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Research Article

Characteristics Of Domperidone Patch With Variation Of Penetration Enhancers (Isopropyl Myristate Or Eucalyptus Oil)

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Abstract
Domperidone shows low bioavailability values when administered orally so this compound is suitable for administration transdermally Penetration enhancer was one component that can increase the diffusion of domperidone which was formulated in patch preparations. The aim of the study was to compare the penetration-enhancing ability of isopropyl myristate (IPM) and eucalyptus oil (EO) on the diffusion profile of the domperidone patch (DP). DP was made by solvent casting method using hydroxyl propyl methyl cellulose (HPMC) and penetration enhancer (IPM and EO) with concentrations of 2%, 5%, and 10%, respectively. DP evaluations carried out were organoleptic, weight uniformity, thickness, moisture content, drug content, and diffusion. DP had the appearance of a round shape with a diameter of 0.9 cm, white, dry, and not cracked. The results of the diffusion profile showed that the diffusion kinetics of DP-IPM and DP-EO were zero order, and the rate of diffusion of DP-IPM ranges from 31.448-37.612 ppm/hour while DP-EO ranges from 30.102-35.394 ppm/hour. The conclusion was that penetration enhancers (IPM and EO) do not affect the diffusion kinetics of PD, but the diffusion rate of DP-IPM is higher than DP-EO.
Keywords: diffusion, domperidone, eucalyptus oil, isopropyl myristate, patch, penetration enhancer.

Karakteristik Patch Domperidone Dengan Variasi Peningkat Penetrasi (Isopropyl Myristate Dan Minyak Kayu Putih)

Abstrak
Domperidone mengalami metabolisme lintas pertama di hati, yang menunjukkan rendahnya nilai bioavailabilitas bila diberikan secara oral. Untuk mengatasinya, domperidone diberikan dalam bentuk sediaan patch. Peningkat penetrasi merupakan salah satu komponen yang dapat meningkatkan difusi domperidone dalam sediaan patch. Penelitian ini bertujuan untuk membandingkan kemampuan peningkat penetrasi isopropil miristat (IPM) dan minyak kayu putih (EO) pada profil difusi patch domperidone (DP). DP dibuat dengan metode pengecoran pelarut menggunakan polimer hidroksi propil metil selulosa (HPMC) dan penambah penetrasi (IPM dan EO) dengan konsentrasi masing-masing 2%, 5%, dan 10%. Evaluasi DP yang dilakukan adalah organoleptik, keseragaman berat, ketebalan, kadar air, kandungan obat, dan difusi. DP tampak berbentuk bulat dengan diameter 0,9 cm, berwarna putih, kering, dan tidak retak. Hasil keseragaman bobot pada DP-IPM berkisar antara 111,19-140,23 mg sedangkan DP-EO berkisar antara 103,01-128,2 mg, kelembaban kadar DP-IPM berkisar antara 5,71-7,16% sedangkan DP-EO berkisar antara 5,33-6,85%, kadar obat DP-IPM berkisar antara 100,62-101,06% sedangkan DP-EO berkisar antara 99,23-100,35%. Hasil profil difusi menunjukkan kinetika difusi DP-IPM dan DP-EO orde nol, dan laju difusi DP-IPM berkisar antara 31.448-37.612 ppm/jam sedangkan DP-EO berkisar antara 30.102-35.394 ppm/jam. Kesimpulannya adalah peningkat penetrasi (IPM dan EO) tidak berpengaruh terhadap kinetika difusi DP, namun laju difusi DP-IPM lebih tinggi dibandingkan DP-EO.
Kata Kunci: isopropil miristat, minyak kayu putih, domperidon, patch, laju difusi, peningkat penetrasi.

