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RESEARCH ARTICLE

Effect of gelling agent and penetration enhancer on the release rate of ibuprofen-PEG 6000 solid dispersion from gel preparations

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Abstract

Introduction: Ibuprofen is a non-steriodal anti-inflammatory drug which shows low bioavailability. For gel preparations it is important to increase the release rate of ibuprofen by using solid dispersion systems. **Objective:** To obtain the optimum release rate of ibuprofen-PEG 6000 solid dispersion from gel, by optimising the gelling agent and the penetrating enhancers. **Method:** Determination of gelling agent was carried out by comparing the ibuprofen release flux. The gel formulation with the best release flux will be used in the determination of penetrating enhancer to obtain the optimum release flux, by using a two-factor factorial design. **Result:** HPMC showed the highest release flux (339.5 g/cm^{2}min). The results showed an increase in the release flux (489.4 g/cm^{2}min) in the optimum formula with 39.9% propylene glycol and 3.3% isopropyl myristate. **Conclusion:** The increase in the ibuprofen solid dispersion release flux has been carried out using HPMC, and propylene glycol-isopropyl myristate as a penetrating enhancer.

Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that is often used for the treatment of pain and inflammation in rheumatism and juvenile idiopathic arthritis (Kim, 2010). Ibuprofen in oral use can cause damage to the gastric mucosa, which can cause ulceration and bleeding. Therefore, it is necessary to develop a topical ibuprofen dosage form in a gel formulation, to minimise ibuprofen gastrointestinal side effects on oral administration (Lakshmi *et al.*, 2011; Kashyap *et al.*, 2020).

Ibuprofen is a Biopharmaceutics Classification System (BCS) class II drug and is practically insoluble in water (46.9g/mL, at 37°C and 29.1g/mL, at 25°C), so it is a big challenge to increase its solubility and release rate (Retnowati & Setyawan, 2010). The pharmaceutical strategy used to increase the solubility is by modifying Ibuprofen in the form of a solid dispersion (Hasnain & Nayak, 2012; Kar & Ahmed, 2017). The results of Hasnain and Nayak's (2012) research showed that the solid dispersion of Ibuprofen-PEG 6000 (1:2) gave the highest release rate; it was therefore decided that ibuprofen-PEG 6000 (1:2) should be used and prepared using solvent evaporation method for this study.

Important components in gel preparations are gelling agents and penetrating enhancers. These two components will affect the effectiveness of ibuprofen gel in penetrating the skin barrier. In this research, optimisation of the gelling agent and a combination of penetrating enhancers was carried out to produce safe and effective ibuprofen-PEG 6000 gel preparations. Gelling agents used in this research were HPMC, Sodium CMC, and Carbopol at 2% concentration in each formula. The combination of penetrating enhancers used is propylene glycol and isopropyl myristate. Two-factor factorial design was used to optimise the combination of penetrating enhancers. Gelling agents and penetrating enhancers used are additives that are often used in the pharmaceutical industry to produce pharmaceutical products, especially topical products.

This study aimed to obtain the best gelling agent and determine the combination of isopropyl myristate and propylene glycol that provided the optimum *in-vitro* release rate of ibuprofen solid dispersion from a gel preparation using a factorial design.

Methods

The tools used are UV-Vis spectrophotometer, dissolution test equipment, pH meter, diffusion cell, cellophane membrane, and Design Expert software. The materials used were Ibuprofen (Merck), PEG 6000 (Merck), ethanol (Merck), Carbopol (Merck), Sodium CMC (Merck), HPMC (Merck), TEA (Merck), Propylene glycol (Merck), and Isopropyl myristate (Merck). All materials were purchased in Indonesia.

Preparation of ibuprofen-PEG 6000 solid dispersion

Solid dispersion of Ibuprofen with PEG 6000 as a carrier was prepared in a ratio of 1:2, using the solvent evaporation method. Ibuprofen and PEG 6000 were dissolved and mixed in ethanol (60°C) then dried (50°C) for 24 hours. The solid dispersion obtained was sieved using a mesh 100 (Hasnain & Kumar, 2012; Thais *et al*., 2018).

The ibuprofen-PEG 6000 solid dispersion was then evaluated for organoleptic and Ibuprofen percentage recovery. Determination of ibuprofen percentage recovery in ibuprofen-PEG 6000 solid dispersion was done by measuring the absorbance of solid dispersions in solution 0.1 N NaOH with UV-Vis spectrophotometer at a wavelength of 222nm.

Determination of gelling agent in ibuprofen gel formulation

Preparation of ibuprofen-PEG 6000 solid-dispersion gel formulation was made in three formulas with differences in the gelling agent used, namely HPMC, Carbopol, and CMC-sodum (Na) with a concentration of 2% each. The release flux of Ibuprofen from gel formulation was obtained by using a paddle over disk type (Type II) dissolution test, equipped with a diffusion cell and cellophane membrane as a semipermeable membrane (Rodyan, 2008). The results of the gel preparation were tested for physicochemical characteristics and release flux of Ibuprofen with a one-way ANOVA test, with a p value < 0.05. The gelling agent, which showed the best ibuprofen release flux, was then used as an excipient to determine the composition of the penetrating enhancer combination.

