Development of Patch Ketoprofen Using Chitosan as Polymer Matrix

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Abstract
Patch is a transdermal dosage form that has increasing number of applications for its simplicity with controlled release profile of drug. The ability to provide controlled release manner of drug is developed by the use of polymer as the matrix. In this research, patch of ketoprofen were formulated using various concentrations of chitosan as matrix. Preparation of the transdermal patch were conducted by using solvent evaporation method. Characterization of patch were included physical characteristic, homogeneity, drug assay, drug permeation and stability study. Permeation test were performed in vitro by using Franz diffusion cells with shed snake's skin of Phyton reticulatus as diffusion membrane for 24 hours. The result showed that Chitosan is a potential polymer to be used as matrix for patches since it was stable and gave peel off ability. Permeability test showed that a decrease in permeation of ketoprofen was in line with the increase of chitosan as matrix. Formula containing chitosan 1% and tween 80 0,3% as permeation enhancer gave the highest permeation number as much as 99,15%.

Keywords: Chitosan, Transdermal patch, Ketoprofen

INTRODUCTION

Analgesics are used to relieve pain without causing loss of consciousness. Analgesics are divided into two groups, namely peripheral analgesics and narcotic analgesics. The peripheral analgesics consists of drugs which are not narcotic and not central working. While narcotic analgesics consists of drugs that are used to banish the pain like fracture and cancer.[1]

Ketoprofen, a derivative of propionic acid, is one of peripheral analgesic. Ketoprofen has the effectiveness in the treatment of rheumatoid arthritis, osteoarthritis, gout, dysmenorrhea, and other painful circumstances.[2] Currently, ketoprofen preparations is sold widely in the market include tablets, capsules, injectiones, suppositories, and topicals. Various forms of these preparations has not been felt quite practical for use by patients and raises some issues.

Tablets or capsules dosage form has drawbacks, especially for patients who have difficulty swallowing tablets or capsules, as well as the existence of a first pass effect in liver.[3] The use of injection preparations in need of experts in assisting the process of granting preparations. Suppository preparations less comfortable because that need administration through rectal. While topical preparations only give local effect on the location of the grant.[4] The options that can be use to overcome these problems is a drug made in the form of transdermal preparations so that the system transfers more controlled drugs. In addition, the transdermal preparations are also more practical and comfortable, and can be faster with systemic effects.[5]

Development of medicinal preparations is currently more focused on transdermal preparations because of these reasons. One kind of transdermal form is patch. Patch preparations provide concentration uniformity of the drug to diffuse so that guarantees constant drug release.[6]

Matrix is an important component for the transdermal system in terms of release and permeation of drugs, as well as in the mechanical properties of a formula that is designed.[7] One of the substances that can be used as a matrix in the form of the polymer is chitosan. Chitosan is a natural polysaccharide that is used in various systems delivering drugs for its biocompatible bonding agent, non-toxic, biodegradable, and their ability to form a gel.[8] Chitosan has the ability to increase the penetration of the mucous membranes by reducing skin impermeability for a while. Chitosan will interact with intracellular lipids and improve hydration at the stratum corneum which will cause the stratum corneum more polar and certain compounds would more easily pass through the stratum corneum in the skin.[4]

Chitosan produces rigid and brittle patch structure. The addition of the plasticizer can improve the mechanical properties of the formula so that it is more flexible and elastic.[9] Chitosan also has better capabilities as a bioadhesif polymer on in vitro permeation test compare with sodium carboxymethylcellulose, gum, poloxamer 407, and carbopol 934P.[10] Bioadhesif properties of chitosan can cause interactions between positive charges and negative charges on the skin so it can formulated into transdermal.[11]

This research aims to formulate ketoprofen patch preparations by using chitosan as a matrix and release profiles observed on in vitro ketoprofen patch preparations using UV-Vis spectrophotometer.

MATERIALS AND METHODS

Materials

The materials used in this study consisted of ketoprofen (PT Kimia Farma), tween 80 (Bratachem), glycerine (Quadrant), chitosan (Biotech Surindo), ethanol 96% (Bratachem), KH_2PO_4 (Merck), NaOH (Merck), glacial acetic acid (Merck), aquadest.

Membrane

The membrane of the skin used is python (*Python reticulatus*) spin-off skin obtained from the Bandung Zoo.

Tools

Tools used in this study consists of a Franz diffusion cell horizontal type, peristaltic pumps (Fisher Scientific), UV-Vis spectrophotometry (Analytic Jena-Specord 200), pH metres (744 Methrom), waterbath (Memmert), analytical balance (OHAUS TM-Adventure), magnetic stirrer (Yellow-MAG HS7), caliper, volumetric flask (Pyrex) beaker glass (Pyrex), measuring cylinder (Pyrex), glass and tools commonly used in the laboratory.

