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Original article

PREPARATION AND EVALUATION OF DIFFERENT GEL FORMULATIONS FOR TRANSDERMAL DELIVERY OF MELOXICAM

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Abstract

The aim of this study was the preparation and in vitro evaluation of different gel formulations of meloxicam, a well-known and important non-steroidal anti-inflammatory drug. In the study, gel formulations of meloxicam at a concentration of 1% were prepared using hydroxyethyl cellulose (HEC) and Carbopol 934 as the gelling agents. Emulgel formulation was prepared by mixing the Carbopol 934 gel with water-in-oil (w/o) emulsion base. The in vitro drug release from these formulations through artificial membrane into phosphate buffer medium was determined using Franz diffusion cells. HEC gel base exhibited significantly higher drug release when compared to the other vehicles. The release profiles were evaluated by zero-order, first-order and Higuchi ($Q\sqrt{t}$) kinetics model. The release of meloxicam from all formulations obeyed the Higuchi model, so the diffusion coefficients were calculated via this equation. According to statistical analysis of the data diffusion coefficients of the drug from the formulations could be ranked as follows: HEC gel ($D= 3.58x10^{-8}$ $cm^2.sec^{-1}$) > Carbopol gel ($D=4.01x10^{-9}$ $cm^2.sec^{-1}$) > Emulgel ($D=1.99x10^{-9}$ $cm^2.sec^{-1}$). This result indicates that gel formulation with HEC is a more suitable gel preparation of meloxicam when compared with the other formulations.

Key words: *Meloxicam, Non-steroidal anti-inflammatory drug, Topical gel formulation, Diffusion coefficient, In vitro drug release.*

Meloksikam'ın Transdermal Verilişine Yönelik Farklı Jel Formülasyonlarının Hazırlanması ve Değerlendirilmesi

Bu çalışmanın amacı, çok iyi bilinen ve önemli bir non-steroidal anti-inflamatuvar etkin madde olan meloksikam'ın farklı jel formülasyonlarının hazırlanması ve in-vitro açıdan değerlendirilmesidir. Bu çalışmada, jel yapıcı ajan olarak hidroksietil selüloz (HEC) ve Carbopol 934 kullanılarak, meloksikam'ın % 1 konsantrasyonda jel formülasyonları hazırlanmıştır. Emuljel formülasyonu, Carbopol 934 jelinin yağ içinde su (S/Y) tipi bir emülsiyon ile karıştırılmasıyla hazırlanmıştır. Bu formülasyonlardan in-vitro etkin madde salımı fosfat tamponu ortamında, yapay membran vasıtasıyla Franz difüzyon hücreleri kullanılarak tayin edilmiştir. Diğer taşıyıcılar ile karşılaştırıldığında HEC jel bazlı formülasyon anlamlı derecede daha fazla etkin madde salımı göstermiştir. Elde edilen salım profilleri birinci derece, sıfır derece ve Higuchi ($Q\sqrt{t}$) *kinetik modelleri ile değerlendirilmiştir. Tüm formülasyonlarda meloksikam'ın salımı Higuchi modeinle uymuştur, bu nedenle difüzyon katsayıları bu eşitlik kullanılarak hesaplanmıştır. Verilerin istatistiksel analizleri, formülasyonlardan etkin maddenin difüzyon katsayılarının HEC jel ($D=3.58x10^{-8}$ $cm^2.s^{-1}$) > Carbopol jel ($D=4.01x10^{-9}$ $cm^2.s^{-1}$) > Emuljel ($D=1.99x10^{-9}$ $cm^2.s^{-1}$) şeklinde sıralandığını göstermektedir. Bu sonuç, diğer formülasyonlara kıyasla, HEC jel formülasyonunun meloksikam'ın daha uygun bir jel preparatı olduğunu göstermektedir.*

Anahtar kelimeler: *Meloksikam, Non-steroidal anti-inflamatuvar etkin madde, Topikal jel formülasyonu, Difüzyon katsayısı, İn vitro etkin madde salımı.*