1. Introduction

In oral administration of domperidone, the absorption process is fast but the systemic bioavailability is quite low, which is only about 15% due to first-pass metabolism in the liver and metabolism in the intestine.[1] One of the preparations that can improve the bioavailability of domperidone is a transdermal preparation in the form of a patch. Patches contain active substances that can passively diffuse at a certain amount through the skin to enter the bloodstream. [2]

The patch has several components, including a polymer and a penetration enhancer. Polymers play a role in regulating drug release in the matrix.[3] Some of the polymers that have been used in the manufacture of domperidone patches include hydroxy propyl methyl cellulose (HPMC), eudragit RL 100, a combination of ethyl cellulose-polyvinyl pyrrolidone, a combination of polyvinyl alcohol-polyvinyl pyrrolidone, and a combination of hydroxy propyl methyl cellulose-sodium carboxy methyl cellulose. From the domperidone patch research that has been carried out, it showed that the use of hydrophilic polymers results in a greater amount of diffused drug than the use of hydrophobic polymers, besides that increasing the amount of polymer did not always increase the amount of drug diffused.[4,5]

Meanwhile, penetration enhancers play a role in increasing the diffusion profile and efficacy of transdermal preparations.[6] Compounds that function as penetration enhancers include terpenes, sulphoxides, pyrrolidones, fatty acids, alcohols, fatty alcohols, surfactants, glycols, and urea. [7] In the glimepiride patch study, it was found that the best flux values were obtained using isopropyl myristate (IPM), eucalyptus oil (EO), and span 80 as penetration enhancers compared to the use of tween 20 and d-limonene.[8] The use of IPM and EO as penetration enhancers is more effective and efficient in increasing drug diffusion. IPM is a penetration enhancer commonly used in topical formulations and can increase skin permeation of most drugs such as amlodipine, flurbiprofen, and azasetron.[9] EO is an essential oil that contains terpenes, so this compound can increase percutaneous drug absorption[10], but EO as a penetration enhancer has not been widely used in patch preparations. There is no information regarding the use of IPM and EO as penetration enhancers for the diffusion profile of the domperidone patch. This is what underlies the need for a patch study of domperidone using penetration enhancers of IPM and EO. The aim of the study was to compare the penetration-enhancing ability of IPM and EO on the diffusion profile of the domperidone patch (DP).

2. Method

2.1. Materials

The materials and instruments used include domperidone (Vasudha Pharma Chem), hydroxy propyl methyl cellulose (Sidley Chemical), isopropyl myristate (Dubois-Natural Ester SDN BHD), eucalyptus oil (PT. Sumber Berlian Kimia), 96% ethanol, aqua dest, polyvinyl alcohol, propylene glycol, dimethylformamide (Merck), potassium phosphate monobasic (Merck), sodium hydroxide (Merck), methylparaben, UV-Vis spectrophotometer 1601 (SHIMADZU), moisture balance (Metler Toledo), and Franz diffusion (PermeGear type) V6- CB-02).

2.2. Procedure

a. Domperidone Patch Preparation

The preparation according to the formula in Table 1 was begin by dispersing the HPMC polymer in distilled water and then adding propylene glycol and IPM/ EO with homogeneous stirring (M1). Then domperidone was dissolved in 96% ethanol and added to M1, stirred homogeneously. Then the solution was poured into the mold and let the solution stand for 2 hours (M2). The backing patch was made by dissolving PVA 10% w/v in aquadest. After that, the backing patch solution was poured onto the half-dry M2. Finally, the patch was put in an oven at 40 0C for 3 hours.[5]

b. DP Characteristics

Patches were evaluated visually for

Table 1. Domperidone Patch Formula

Ingredients	DP-IPM			DP-EO		
	2%	5%	10%	2%	5%	10%
Domperidone (mg)	240	240	240	240	240	240
HPMC (mg)	450	450	450	450	450	450
IPM (mg)	158	350	791	-	-	-
EO (mg)	-	-	-	158	350	791
Methylparaben (mg)	2	2	2	2	2	2
96% ethanol (mL)	2	2	2	2	2	2
Propylene glycol (mL)	0.2	0.2	0.2	0.2	0.2	0.2
Aqua dest (mL)	4.5	4.5	4.5	4.5	4.5	4.5

their physical appearance, including color, odor, and surface condition of patch.[11] The patch weight uniformity test was carried out by randomly weighing 5 patches on each formula, then calculating the average and standard deviation.[12] The standard deviation requirement for patch weight uniformity is < 2%.[13] The thickness test is carried out by measuring the patch at three different points using a vernier caliper, then determining the average thickness and standard deviation to ensure the same thickness in each patch.[14,15] The patch moisture content was carried out with a moisture analyzer at a temperature of 105 ºC, a good patch preparation has a moisture content in the range of 1-10%.[16]