Method

The method of research conducted include the formulation of ketoprofen patch preparations with chitosan matrix, the physicochemical evaluation of ketoprofen patch preparations, permeation test ketoprofen patch preparations with Franz diffusion cell method using python (*Python reticulatus*) spin-off skin, the measurement of percent ketoprofen patch permeation preparations, then processing and interpretation of research results.

Formulation of Ketoprofen Patch Preparations

Ketoprofen was the active substances used in the manufacture of the patch. Chitosan was a substance that acts as a matrix. Glycerin was used as a plasticizer and tween 80 as enhancer. Ethanol 96% was used as a solvent of ketoprofen. Acetic acid (0.1% v/v) was used as a solvent of chitosan and as major solvent in the mix.

The procedure was begun with the preparation of chitosan dissolved with acetic acid (0.1% v/v) for 30 min. For formula F1, F2, and F3 added glycerine and tween 80, and stirred for 30 min. While the formula F4, F5, and F6 added glycerine and stir for 30 min. Ketoprofen was dissolved with 96% ethanol and mixed with a solution of chitosan, homogenize using magnetic sitrrer for 1 h. Solution was poured into the mold as much 17.140 gram for each and dried for 48 h at temperature $40^{o}C$. Dry patch removed from the mold and stored in the container.

Table 1. Design of Formula Ketoprofen Patch Preparations

Material	Formula (% w/w)					
	1	2	3	4	5	6
Ketoprofen	0,63	0,63	0,63	0,63	0,63	0,63
Glycerine*	30	30	30	30	30	30
Tween 80	0,3	0,3	0,3	-	-	-
Ethanol 96%	10	10	10	10	10	10
Chitosan	1	2	3	1	2	3
Acetic acid (0,1% v/v)	Ad 100	Ad 100	Ad 100	Ad 100	Ad 100	Ad 100

(*) based on the weight of the polymer.

Evaluation of Ketoprofen Patch Preparations

Evaluation of patch was required to maintain the quality. Evaluation of patch was done both in terms of physical or chemical. Physical evaluation performed during storage, includes:

1. Physical appearance
   All patches observed color change, texture, and smell.
2. The thickness of the patch
   The thickness of the patch measure on several different locations using a caliper and its average value calculated.[12]
3. Weight variation test
   Patch cut into pieces with a size of 1 x 1 cm and weights of each patch was determined using digital scales. The average weight of each patch and standard deviation was calculated.[13]
4. Percent humidity
   The percentage of humidity determined by keeping patch at room temperature in the desiccator containing silica for 24 h. Weight of the beginning and end of the patch weighed.[14,15]

$$\% \text{ moisture} = \frac{\text{initial weight} - \text{final weight}}{\text{final weight}} \; x \; 100\%$$

5. Drying shrinkage
   Calculate initial weigh of patch, then put in a desiccator containing silica at room temperature during storage.[16,17]

While the stages of chemical evaluation conducted to measure the levels of ketoprofen patch in preparations, including:

1. Making the ketoprofen standard curve in ethanol solvent
   As much as 25 mg ketoprofen dissolved in ethanol with up to 50 mL to get 500 ppm stock solution. The solution then diluted with ethanol to get ketoprofen concentration 4, 6, 8, 10, and 12 ppm. Furthermore, measure each solution absorbance using a UV-Vis spectrophotometer at the maximum wavelength, and then determined the correlation coefficient and linear equations (r).
2. Content uniformity test of ketoprofen in patch preparations
   Patch drawn at random to serve as samples, then each patch is dissolved with ethanol up to 25 mL. A solution of 0.1 mL was taken from each volumetric flask and dilute to 10 mL with ethanol. Each solution absorbance measurements were performed using UV-Vis spectrophotometer at maximum wavelength so that the dosage levels of each patch can be known.
3. Content homogenity test of ketoprofen in patch preparations
   The patch was taken at random, then the patch was divided into four equal parts. Each part of the patch was then dissolved up to 25 mL with ethanol. 0.1 mL of solution was taken as much from each volumetric flask and then dilute with ethanol to 10 mL. Measure the absorbance from each sample by using a UV-Vis spectrophotometer instrument at maximum wavelength so that the dosage levels of each part of the patch can be known.
4. Ketoprofen content test during storage
   The patch was taken at random, then the patch was divided into four equal parts. Each part of the patch was

then dissolved up to 25 mL with ethanol. 0.1 mL of solution was taken as much from each volumetric flask and then dilute with ethanol to 10 mL. Measure the absorbance from each sample by using a UV-Vis spectrophotometer instrument at maximum wavelength, then the results accumulated so that the dosage levels of total four patches can be known. The measurement was done on day 0, 30, and 60.