Optimisation of the penetrating enhancer

The factorial design was used to obtain the optimum composition of propylene-isopropyl myristate in the gel preparation. The levels of propylene glycol and isopropyl myristate were determined based on a study conducted by Lakshmi and colleagues (2011) and Rachmawati (2012), as shown in Table I. The viscosity response and ibuprofen release flux were used to determine the optimum formula, using Design-Expert software.

Table I: Gel formulations of Ibuprofen solid dispersion

Ingredients	F1	F2	F3	F4
Ibuprofen-PEG 6000 solid dispersion	1%	1%	1%	1%
HPMC	1%	1%	1%	1%
TEA	2%	2%	2%	2%
Propylene glycol	20%	40%	20%	40%
Isopropyl myristate	2.5%	2.5%	6%	6%
Tween 80	2%	2%	2%	2%
Aquadest	71.5%	51.5%	68%	48%

Results

The solid dispersion of ibuprofen-PEG 6000 1:2 obtained showed organoleptic of white crystalline powder, odourless, and the value of ibuprofen recovery was 96.4% ± 0.6. The percentage recovery of Ibuprofen will be used in calculating the release flux of Ibuprofen in the gel formulation of ibuprofen-PEG 600 solid dispersion.

Release flux of Ibuprofen from gel formulation with the difference gelling agent

The result of ibuprofen release flux from gel formulation with the gelling agent of HPMC, Carbopol and CMC-Na was 339.5 ± 2.9g/cm^{2}min, 301.5 ± 4.1g/cm^{2}min, and 321.4 ± 7.6g/cm^{2}min, respectively. Based on the one way ANOVA test, the drug release flux data had a significant difference between each formula with significance < 0.05.

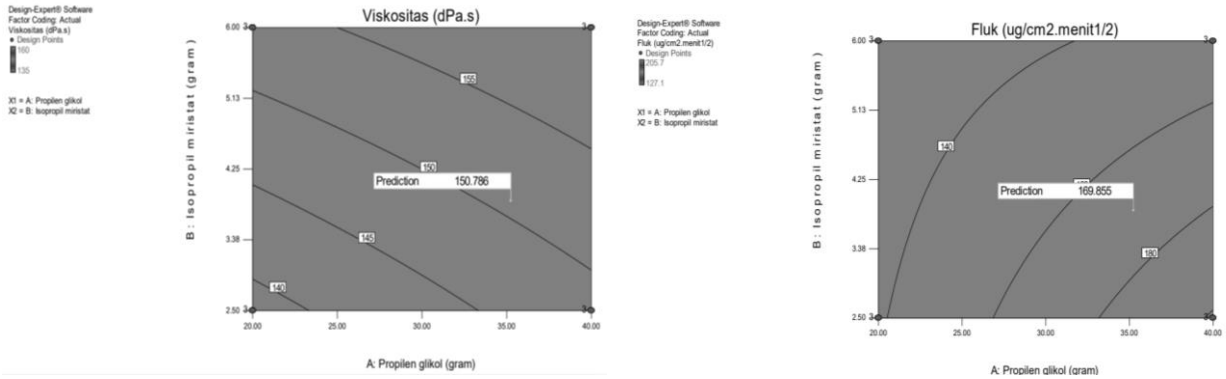
Optimum formula of ibuprofen solid dispersion gel

The optimum formula was determined using a factorial design optimisation method with viscosity and ibuprofen release flux from the gel formulation as a response. The results of the viscosity test and the release flux of Ibuprofen can be seen in Table II. Based on the optimisation with the factorial design method, 100 combinations of propylene glycol and isopropyl

myristate were obtained, which showed gels formulation with viscosity and release flux values according to the desired criteria. The propylene glycol used to obtain the optimum formula was between 29.5% to 39.9%, while isopropyl myristate was between 3.2% to 5.6% (Figure 1). The optimum formula obtained with the composition of propylene glycol 39.9% and isopropyl myristate 3.3% showed a release flux of 489.4g/cm^{2}min and a viscosity of 150.8 dPa.s.