Determination of the domperidone content in the patch was carried out by inserting the crushed patch into a 50 ml volumetric flask and adding 2 mL of dimethylformamide, then adding 70% ethanol until the mark and the solution was filtered. Then 0.5 ml of the solution was taken and diluted with 70% ethanol in a 10 ml volumetric flask. After that, absorption measurements were carried out using a UV-Vis Spectrophotometer at a wavelength of 285nm, then the amount of domperidone in each patch was determined using a domperidone calibration curve (70% ethanol solvent) which has a straight line equation, namely: y = 0.0163x + 0.0613 with r = 0.9997, and finally calculate the domperidone content.

c. DP Diffusion Profile

The diffusion test was carried out using a Franz diffusion cell, and the membrane used was a cellophane membrane with a diameter of 0.9 cm.[17] The liquid medium used was 15 ml of phosphate buffer pH 7.4 at a temperature of 37 ± 0.5ºC and a speed of 50 rpm. A sampling of 1 mL was carried out at 30, 60, 120, 180, 240, 300, 360, 420, and 480 minutes. Then the absorption was observed at a wavelength of 284 nm[18], and the amount of diffused domperidone was determined using the domperidone calibration curve equation (solvent phosphate buffer pH 7.4): y = 0.0229x + 0.0381 with r = 0.9988 . Followed by determining the diffusion profile (kinetic and rate of diffusion) in each formula. Diffusion-order kinetics refers to four kinetic models, namely zero-order, first-order, Higuchi, and Korsmeyer Peppas models. Determination of domperidone diffusion kinetics from transdermal patches was carried out to determine how much drug was diffused at a certain time.[19]

3. Result and Discussion

The patch was a thin white layer with a diameter of 0.9 cm, has a flat surface texture, and the top was slightly glossy. DP-IPM had no odor while DP-EO had a characteristic odor of eucalyptus oil.

DP-IPM had a greater average weight than DP-EO, this is due to the density and viscosity of IPM being greater than EO.[20] The standard deviation obtained based on the average weight was less than 2%, namely: 0.69 – 1.49%, this indicated that the DP weight was uniform. Other factors that affect the weight of the patch are the density, molecular weight, and concentration of the polymer, as well as the moisture contained in the patch.[11]

DP-EO had a smaller thickness than DP-IPM, this is because eucalyptus oil is a volatile oil causing the patch thickness to

Table 2. Characteristics of DP

Ingredients	DP-IPM			DP-EO		
	2%	5%	10%	2%	5%	10%
Weight uniformity (mg)*	111.19 ± 1.21	124.22 ± 1.49	140.23 ± 1.33	103.01 ± 0.69	115.13 ± 0.93	128.20 ± 1.08
Thickness (mm)*	1.64 ± 0.03	1.70 ± 0.03	1.72 ± 0.03	1.65 ± 0.01	1.67 ± 0.01	1.72 ± 0.01
Moisture content (%)*	5.71 ± 0.13	6.46 ± 0.16	7.16 ± 0.22	5.33 ± 0.06	5.74 ± 0.11	6.85 ± 0.30
Drug content (%)*	100.84 ± 0.17	100.62 ± 0.12	101.06 ± 0.30	99.23 ± 0.47	100.35 ± 0.40	99.71 ± 0.36

*n = 3

decrease. Another factor that can affect patch thickness is the use of a film matrix. The greater the concentration of the film matrix, the thicker the patch will be, this kind of patch is less popular because of the reduced comfort during use. The film thickness can reduce the permeability and permeability coefficient of the drug that penetrates the film.[3] Several other factors also affect the thickness of the patch preparation, namely: the volume of the solution, the area of the impression, and the number of total solids in the solution.[21] The standard deviation obtained was less than 5%, namely: 0.01 – 0.03% indicating that the components of the material (drugs, polymers, penetration enhancers) used in the formula are evenly distributed over the printed surface of patch.[11]

High moisture content can trigger contamination by microorganisms and result in reduced patch stability. Meanwhile, moisture content that is too low will reduce the comfort of using the patch. The test results (Table 2) from DP-IPM and DP-EO showed that they were in the desired moisture content range of 1-10%. Patch moisture is also affected by the amount of penetration enhancer used because isopropyl myristate and eucalyptus oil are liquids. In addition, propylene glycol and HPMC have hygroscopic properties that are easier to absorb moisture from the surrounding environment, thus affecting the moisture of the patch.

