et al (2016)). Nasal irritation could be minimized when Formulation 2 is used. It is in tolerable range in contact with nasal mucosa.

### Conductivity

The O/W emulsions provided higher conductivity values than the W/O emulsions due to the conductivity properties of the aqueous external phase (Salager (2000)). The characteristics of O/W emulsions such as conductivity measurements and final drug loading were given in Table 2.

### Drug content

IND& contents of the formulations F1-F2 were found 1.0-1.1 respectively. XYL contents for the F1-F2 formulations were found to be 2.8-1.7 respectively. The drugs contents of the formulations as shown in Table 2.

### In vitro permeation studies

The profiles of permeation of IND & XYL from F1 and F2 emulsion formulations through the cellulose ester membrane were shown in Fig. 1 In the study of Karasulu et al. (2008) it was shown that, different syntetic membrane filter separating the drug from the release medium did not impede drug release appreciably. According to the

experimental results, in vitro flux values of IND&XYL from these emulsions during 24 hours was found. The flux value of IND&XYL during continuous permeability studies has been showed by a gradual increase in the receptor compartment as a function of time. The formulations of flux and peff IND&XYL values as shown in Table 3. The release profiles of IND from F1 and F2 formulations are similar.

### Viscosity

The viscosity of F1 and F2 formulations were found to be  $204.6\pm 5$  and  $192.2\pm 14$  respectively. Emulsions are more viscous systems that release solutions, and they extend the duration of the drug in the nasal cavity. Therefore, emulsions to solution are preferred for nasal administration, as the residence time of the drug at the site of action is extended (Kan et al. (1999), Tirucheraï et al. (2002)).

Particle size distribution, viscosity and pH are the most important characterizations of formulation for evaluation of stability. A problem with the stability of the developed formulations has not been identified.

In conclusion, it is clear that emulsion formulation loaded with IND and XYL is potentially useful for in nasal delivery. Formulation of o/w emulsion IND and XYL may be considered as an alternative to iv and po administration. This administration may be IND and XYL delivery to achieve rapid onset of its pharmacological effect.

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