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the long-term treatment of chronic rheumatic diseases. Meloxicam is a potent, new NSAID approved by the Food and Drug Administration (FDA) in 2000 and is used in the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases. Although meloxicam is an enolic-class NSAID that inhibits the cyclooxygenase (COX)-2 isoenzyme more potently than the COX-1 isoenzyme, it still has 10-20% incidence of gastrointestinal irritation, such as gastric mucosal ulceration and hemorrhage, at the standard oral administration dose. As a result, meloxicam is not suitable for the treatment of rheumatological patients with gastric ulcer (1-6).

Topical administration of NSAIDs via the dermal route has been recognized as a viable alternative to the oral route. Meloxicam has poor aqueous solubility and wettability, leading to difficulties in the design of pharmaceutical formulations but it possesses appropriate physicochemical properties for potential transdermal delivery such as low molecular weight, low daily therapeutic dose, lipid solubility and excellent tissue tolerability. Thus, transdermal drug delivery can also be considered as an additional route for meloxicam administration (1,7,8). In recent years, a number of studies have been attempted to prepare transdermal dosage forms of meloxicam such as gels, patchs, microemulsions (9) and various strategies have been developed to enhance topical administration of meloxicam such as using ita sodium or ethanolamin salt forms (2,4,10,11). However, only a few studies have been done on the investigation of the effect of the vehicle compound of gel formulations for transdermal delivery of meloxicam to improve the drug release and skin permeation (5).

It is well known that therapeutic efficacy of a topical formulation depends on both the physicochemical properties of the drug and the vehicle composition. The vehicle composition can affect drug release, and a number of vehicles, including simple creams, gels and emulsion-based formulations (Emulgel) have been utilized in topical preparations (9,12,13). Therefore, it was aimed in this study to prepare different gel formulations for transdermal delivery of meloxicam and to determine the *in vitro* drug release from these formulations by the method of Franz diffusion cells.

EXPERIMENTAL

Materials

In this study, Meloxicam (Ulkar, Turkey), Carbopol 934 (BF Goodrich Co., Cleveland, USA), HEC (Fluca, Switzerland), triethanolamine (Merck, Germany), propylene glycol (Aklar Chemical Inc., Turkey), liquid paraffin (Aklar Chemical Inc., Turkey), cetyl alcohol (Aklar Chemical Inc., Turkey), stearyl alcohol (Aklar Chemical Inc., Turkey), lanolin (Aklar Chemical Inc., Turkey), wax (Aklar Chemical Inc., Turkey), glycerine (Aklar Chemical Inc., Turkey), magnesium sulfate (Merck, Germany), Tween 40 (Merck, Germany), Tween 80 (Merck, Germany), potassium dihydrogen phosphate (Merck, Germany) and sodium hydroxide (Merck, Germany) were used. All other chemicals were of reagent grade.

Methods

Preparation of meloxicam formulations

The composition of gel formulations used in this study are shown in Table 1. All formulations contained 1% w/w meloxicam.

Table 1. Composition of the formulations.

Content (g)	***Carbopol gel***	***HEC gel***	***Emulgel***
Meloxicam	1	1	1
Carbopol 934	1	-	0.7
HEC	-	7.5	-
Liquid paraffin	-	-	2.5
Cetyl alcohol	-	-	4.9
Stearyl alcohol	-	-	13.1
Lanolin	-	-	6.1
Wax	-	-	1
Glycerine	-	-	3.1
Magnesium sulfate	-	-	0.2
Tween 40	-	-	3.3
Tween 80	-	-	4.9
Propylene glycol	23	23	-
Triethanolamine	2.5	2.5	1.6
Distilled water	72.5	66	57.6

Preparation of gel formulations

Gel formulations of meloxicam were prepared using Carbopol 934 and HEC. The gel base was poured into a 100 mL beaker and soaked in water at room temperature for 12 h. HEC-water and also Carbopol 934-water mixtures were homogenized by magnetic stirring at 500 rpm for 30 min. The gelation was achieved by the addition of triethanolamine. In the final step, the required amounts of propylene glycol and meloxicam were mixed together. Solubility of meloxicam in propylene glycol is given 0.307 mg/mL (14). Thus, the drug is partly soluble and partly dispersed in this mixture which was added into gels and the pH of the gels were adjusted between pH 5 and 7.2 with triethanolamine.