Based on the requirements of the Indonesian Pharmacopoeia, domperidone tablets contain domperidone not less than 95.0% and not more than 105.0%, of the amount stated on label.[22] The requirements for domperidone tablets are used because there is no domperidone patch on the market yet. Based on these requirements, all DP is included in the required level range requirements.

The results of the diffusion test (Table 3) showed that the cumulative amount of domperidone that was diffused was quite low, around 1.4 – 1.74% within 8 hours. Several DP studies reported cumulative amounts of domperidone in 8 hours, including 40%, 28%, and 815.47 g.4,5,18 Factors affecting the diffusion process include particle size, membrane thickness, area, distance, temperature, drug concentration, penetration coefficient, viscosity, and partition coefficient. Diffusion through the membrane pores can be affected by the size of the molecules passing

Table 3. The cumulative amount of domperidone diffused in DP*

Time (hour)	Cumulative amount of domperidone diffused (µg)					
	DP-IPM			DP-EO		
	2%	5%	10%	2%	5%	10%
0.5	53.416 ± 3.054	57.785 ± 2.786	64.316 ± 1.442	48.676 ± 3.938	56.016 ± 2.299	60.363 ± 2.073
1	70.149 ± 5.028	72.974 ± 2.244	82.082 ± 1.285	63.302 ± 2.084	68.357 ± 2.386	78.782 ± 5.384
2	97.699 ± 4.18	98.29 ± 2.736	109.854 ± 1.659	84.038 ± 1.335	95.666 ± 3.476	107.116 ± 5.526
3	130.961 ± 19.779	129.224 ± 3.355	142.278 ± 5.197	111.023 ± 2.225	123.089 ± 3.324	138.755 ± 4.551
4	153.308 ± 6.2395	162.979 ± 4.3	180.655 ± 4.642	138.941 ± 6.524	153.392 ± 5.239	171.652 ± 6.638
5	187.874 ± 5.888	198.277 ± 3.07	218.321 ± 6.252	172.956 ± 4.648	184.466 ± 6.28	207.768 ± 5.099
6	222.98 ± 4.358	235.936 ± 3.279	261.693 ± 5.947	204.403 ± 4.008	216.543 ± 4.234	244.476 ± 7.831
7	255.228 ± 5.593	273.399 ± 6.789	303.013 ± 4.078	238.892 ± 5.137	255.512 ± 4.742	287.706 ± 5.333
8	293.658 ± 6.309	313.198 ± 5.329	348.056 ± 3.479	276.944 ± 5.865	293.455 ± 2.647	330.268 ± 3.246

*n = 3

Table 4. The diffusion kineticks of domperidone in DP*

Sample		Parameter		
		Kinetics	K	R
DP-IPM	2%	Zero-order	31.448	0.9987
		First order	0.2172	0.9807
		Higuchi	110.98	0.9791
		Korsmeyer peppas	0.616	0.9873
	5%	Zero-order	33.981	0.9979
		First order	0.2211	0.9870
		Higuchi	119.39	0.9741
		Korsmeyer peppas	0.6186	0.9804
	10%	Zero-order	37.612	0.9975
		First order	0.2199	0.9876
		Higuchi	132.05	0.9730
		Korsmeyer peppas	0.6147	0.9799
DP-EO	2%	Zero-order	30.102	0.9969
		First order	0.2255	0.9877
		Higuchi	105.55	0.9711
		Korsmeyer peppas	0.6017	0.9809
	5%	Zero-order	31.339	0.9976
		First order	0.2163	0.9872
		Higuchi	110.1	0.9738
		Korsmeyer peppas	0.6052	0.9806
	10%	Zero-order	35.394	0.9978
		First order	0.2181	0.9854
		Higuchi	124.44	0.9746
		Korsmeyer peppas	0.613	0.9835

through the membrane and the diameter of the pores.[23] For drug compounds that have a large molecular weight and particle size larger than the pore size of the membrane, the diffusion process of the drug compound will be hampered or even unable to diffuse into the receptor compartment. The thickness of the membrane can also inhibit the diffusion process because the thicker the membrane, the slower the drug will diffuse.[24]