In Vitro Permeation Test Preparation of Ketoprofen Patch

Stages of testing begins with preparing the required materials, there were:

1. Phosphate buffer pH 7.4

   Based on Indonesian Pharmacopeiea 3rd edition, phosphate buffer pH 7,4 manufacture was done by mixing 50 mL KH2PO4 0.2 M with 39.1 mL NaOH 0.2 N, then added up to 200 mL water free of CO_2 200 mL.[18]

2. Acetic acid 0.1% v/v

   Acetic acid 0.1% v/v was made by dissolving 0.1 mL of glacial acetic acid with aquadest up to 100 mL.

3. Snake spin-off skin membrane

   The membrane used was dorsal (back) python (*Python reticulatus*) spin-off skin. Snake skin may be cleaned first with aquadest, then dried at room temperature. The membrane was cut by 2 x 2 cm for use at the time of the diffusion.

After that, do in vitro permeation test of ketoprofen patch with Franz diffusion cell method and analyzed by using Spectrophotometer UV-Vis. The stages done, include:

1. Making the ketoprofen standard curve in buffer phosphate pH 7.4

   As much as 25 mg ketoprofen dissolved in buffer phosphate pH 7.4 with up to 50 mL to get 500 ppm stock solution. The solution then diluted with buffer phosphate pH 7.4 to get ketoprofen concentration 4, 6, 8, 10, and 12 ppm. Furthermore, measure each solution absorbance using UV-Vis spectrophotometer at the maximum wavelength, and then determined the correlation coefficient and linear equations (r).

2. Permeation test ketoprofen from patch preparations

   Permeation test ketoprofen was done by using Franz diffusion cell method. Diffusion tools arrangement that was used consists of the waterbath, magnetic stirrer, beaker glass, peristaltic pump with controlled regulator flow, Franz diffusion cells, and hose diameter 5 mm. Patch that has been cut by 2 x 2 cm affixed on the upper surface of the membrane in the cell diffusion and placed on top of the waterbath. Part of the receptor consists of a beaker filled with phosphate buffer pH 7.4 and was placed on a magnetic stirrer with temperature settings are keep on 37°C. Then the hose between the receptors coupled to Franz diffusion cell. Diffusion test was carried out during 24 h and conducted sampling at hour 0; 1; 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; and 24. At the time of sampling, the samples were taken as much as 5 mL then directly recharged using phosphate buffer pH 7.4 with same volume. The entire sample was measured its absorbance using spectrophotometer UV-Vis.

3. Statistical analysis for permeation test data results of ketoprofen patch

   Results of permeation test were analyzed statistically using analysis of varians (ANOVA) with IBM SPSS Statistics version 20 software.

RESULTS AND DISCUSSION

Formulation Results of Ketoprofen Patch Dosage

Ketoprofen transdermal patch preparations produced by the process of stirring the respective formula for 2 h. Solution was then poured into molds and dried for 48 h in oven at 40°C.[19] The entire formula produces dry patch and can be removed from the mold.

Ketoprofen patch preparations was created with matrix system. The making of matrix system gives continuously drug release from transdermal patches due to molecular medicine was incorporated into polymer matrices.[20] The advantages of this system was easy, fast, and cheap manufacturing process.[21] Ketoprofen patch preparations created using polymer chitosan. Chitosan is a natural polymer that used in controlling the release of drugs along with serves as the matrix of the drug and the polymer base. The use of Chitosan as a polymer in the formulation of ketoprofen transdermal preparations produce uniformity of drug distribution in the base.[19] Glycerine was used in the formula as a plasticizer in order to improve the elasticity and power curves of polymer base so that the resulting patch have good flexibility and not easy brittle or broken. The penetration enhancer tween 80 was used. Tween 80 is a nonionic surfactants that work by dissolving lipophilic compounds and lipid layer on stratum corneum of the skin thereby increasing freedom of lipid movement or the fluidity.[22] Solvent used in the manufacture of this patch was acetic acid (0.1% v/v) and ethanol 96%. Acetic acid 0.1% v/v was used to dissolved chitosan, while ethanol 96% used to dissolved active substances, ketoprofen. This research can be observed the effect of various concentrations matrix and also the effect given by the penetration enhancing substances against patch permeation.

The techniques used in the making of this patch was solvent evaporation method. At the time of making patch, chitosan was first dissolved with acetic acid 0.1% v/v, and then added glycerine and tween 80. After that, ketoprofen dissolved with ethanol 96% poured little by little into the solution matrix so that dispersed evenly. The mixed results produce white solution. Penetration enhancing formula with tween 80 (F1, F2, and F3) looks homogeneous, while on the formula without tween 80 (F4, F5, and F6) form vapour between chitosan and ketoprofen. In addition to penetration enhancing, presence of tween 80 acts as a surfactant.[23] The presence of tween 80 cause a decrease in surface tension between molecular chitosan and ketoprofen molecules, making it easier to mix. Once the process was completed, the solution poured into molds and left to dry for 48 h in oven at 40°C to vaporize solvent.