Preparation of emulsion-based gel formulation

All the aqueous phase materials and oil phase ingredients were placed separately in two beakers and stirred on a water bath at 70^0C. Then the water phase was slowly added to the oil phase under continuous agitation and a resultant w/o type emulsion was prepared. Mixing and then homogeneously stirring of this emulsion base with Carbopol gel at room temperature (25^0C) was achieved and the Emulgel formulation of meloxicam was prepared. Meloxicam was added at a concentration of 1% w/w into the oil phase.

Analytical method

The drug concentrations in the samples were determined by UV-visible spectrophotometry (Shimadzu UV-1202 visible) at 270 nm (n=6). The analytical method validation was checked for precision (repeatability, reproducibility), accuracy, specificity, linearity and range, according to USP 30/NF 25 criteria (15).

Determination of the viscosity of gel formulations

The viscosities of the gel formulations were determined at room temperature via Brookfield Digital Viscometer Model DV-II. The measurements were made using spindle number RV-7 at 20 rpm.

pH determination of the gel formulations

The pH of each gel formulation was measured, using a pH-meter (Orion Research Model 701), which was calibrated before each use with buffer solution at different pH.

Determination of diffusion coefficients of the gel formulations

Diffusion coefficients of the gel formulations were calculated using the data obtained from drug release studies and Higuchi equation given in Equation 1 (16-18).

$$Q = 2C_0(Dt/\pi)^{1/2} \quad (1)$$

In this equation, Q is the amount of drug released into the receptor phase per unit area of exposure (mg/cm^2), C_0 is the initial drug concentration in the vehicle (mg/mL), D is the apparent diffusion coefficient of the drug (cm^2/sec), t is the time after the application (sec), and π is a constant. According to the Higuchi theory, Equation 1 is valid if the percentage released is less than 30% of the total drug in the vehicle.

In vitro drug release studies

Meloxicam release from the different formulations was measured through 0.22 μm cellulose acetate membranes (Millipore, Ireland) using modified Franz diffusion cells with an available diffusion area of 1.32 cm^2. A 2 g sample of each formulation was spread evenly on the membrane in the donor compartment. Since a human skin and body fluids generally have pH values of 5 and 7.2 respectively, a phosphate buffer solution at pH 7.4 was selected as release medium in order to simulate human body conditions. The receptor compartment was filled with a phosphate buffer solution at pH 7.4. The medium in receptor cell was shaken on a magnetic stirrer at 100 rpm through the assay to ensure sink condition. The membranes were immersed into the buffer solution for 1 h before the experiment. The system was maintained at a constant temperature of 37°C ± 1°C by means of water jacket surrounding each cell. Samples (0.5 mL) were withdrawn at intervals of 15, 30, 60, 90, 120, 180, 240 and 300 min, and the volume of each sample was replaced by the same volume of fresh buffer at 37°C ± 1°C to maintain constant volume. The *in-vitro* experiments were carried out in triplicate. The data obtained from the drug release studies were kinetically evaluated using SPSS 9.0 for Windows (SPPS, Chicago, IL).

RESULTS AND DISCUSSION

In this study, the influence of the gel vehicle on the release of meloxicam was investigated by comparing release rates of the drug from each formulation through cellulose acetate membrane between the donor and receptor compartments of the Franz diffusion cells.

