FORMULATION AND EVALUATION OF KETOPROFEN TRANSDERMAL MATRIX PATCH CONTAINING DIFFERENT POLYMER COMPONENTS

ALI AFFAN SILALAHI*, KASMIRUL RAMLAN SINAGA, SUMAIYAH SUMAIYAH

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Sumatera Utara, Medan, Indonesia.

Email: aliaffansilalahi@gmail.com

Received: 14 May 2018, Revised and Accepted: 16 July 2018

INTRODUCTION

Topical drug delivery methods have advantages over other delivery methods, one of which is to avoid the metabolism of the first pass effect on the liver [1]. Physical-chemical characteristics of drugs and excipients are taken into consideration in designing formulas to produce a product that is stable, efficacious, attractive, easy to formulate, and safe. These characteristics affect several factors: Particle size distribution, drug dissolution rate, bioavailability, uniformity of content, taste, texture, color, and stability. The particle size and solubility of the drug have an effect on the formulation because the drugs entering the blood circulation must be in solution form to produce the desired effect (Fig. 1).

Ketoprofen is included in Class II of Biopharmaceutical Classification System means, including a class of low solubility and high permeability, the increased solubility of this drug is of concern to pharmaceutical researchers [2]. The absorption of ketoprofen is only not maximal due to the solubility and the side effects it causes; to overcome the deficiencies of this conventional system a new drug delivery system is required. Topical ketoprofen available on the market today such as cream has side effects such as rash, itching, irritation, pain, and redness; therefore, to overcome this problem requires a new drug delivery system such as nanoemulsion. Nanoemulsions have been widely used as a vehicle in topical medicine and is an alternative to insoluble, topical, or oral drugs.

Nanoemulsions are thermodynamically stable dispersions of two immiscible liquids (oil and water) which is stabilized using surfactant and cosurfactant molecule. They may be either transparent or translucent and have a droplet size of 5-200 nm [3]. They are well-tolerated orally, on the skin and mucous membrane when used to deliver topically active drugs. Nowadays, increasing drug loading, enhancing drug solubility, and bioavailability are the most important advantages of encouraging the usage of nanoemulsion as drug delivery carriers. A topical nanoemulsion is a form of delivery for a drug that is difficult to dissolve and has side effects when administered orally by increasing the penetration of the drug through the skin [4]. Nanoemulsions comprise safe surfactants with or without other emulsifiers to improve stability, oil (natural/synthetic/semi-synthetic), and cosurfactant [4]. The method of nanoemulsion formulation is divided into two methods that use high energy and low energy. High energy formulations require tools such as high-pressure homogenizers, Microfluidizers, and sonicators, and low energy formulation methods dependent on the solubility of the active substance so that it is more efficient to make a small droplet nanoemulsion. Nanoemulsions produced with low energy methods depend on the spontaneous formation of emulsions based on the phase behavior of certain surfactant, oil, and water systems. There is interest in using lower energy techniques in the emulsion formation process due to the economic benefits, and increasing amounts of research have been conducted to investigate the utility of different low-energy approaches. Self-emulsifying systems offer a strategy for dealing with the low bioavailability of compounds (drugs and oils) that are not easily dissolved in water [5].

A low energy emulsification or spontaneous emulsification method used by the laboratory scale to achieve small droplet size using simple instruments [6]. The advantage of the low energy method is that it can use simple equipment such as a magnetic stirrer which includes low energy manufacturing methods are phase inversion temperature and phase inverse composition. The nanoemulsion method of PIC which is often performed for laboratory scale is by spontaneous emulsification [7-10].

MATERIALS AND METHODS

Materials

Ketoprofen was purchased from PT. Dexa Medica (Indonesia). Polyethylene glycol (PEG) 400 (Merck), polyvinylpyrrolidone (PVP) K-30 (Merck), ethyl cellulose (EC) (Merck), Chloroform (Merck), Methanol (Merck), and Menthol (Merck) were used. All the ingredients were of analytical grade.
Formulation of ketoprofen matrix transdermal patch
Matrix transdermal patch of ketoprofen was prepared using the solvent evaporation method. The polymeric solvent was prepared by dissolving all the polymer (PEG, PVP, and EC), menthol and active chemical compound (ketoprofen) in the blend of chloroform and methanol (1:1). The polymeric mixtures then poured into a mold and kept at room temperature until dry. The formulas design of ketoprofen matrix transdermal patch is shown in Table 1.