Table II: Results of viscosity and release flux of Ibuprofen

Formula	Viscosity (dPa.s)	Release flux(g/ cm^2.min)
F1	138.3 ± 2.9	348.33 ± 1.0
F2,	148.3 ± 2.8	491.57 ± 3.6
F3	153.3 ± 2.7	337.60 ± 1.7
F4	160.0 ± 0.04	348.10 ± 0.70



(a) (b)

Figure 1: Contour plot of 2D viscosity (a) and ibuprofen release flux (b) responses

Discussion

Release flux of Ibuprofen from gel formulation with the difference gelling agent

The release flux test showed that F1 (HPMC) had the highest release rate compared to F2 and F3, which used Carbopol and CMC-Na. This is due to the release of the active ingredient in semisolid preparations being influenced by the viscosity of a gel base, which varies depending on the polymer used. The higher the viscosity of a substance, the smaller the diffusion coefficient and the more difficult it becomes for the drug to be released from the base. High viscosity indicates that the gelling polymer is bonded too strongly, which will inhibit drug release. On the other hand, low viscosity indicates that the polymer does not bind strongly, so there is a lot of space for the drug to diffuse from the system (Sinko, 2011). This can be proven by the viscosity value of the three gel formulations, which indicates that F2 > F3 > F1. In this case, F1 has the lowest viscosity compared to the other formulas, so it can be said that the HPMC base has a low polymer binding capacity to the drug, and the release process of Ibuprofen from the gel formulation can occur immediately.

Based on the pH determination of gel formulation, F1 has the highest pH compared to other formulas. The higher the pH of preparation, the weakly acidic Ibuprofen will be in the ionised form and be more soluble. The increase in solubility will result in an increase in the drug release rate from the gel formulation to the skin barrier.

Optimum formula of ibuprofen solid dispersion gel

The ideal viscosity of semisolid preparations is in the range of 50-200 dPa.s (Wood, 2007). The results of the viscosity test of the four formulas showed that the viscosity of the gel preparations had met the criteria for a good semisolid viscosity based on the literature. The F4 formulation has the highest viscosity due to the high composition of propylene glycol and isopropyl myristate, so the amount of water used is smaller than other formulas.

The release rate of Ibuprofen from the gel preparation is influenced by the affinity between the drug substance and the carrier. The release rate profile of Ibuprofen from the gel formulation can be seen in Figure 2. Ibuprofen is a drug substance that has high lipophilicity, so it will be difficult to diffuse from the base and absorbed by skin membrane (Idson & Lazarus, 1994; Clarke *et al*., 2004). This study shows that the more isopropyl myristate is added, the release rate of Ibuprofen from the base will be decreased. Isopropyl myristate is a lipophilic substance because it is a fatty acid group that is insoluble in water. F3 has the lowest discharge flux; this is because the amount of isopropyl myristate added is the highest, so Ibuprofen is strongly

bound by isopropyl myristate. As a result, Ibuprofen is difficult to release, so its release rate from the carrier will decrease. The F2 preparation contains a small amount of isopropyl myristate and a large amount of propylene glycol so that only a small amount of Ibuprofen is bound to isopropyl myristate. On the other side, the high amount of propylene glycol causes the bond between the hydrophilic base and the lipophilic Ibuprofen to become weaker so that Ibuprofen will be easily released from the base (Sinko, 2011).

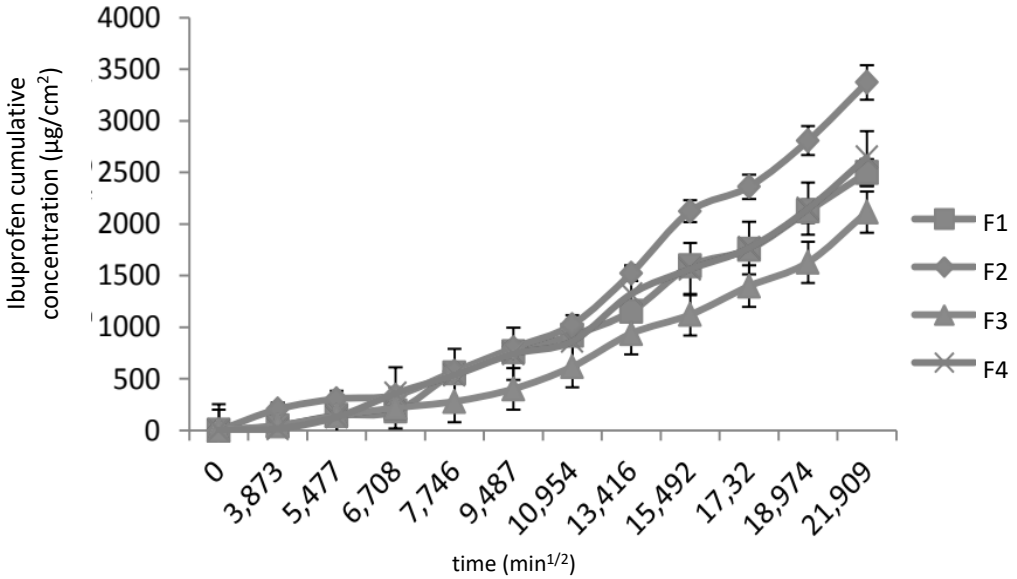


Figure 2: The release profile of Ibuprofen in saline phosphate buffer pH 7.4

Conclusion

The ibuprofen solid dispersion was successfully formulated into gel formulation, which can provide optimum release flux by using HPMC 2% as a gelling agent and a combination of penetrating enhancer, propylene glycol and isopropyl myristate at concentrations of 39.9% and 3.3%, respectively.

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