Diffusion of Sodium Diclofenac from Carbopol 940 Gel at Various pH

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ABSTRACT

Diffusion of sodium diclofenac in Carbopol 940 gel has been investigated. Diffusion test was performed in diffusion cells with artificial membranes of Whatman no.1 filter paper which immersed with Spangler solution. Measurement of active ingredient concentration that diffuses was performed using UV spectrophotometer at a wavelength of 277 nm.

The results showed that diffusion rate of sodium diclofenac from Carbopol gel increased at higher pH. The highest diffusion of diclofenac sodium occurs at pH 8 with a mean percentage of diclofenac sodium which diffuses after 240 minutes was 48.06 $\pm$ 4.83%. The mean percentage of diclofenac sodium which diffuses from the gel Carbopol 940 at pH 6 after 240 minutes was 11.47 $\pm$ 1.71% while the Carbopol 940 gel at pH 7 is 22.44 $\pm$ 3.71%.

Key words: diffusion, diclofenac sodium, pH, gel Carbopol 940

INTRODUCTION

Diclofenac sodium is one of drug for rheumatoid arthritis, osteoarthritis or acute pain of skeletal muscle that has a great potency and lower side effects than other similar drugs. Diclofenac sodium is a strong inhibitor of cyclooxygenase with analgesic and antipyretic effects. Provision of diclofenac in systemic resulted gastric ulcer side effects due to reduced gastric mucosal protective properties [1]. Therefore, topical preparations for local use was developed in order to reduce side effects and overcome the effects of reduced bioavailability by metabolism in the liver. Gel was widely used in pharmaceutical preparations. The nature of gel which is not sticky on the skin,

comfortable to use and good appearance has made gel chosen as carrier in topical preparations [2,3]. Excellent quality of nature leads to the development of gel formulations.

Topical preparations with diclofenac sodium as active ingredient should have the ability to diffuse through the skin in order to reach the dermis. One of quality parameters for topical preparations is ability of active ingredients to diffuse through the skin [4]. Research conducted on the ability of diclofenac sodium to diffuse from semisolid Carbopol 940 gel. Diffusion of active ingredients are also influenced by the pH of the preparations, therefore the effect of pH on the diffusion were investigated in this study [5]. Determination of the amount of active ingredient that diffuses was performed in vitro through a membrane that immersed with Spangler solution. The purpose of this study was to determine the effect of pH on diffusion of sodium diclofenac in Carbopol gel. The result of this reasearch was expected to develop an effective semisolid preparations as carriers of diclofenac sodium.

MATERIALS AND METHODS

Material

Diclofenac sodium, Carbopol 940, 95% ethanol, propylene glycol, Triethanolamine, potassium dihydrogen phosphate, sodium hydroxide, coconut oil, oleic acid, white vaseline, cholesterol, stearic acid, skualen, solution paraffin, palmitic acid, and olive oil.

Equipment

Diffusion cell, ultra-violet spectrophotometer, digital scales and chemical glassware commonly used in laboratories.

Methods

Preparation of Carbopol Gel

Carbopol 940 was dispersed into the water. Sodium diclofenac and methyl paraben which is dissolved in 95% ethanol and propylene glycol was added into the system dispersion. Triethanolamine was added until the pH of the dispersion system sufficient to achieve the desired pH. This mixture was stirred with stirer at speeds of 600 rotations per minute until homogeneous [6,7,8]. The composition of the formula can be seen in Table 1.

Table 1. Composition of Carbopol 940 Gel

Composition	Percentage in preparation (% w/w)		
	pH 6	pH 7	pH 8
Diclofenac sodium	1	1	1
Carbopol 940	1	1	1
Ethanol 95%	10	10	10
Propilenglikol	10	10	10
Methyl paraben	0,1	0,1	0,1
TEA	qs ad pH 6	qs ad pH 7	qs ad pH 8
Distillated water	ad 100	ad 100	ad 100

Assay of sodium diclofenac in the preparation

Amount of 100 mg gel was diluted by phosphate buffer pH 7.4 in a pint flask up to volume 50 mL. Solution absorption was measured with a spectrophotometer at 277 nm wavelength of ultra violet.

Maximum Absorption Wavelength Measurement in pH 7.4 phosphate buffer solution

Diclofenac sodium prepared with a concentration of 10µ g / mL in pH 7.4 phosphate buffer solution. Uptake solution was measured at a wavelength of 200-400 nm with a UV spectrophotometer [9].

Preparation of calibration curve in pH 7.4 phosphate buffer solution

Diclofenac sodium solution with 1mg/mL concentration in pH 7.4 phosphate buffer solution was created. Amount of 2.5 mL solution was taken and diluted to 50 mL threfore obtained stock solution with a concentration of 50 µg / mL. Stock solution was taken 0.5, 2.5: 5.0: 7.5: 10; 12.5 and 15.0 mL of solution and then put into 25 ml measuring flask and fulfilled up to volume 25 mL with a solution phosphate buffer pH 7.4. Obtained a solution with a concentration of 1, 5, 15; 20; 25 and 30 µ g / mL. Solution absorption was measured at a wavelength corresponding to the maximum wavelength of the measurement results.