Physicochemical compatibility of drug and polymers
The compatibility of the drug and polymers was studied using a Shimazu Fourier-transform infrared (FTIR) spectrophotometer in range 4000–400/cm. The FTIR spectra of drug and polymers in the mixture are compared for the presence or absence of incompatibility [11].

Evaluation of ketoprofen matrix transdermal patch
Visual
The visual of matrix transdermal patch parameters is color, odor, texture, and film flexibility [12].

Weight variation
The weight variation five patches were weighed on an electronic balance, and the average of weight was taken with SD [12].

Film thickness
The thickness of films was measured by micrometer screw at five different sites, and average of five readings was taken with SD [12].

Moisture uptake
The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [12].

% of Moisture uptake = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100\%

Folding endurance
The folding endurance was measured manually for prepared films. A strip of film was folded at the same place till it broke. The number of time the film can be folded at the same place without breaking was the folding endurance value [13].

Drug content
A 0.1 mm thickness of the film was cut and put it into a 100 ml phosphate buffer (pH 7.4) and ultrasonicated for 15 min with a stirrer. After filtration, the drug was estimated spectrometrically at wavelength of 260 nm and determined the drug content compared using the calibration curve of ketoprofen [12].

RESULTS AND DISCUSSION
Physicochemical compatibility study
All the characteristic peaks of the pure drug ketoprofen were retained in drug and polymers physical mixtures, which indicate that the drug and polymers are compatible. The result of the FTIR studies was shown in Figs. 2 and 3.

Evaluation of ketoprofen matrix transdermal patch
The results of evaluation of various visual and physicochemical parameters of the ketoprofen matrix transdermal patch were presented in Table 1.
Table 3: Physicochemical evaluation and drug content

| Formula | Weight (mg) | Thickness (mm) | Moisture uptake (%) | Folding endurance | Drug content (%) |
|---------|-------------|----------------|---------------------|------------------|-----------------|
| F1      | 272±5.89    | 0.977±0.00557  | 1.1±0.015           | <200             | 97.68           |
| F2      | 2.82±1.52   | 0.968±0.00557  | 2.57±0.214          | <200             | 95.26           |
| F3      | 283±2.51    | 0.961±0.00557  | 2.83±0.050          | <200             | 97.98           |
| F4      | 265±3       | 0.989±0.0066   | 1.68±0.158          | <200             | 97.50           |

Fig. 4. The calibration curve of ketoprofen

in Tables 2 and 3. The calibration curve of ketoprofen was presented in Fig. 4. All the physicochemical parameters meet the applicable requirements. The drug content was also studied for all formulations indicating that the method used to formulated this ketoprofen matrix transdermal patch was suited or not.

F3 showed the heaviest weight compared to other formulas. In F3, it showed that the PVP is the main factor that affects the weight because PVP is a hygroscopic agent. F4 showed the thickest thickness layer compared to other formulas. It can happen due to the ES content. This is because the ES polymer if excessively given will form a thick and uneven fiber that affects the weight of the patch [14-16]. The calibration curve of ketoprofen in 260 nm wavelength showed a good coefficient correlation (0.9998). The coefficient correlation can be accepted which the value of the coefficient correlation should not smaller than 0.995 [17,18]. Moisture uptake and drug content result, all the formula showed a good percentage in the range that can be accepted. Folding endurance result showed that all formula can be accepted [19,20].

CONCLUSIONS

In the present study, various formulations of the ketoprofen matrix transdermal patch were prepared. On the evaluations and FTIR study, all the formulas showed good uniformity and acceptable. Hence, it can be concluded that these three type of polymers (PEG, PVP, and ES) can be used as a polymer base for formulating ketoprofen transdermal drug delivery system.

ACKNOWLEDGMENTS

I express my thanks to Mr. Iksen, S. Farm., M.Si (Department of Pharmacy, STIKes Senior Medan), for his never-ending guidance and suggestions throughout the preparation of this research project and manuscript article.

AUTHOR’S CONTRIBUTION

All the author have contributed equally.