In the formulations, Carbopol gel, HEC gel and Emulgel were used as vehicles. The pH of all formulations were adjusted between pH 5 and 7.2 to minimize any effect of pH. Propylene glycol was selected as cosolvent to increase the solubility of meloxicam in the vehicle (16,19). A preliminary study has indicated the importance of the water:cosolvent ratio (19). The maximum penetration rate was found from the vehicle containing water and cosolvent in an exact volume ratio of 3:1 (water:cosolvent), while the minimum penetration rate was observed

from the vehicle containing water and cosolvent in the exact volume of 3:2 (water:cosolvent). Therefore, in this study, the ratio of water:cosolvent was chosen as approximately 3:1 (19).

The analytical method used for the assay of meloxicam was validated with respect to analytical performance parameters: precision (repeatability, reproducibility), accuracy, specificity, linearity and range. As a result, the calibration curve obtained for phosphate buffer solution at pH 7.4 was observed to be linear and the related equations had a determination coefficient of 0.999, showing the existence of a linear relationship. None of the excipients gave any absorbance at the wavelength between 200 and 400 nm, nor did show any interaction with the drug, indicating the specificity of the method. The values of relative standard deviation for accuracy, repeatability and reproducibility were found to be less than 2%, which indicated the suitability of the analytical method used.

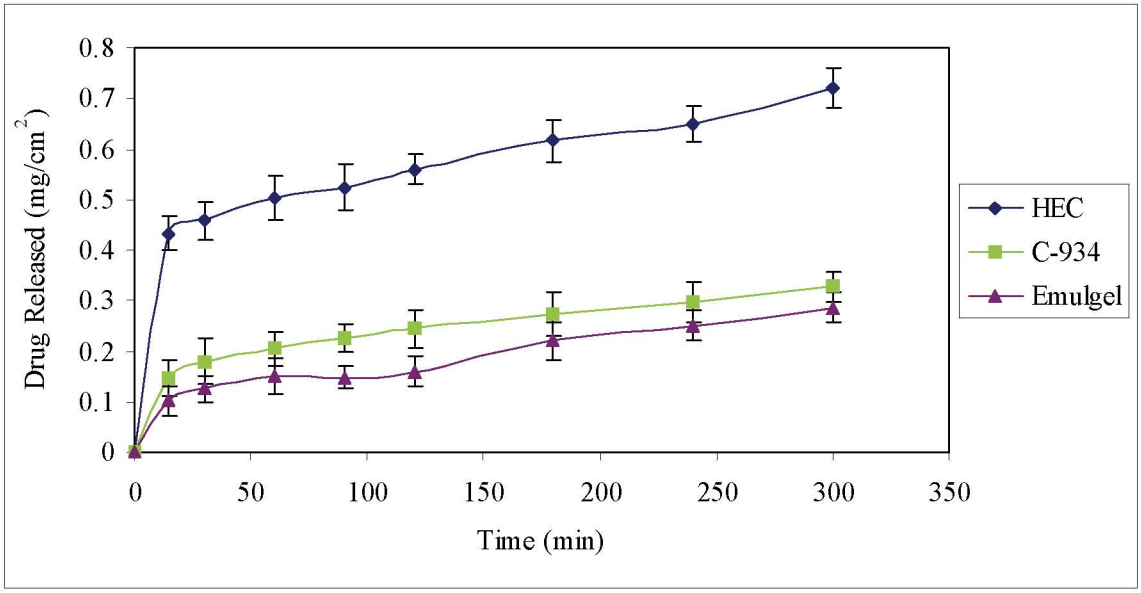

Figure 1. *In vitro* drug release profiles of the different gel formulations. The bars denote standard error.

The different release rates of meloxicam from three vehicles through the cellulose acetate membrane are shown in Figure 1. The dissolution data for the gel formulations were evaluated statistically by paired t-test, and the difference was significant ($p<0.05$). The amount of drug was constant in all formulations. As expected from the results of diffusion coefficients and viscosity values, drug release from the HEC gel base was much greater than the release from both the Carbopol gel base and Emulgel, which were similar in release potential.