Making receiver solution

Receiver solution of pH 7.4 phosphate buffer solution was created by mixing 500 mL of 0.1 M potassium dihydrogen phosphate and 391 mL of 0.1 N sodium hydroxide solution. Solution was accomplished with carbon dioxide-free distilled water to exactly 1 L.

Preparation of artificial membranes

Whatman no.1 paper was immersed with Spangler solution. Spangler solution composition: 15% coconut oil, oleic acid 15%, 15% of white vaseline, cholesterol 5%, 5% stearic acid, skualen 5%, solution paraffin 10%, 10% palmitic acid and 20% olive oil. All material was melted, begins with the highest melting dotted. Whatman paper was weighed before treatment. Whatman paper was soaked in a Spangler solution for 15 minutes. Paper was raised and left between 2 paper filter to reduce dripping Spangler solution. Artificial membranes that have been prepared was weighed to determine the amount of fluid absorbed. The amount of fluid absorbed was calculated by the formula:

Absorbed Spangler solution =

$$\frac{W_1 - W_0}{W_0} x100\%$$

with W_0 is weight of the membrane before treatment and W_1 is the weight of the membrane after treatment. Membrane was eligible in uniformity test if the percentage of absorbed Spangler solution in membrane was between 102.19 to 131.22% [10].

Diffusion test

Diffusion cell was prepared for diffusion test. Amount of 2 g gel were weighed and flattened on the Spangler plate membrane in diffusion cell. Avoid intake of air between membrane and gel. Membrane was pinched with circular clip. Buffer solution of pH 7.4 was prepared as a receiver solution. Diffusion membrane surface area was 2545 cm^2. The connection between donor and receptor compartments fitted. Vaseline was smeared in connection between compartement to prevent leakage. Amount of 200 mL phosphate buffer pH 7.4 was incorporated into the receptor compartment. Both compartments were closed and stirred at 40 ppm. Diffusion cell is inserted into water bath at 37^o C, and then observed for 4 hours. Conducted sampling of the receptor compartment at 5, 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240 minutes by 10 mL. The solution was

replaced with 10 mL of buffer solution pH 7.4. Diclofenac sodium uptake was measured by UV spectrophotometer at the wavelength obtained from the determination of the maximum wavelength. Correction is done by use of a pH 7.4 buffer solution as a blank. Relationship curve between the percentage of diclofenac sodium which diffuses from the preparations to time was created [10].

RESULTS AND DISCUSSION

Research on the diffusion in the skin membrane was determine to find out how the flux of drug cross the skin, whether a drug was bound to stratum corneum or form a depot in subcutaneous fat. This data was important to determine the ability of diclofenac sodium in topical gel to penetrate the skin barrier. Diffusion in skin membrane can be tested with an artificial membrane that resembled features of the skin such as cellulose acetate, silicone rubber, isopropyl myristate or eggshell membrane. This study used membrane immersed with Spangler solution consisted of 15% coconut oil, oleic acid 15%, 15% of white vaseline, cholesterol 5%, 5% stearic acid, skualen 5%, solution paraffin 10%, 10% palmitic acid and 20% olive oil. Spangler solution components in this condition resemble human skin. Despite having the skin-like properties of these materials but do not have the trait as complex as real skin.

Drug in a carrier must dissoluted then diffuse from the carrier to the skin surface to be absorbed through the skin. Drug can pass through transepidermal or transfolikular route of skin. At the transepidermal route, drug will experience partition into the stratum corneum and then diffuses through the lipid-protein matrix in the stratum corneum. Drug will experience partition into sebum and then diffuses through the lipids in the sebaceous pores on transfolikular route. After going through one of these routes, drug will participate actively to the epidermis and then diffuses through the cellular mass in the epidermis. Drug will diffuse through the fibrous mass of the upper dermis and penetration of capillaries and systemic dilution experienced.

Kinetics of transdermal follow Ficks law of diffusion:

$$Js = \frac{Km.D.Cs}{E}$$

with Js is the equilibrium of the solute flux, Km is the drug distribution

coefficient between the carrier with the stratum corneum, Cs is the solute concentration difference across the membrane, E is the thickness of the stratum corneum and diffusion coefficient D is the average of the membrane to the solute in the stratum corneum.

Thus the amount of drug absorbed per unit area in unit time depends on the solubility of the drug and the characteristics of the distribution, the drug concentration difference across the membrane, the nature of the carrier used and the thickness of the stratum corneum. Test results from the diffusion of diclofenac sodium gel Carbopol 940 at pH 6.7 and 8 can be seen in table 2.