CONFLICTS OF INTEREST

Declared none.

REFERENCES

1. Shankar R, Tiwari V, Mishra CP, Singh CK, Sharma D, Jaival S. Formulation and evaluation of ketoconazole nanoemulsion gel for topical delivery. Am J Pharm Sci Res 2015;5:455-62.
2. Patel HC, Parmar G, Seth AK, Patel JD, Patel SR. Formulation and evaluation of o/w nanoemulsion of ketoconazole. Pharm Sci Monit 2013;4:338-51.
3. Khatab A, Ismail S. Formulation and evaluation of oxiconazole nitrate microemulsion based gel for treatment of fungal vaginal infection. Int J Pharm Sci Pharm 2016;8:34-40.
4. Chellapa P, Mohamed AT, Kelebi EI, Elmahgoubi A, Eid AM, Issa YS, et al. Nanoemulsion and nanoemulgel as a topical formulation. IOSR J Pharm 2015;5:43-7.
5. Giongo JL, Vaucher RD, Ourique AF, Steffler MC, Frizzo CP, Nememman B, et al. Development of nanoemulsion containing Pelargonium graveolens oils: Characterization and stability study. Int J Pharm Sci Pharm 2016;5:271-6.
6. Lee KW, Omar D, Abdan K, Wong MY. Physicochemical characterization of nanoemulsion formulation of phenazine and their antifungal efficacy against Ganoderma boninense PER71 in vitro. Res J Pharm Biol Chem Sci 2016;7:3056-66.
7. Chime SA, Kenetukwu FC, Attama AA. Application of Nanotechnology in Drug Delivery. London: Intech; 2014.
8. Mishra RK, Soni GC, Mishra RP. A review article on nanoemulsion. Word J Pharm Sci 2014;3:258-74.
9. Costa SD, Basri M, Shamsudin N, Basri H. Stability of positively charged nanoemulsion formulation containing steroidal drug for effective transdermal application. J Chem 2014;20:1-8.
10. Sharif Makmalzadeh B, Torabi S, Azarpanah A. Optimization of ibuprofen delivery through rat skin from traditional and novel nanoemulsion formulations. Iran J Pharm Res 2012;11:47-58.
11. Patel RR, Patel ZK, Patel KR, Patel MR. Formulation and evaluation of microemulsion based gel of ketoconazole. Int J Univers Pharm Bio Sci 2014;3:93-111.
12. Derie DV, Burade KB, Kotwal RS, Galkwad VB. Formulation and evaluation of microemulsion based gel for topical delivery of ketoconazole. Indian Drugs 2008;45:138-40.
13. Jufri M, Natalia M. Physical stability and antibacterial activity of black cumin oil (Nigella sativa L.) nanoemulsion gel. Int J PharmTech Res 2014;6:1162-9.
14. Patil MP, Shinde GP, Kshirsagar SJ, Parakh DR. Development and characterization of ketoconazole loaded organogel for topical drug delivery. Inventi J 2015;3:1-10.
15. Fletcher J. Making the Connection-Particle Size, Size Distribution, and Rheology. Chemie. DE Information Service GmbH; 2012. Available from: https://www.chemeurope.com/en/whitepapers/61207/making-the-connection-particle-size-size-distribution-and-rheology.html.
16. Saberi AH, Fang Y, McMclbens J. Fabrication of Vitamin E-enriched nanoemulsions: Factors affecting particle size using spontaneous emulsification. J Colloid Interface Sci 2013;391:95-102.
17. Kishore RS, Pappenberger A, Dauphin IB, Ross A, Buergi B, Staempfli A, et al. The degradation of polysorbates 20 and 80 and its potential impact on the stability of biotherapeutics. Pharm Res 2011;28:1194-210.
18. Mohanraj VJ, Chen Y. Nanoparticles-a review. Trop J Pharm Res 2006;5:561-73.
19. Togatorop B, Sinaga KR, Suwarso E, Iksen I. Effect of different polymer and oleic acid enhancer in nifedipine matrix transdermal patch formulation and evaluation. Rasayan J Chem 2018;11:516-21.
20. Mhaske RA, Sahasrabudhe S. Identification of major degradation products of ketoconazole. Sci Pharm 2011;79:817-36.