In order to obtain meaningful information for the release kinetic models, the drug release data were kinetically evaluated and the fitness of the release profiles to the three different kinetic models, zero-order, first-order and Higuchi was evaluated (Table 2). After fitting the release profiles to these kinetic models, the selection was based on the comparison of higher determination coefficient and smaller residual mean square. Drug release from gel formulations confirmed the Higuchi kinetics model ($Q\sqrt{t}$).

Table 2. Kinetic assessment of release data of meloxicam.

Kinetic model	Rate constant (unit)	Statistics	Formulation		
			HEC gel	Carbopol gel	Emulgel
Zero-order	k_0 (mg h^{-1})		0.003	0.001	0.001
		r^{2a}	0.791	0.842	0.902
		RMS [b]	0.067	0.009	0.003
First-order	k_1 (h^{-1})		0.003	0.006	0.008
		r^{2a}	0.384	0.486	0.466
		RMS [b]	0.270	1.306	1.977
Higuchi (Q $\sqrt{t}$)	k(mg.cm^{-2}.$h^{-1/2}$)		0.482	0.211	0.166
		r^{2a}	0.944	0.972	0.987
		RMS [b]	0.018	0.001	0.001

[a]: Determination coefficient
[b]: Residual mean square

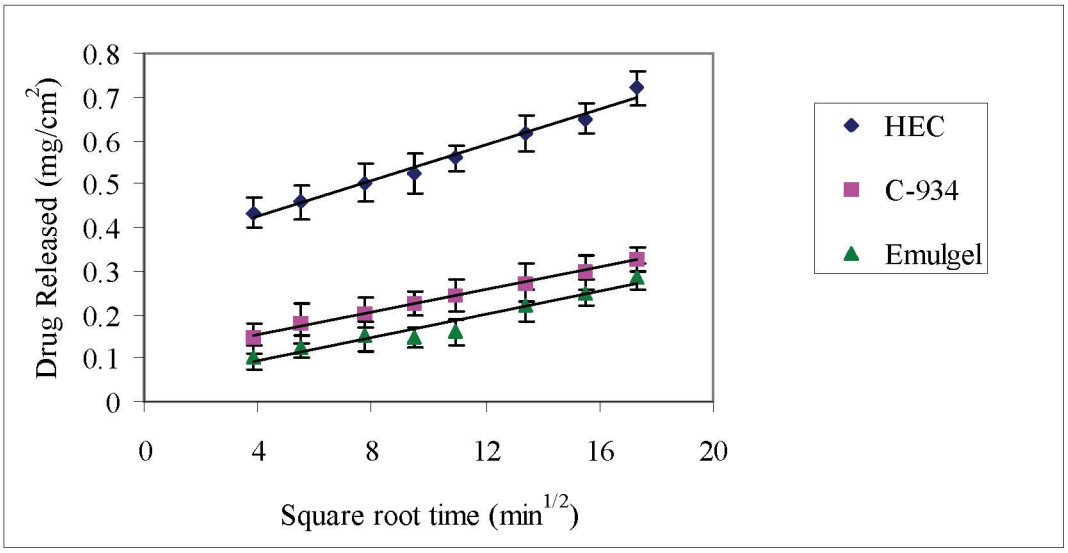

Figure 2. Drug release profiles of various formulations of meloxicam showing compliance to the Higuchi equation.