Table 2. Diffusion Test Results of Carbopol 940 Gel

Time (minutes)	Percentage of Diffused Sodium Diclofenac (%)		
	pH 6	pH 7	pH 8
5	0,00 ± 0,00	1,10 ± 0,57	0,96 ± 0,88
15	1,21 ± 1,06	1,80 ± 0,50	2,03 ± 1,09
30	1,72 ± 1,13	2,82 ± 0,43	3,59 ± 0,43
45	2,52 ± 0,91	4,48 ± 0,61	5,70 ± 0,59
60	3,44 ± 1,06	5,93 ± 1,02	8,56 ± 1,09
75	4,53 ± 1,47	7,42 ± 1,51	11,10 ± 1,51
90	5,21 ± 1,15	8,91 ± 1,25	14,83 ± 2,01
120	6,58 ± 0,80	12,10 ±1,72	20,13 ± 3,39
150	7,99 ± 1,31	14,88 ± 1,92	26,25 ± 6,62
180	9,27 ± 1,41	17,58 ± 3,07	33,40 ± 6,29
210	10,31 ± 1,55	19,36 ± 3,63	40,80 ± 6,02
240	11,47 ± 1,71	22,44 ± 3,71	48,06 ± 4,83

The results showed that the diffusion of sodium diclofenac highest occurred at pH 8 with a mean percentage of diclofenac sodium which diffuses after 240 minutes was 48.06 ± 4.83%. The mean percentage of diclofenac sodium which diffuses from the gel Carbopol 940 at pH 6 after 240 minutes was 11.47 ± 1.71% while the Carbopol 940 gel at pH 7 is 22.44 ± 3.71%. A substance must be dissolved first in the carrier medium to be able to diffuse well. Diclofenac sodium has a high solubility at alkaline pH. This is what causes the Carbopol gel diclofenac sodium has the highest percentage of diffusion at pH 8. Selection of pH at pH 6, 7 and 8 based approach to natural skin pH is at pH 7. Increased pH with the aim of increasing the rate of

diffusion must still consider the convenience of using preparations. Preparation of Carbopol 940 gel at pH 8 are expected not to cause irritation to the skin and has a good penetration rate.

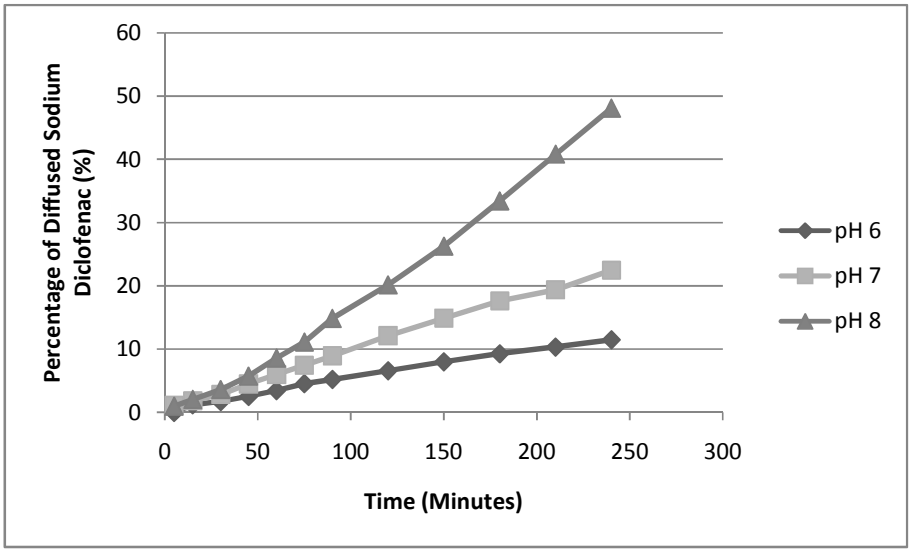

Figure 1. Percentage of Diffused Diclofenac Sodium to Time Curve

The data obtained are plotted a curve of the percentage of diclofenac sodium which diffuses with time. The slope of the curve the percentage of diclofenac sodium which diffuses with time is proportional to the rate of diclofenac sodium diffusion through the membrane.

The curve in Figure 1 shows that the higher the pH the rate of diffusion of sodium diclofenac from Carbopol gel increased. On the curve can be seen that the rate of diffusion of diclofenac sodium gel Carbopol highest at pH 8.

CONCLUSION AND SUGGESTIONS

Conclusions

1. Diffusion rate of diclofenac sodium from Carbopol 940 gel increased at higher pH.
2. The highest percentage of diffused diclofenac sodium from Carbopol 940 gel was at pH 8.

Suggestions

Furthermore diffusion study in other material form is necessary to get a better topical preparation for diclofenac sodium

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