The result of the accumulation of the highest amount of diffused domperidone was seen at a penetration enhancing concentration of 10%, both using IPM and EO. However, DP using 10% IPM resulted in a higher amount of diffused domperidone compared to 10% EO. This indicates that the ability of IPM in assisting the diffusion of domperidone in the patch preparation is greater than the use of EO. This condition is probably caused by the nature of EO which is easily oxidized and volatile, lowering the EO content in the patch, and thereby reducing its ability to increase the diffusion of domperidone. The buflomedil hydrochloride patch also showed that the use of 5-10% IPM resulted in a better increase in the rate of diffusion compared to the use of oleic acid.[25] Meanwhile, the manufacture of dimenhydrinate patches showed that the use of 5% EO was the best penetration enhancer because it produced the highest flux value compared to the use of propylene glycol and oleic acid.[26] In addition, the use of 5% EO as a penetration enhancer also showed the cumulative amount of domperidone diffusion was better than the use of 5% menthol.[18]

Both the use of IPM and EO as penetration enhancers have been shown to increase the amount of domperidone that is diffused per unit of time. IPM is a lipophilic penetration enhancer that works by entering the stratum corneum and disrupting the rigidity of lipids in the stratum corneum resulting in lipid instability[27] thereby increasing drug

diffusion into the skin. The mechanism of IPM in the skin has been reported, namely: integrating the drug into the lipid layer and increasing the solubility of the drug in the skin.[9]

EO is a chemical penetration enhancer of the essential oil group with the mechanism of modifying the solvent properties of the stratum corneum so that it can increase drug partitioning.[28,10] Based on the study of minoxidil nanoemulsion also showed that the use of 15.93% EO as a penetration enhancer could increase minoxidil retention in the deepest layers of the skin compared to oleic acid.[29]

Furthermore, the diffusion profile of domperidone can be described by the kinetics of drug release through the order and rate of diffusion. Then, each drug release profile of each formula was studied using several drug release kinetics equations, including zero-order, first order, Higuchi, and Korsmeyer peppas. From each kinetic equation, the drug release rate constant (k) and correlation coefficient (r) were obtained. Based on the results of the kinetics of drug release for DP preparations (Table 4), all formulas followed zero-order kinetics, in this zero-order release system drug release occurs at a constant rate, independent of concentration.[23] One of the advantages of patch preparations is that they can provide controlled drug delivery through a diffusion process.[30] Pantoprazole sodium patch also gets the same order kinetics, namely zero-order.[31] The amount and type of penetration enhancer used in the patch do not affect the order of diffusion. However, both of these affect the diffusion rate constant. The greatest diffusion rate constant was obtained in PD using a 10% IPM penetration enhancer (37.612 µg/hour) compared to 10% EO (35.394 µg/hour).

Based on the results of the one-way ANOVA test for each of the DP-IPM and DP-EO diffusion rate constant data, it was known that the sig value is 0.000 (α <0.05), this showed that increasing the number of IPM or EO can produce different values of the diffusion rate constant significantly. Furthermore, the Tukey HSD test was carried out which showed that the use of IPM with an interval of 3% could significantly increase the value of the diffusion rate constant, while the use of EO with an interval of 8% could only significantly increase the value of the diffusion rate constant. The results of the independent parametric sample t-test on the diffusion rate constants of DP-IPM 10% and DP-EO 10% showed the value of Sig. 0.005 < (0.05) which indicates there is a significant difference between the use of IPM and EO as a penetration enhancer at a concentration of 10% to the diffusion rate constant of domperidone.

4. Conclusion

The use of penetration enhancers (IPM and EO) in the patch preparation did not change the diffusion order but could increase the diffusion rate constant of domperidone. The diffusion rate constant of DP-IPM was higher than DP-EO so the use of IPM is more effective and efficient than EO as a penetration enhancer.

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