When the amounts of drug released per unit area (mg/cm^2) were plotted against the square root of time, a linear relationship was obtained for each vehicle, showing that the release of drug from the gels could be well described by the Higuchi model, where the rate-controlling step is the process of diffusion through the gel matrix (Figure 2) (20). As shown in Figure 2, the release profile for HEC was higher than the release profiles for Carbopol gel and Emulgel which is seemed to be similar. According to the result of statistical analysis with ANOVA, the profil for HEC was different than the other profiles ($p<0.05$) and the difference between the profiles

Carbopol gel and Emulgel was not significant ($p>0.05$). In our study, these results indicated that the physical parameters of the vehicle are more efficient than the chemical parameters during the control of meloxicam release from the gel formulation. Following the creation of a drug depletion zone by the removal of meloxicam from the vehicle/membrane interface, meloxicam slowly replenished from the gel core to the vehicle/membrane interface by diffusion. This diffusion is prevented by the viscosity of the vehicle, hence the decline in meloxicam release rate over time. This finding is in agreement with previous studies (21).

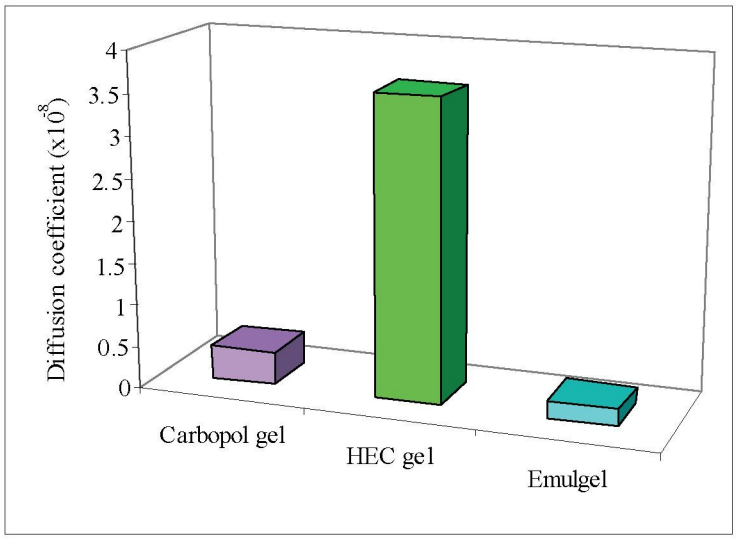

Figure 3. Comparison of the diffusion coefficients of the various meloxicam formulations.

The diffusion coefficients were calculated via Higuchi's procedures (17,18,22). Figure 3 shows the diffusion coefficients of the drug from vehicles could be ranked in the following order: HEC gel ($D=3.58x10^{-8}$ $cm^2.sec^{-1}$) > Carbopol gel ($D=4.01x10^{-9}$ $cm^2.sec^{-1}$) > Emulgel ($D=1.99x10^{-9}$ $cm^2.sec^{-1}$). Different formulations significantly affected the diffusion coefficient ($p<0.05$). According to the results, the HEC gel formulation showed the highest drug diffusion coefficient. Differences between these rates are mainly due to the differences in the rheological parameters of the systems as both the solubility of the drug in the vehicle and the viscosity of the gel matrix (10,23,24). The viscosity of the gel base may play an important role in modifying the release of the drug into the receptor compartment when the drug diffusion through the gel matrix is a rate-determining step (25,26). Viscosity values of the Carbopol 934 gel, HEC gel and Emulgel formulations were found to be 33000 cps, 22000 cps and 30000 cps, respectively. Our investigation revealed that the Carbopol gel and Emulgel have greater viscosity than the HEC gel formulation. Consequently, there was a decreased release of meloxicam from the Carbopol gel and Emulgel compared to the HEC gel. The enhanced drug release from the HEC gel formulation could be due to the lower viscosity of this formulation. These results indicated that Carbopol gel and Emulgel, with their compact and close structure, may have a slower drug release rate than a vehicle of lower consistency.

CONCLUSION

In conclusion, the results presented in this article show that the release rate of meloxicam from gel formulations seems to be related mainly to the rheological parameters of the vehicles. The viscosity of gel formulations plays an important role in controlling the release of the drug. The formulation with HEC gel base exhibited better properties for topical delivery of meloxicam when compared with the other formulations.

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