Evaluation Results of Ketoprofen Patch Preparations

The patch preparations need to be evaluated to get good quality preparations and can proceed to in vitro evaluation. Evaluation was done in terms of the physical

and chemical evaluation. Physical evaluation include organoleptic observations, weights, thickness variation, percent humidity, and drying shrinkage. While chemical evaluation done by measuring levels of ketoprofen in preparations, including homogeneity test and uniformity test from patch preparations.

Physical Evaluation Results of Ketoprofen Patch Preparations

The aesthetics of a material is an important factor to note and can be observed from the physical appearance. Observations from organoleptic patch preparations, resulting yellow transparent patch. The yellow color was occurring due to β-(1-4)-2-amino-2-deoxy-D-glucopyranose. On day 60 occurring discoloration patches become more yellowish because β-(1-4)-2-amino-2-Deoxy-D-glucopyranose undergoes oxidation. On the formula F1, F2, and F3, the color yellow intensity also increasing by the presence of tween 80.[24] The smell of acid that appears to originate from the rest of the acetic acid is trapped in the patch preparations. On day 60, the smell of acid began to wane and indicates that residual acid trapped slowly began to disappear.

The next evaluation was the physical evaluation test of thick and variations of weights, to find out the thickness and weight of the patch that will affect the amount of deposits of ketoprofen in the patch. If the patch does not match the weight that has been determined, then it was likely to occur irregularities amount of active substances contained in preparations patch. Weight variation test has value that varies between a formula because various concentration of chitosan and effect on the weighting of the patch. Weights and thickness of the patch will be greater in value along with the increase in the concentration of chitosan. In addition, patch F1, F2, and F3 (formula with penetration enhancer) have greater weight than patch F4, F5, and F6 (formula without penetration enhancer) due penetrations-enhancing substances can add to the weight of patches were made. Thickness and weight variations patches were qualified, there were < 2%.[25]

Furthermore, percent humidity test was performed to know the magnitude of the water content in the patch. The test results for 24 h meets the criteria, i.e. contain a little water with a percentage of less than 10%.[3] Low humidity percent indicates that the patch dry and stable and can be protected from microbial impurities.[26] The results of the percentage moisture preparations indicate that the sixth patch formula is experiencing shrinkage weights. This happens because water contained in the patch and the main component of solvent in the process of making this patch is undergoes evaporation during storage. The lower the concentration of chitosan, the percent of moisture became higher. This happens because in the manufacture of chitosan with lower concentration using more solvent, so the moisture levels become higher.

In addition, shrinkage drying test was performed to see a decrease in the weight of formula from the sixth patch preparations that have been made, there was weight shrinkage from chitosan. This was allegedly due to the components undergo evaporation during storage.

Table 2. Thickness and Weight Variation Results of Ketoprofen Patch Preparations

Formula	Parameters			
	Mean thickness± SD (mm)	CV(%)	Mean weight variations± SD (mg)	CV(%)
F1	0,027 ± 0,0046	0,23	0,011 ± 0,0024	0,23
F2	0,056 ± 0,0051	0,09	0,020 ± 0,0018	0,09
F3	0,076 ± 0,0051	0,15	0,026 ± 0,0038	0,15
F4	0,033 ± 0,0046	0,14	0,010 ± 0,0013	0,14
F5	0,059 ± 0,0035	0,13	0,017 ± 0,0023	0,13
F6	0,092 ± 0,0041	0,12	0,026 ± 0,0032	0,12

Table 3. Moisture Content Results of Ketoprofen Patch Preparations

Formula	Initial mass	Final mass	Moisture (%)
F1	0,4064	0,3857	5,3669
F2	0,6821	0,6614	3,1297
F3	0,9677	0,9567	1,1498
F4	0,3209	0,3164	1,4223
F5	0,6173	0,5950	3,7479
F6	0,9413	0,9310	1,1074

Description:
F1 = Formula with 1% chitosan & tween 80
F2 = Formula with 2% chitosan & tween 80
F3 = Formula with 3% chitosan & tween 80
F4 = Formula with 1% chitosan
F5 = Formula with 2% chitosan
F6 = Formula with 3% chitosan

Ketoprofen Content Measurement Results from Patch Preparations

Content of ketoprofen patch in the preparations need to be measured to ensure uniform levels of ketoprofen in each patch and the suitability ketoprofen content by formula that have created. A sample taken at random and patch are dissolved by using solvent ethanol 96%, then measured using a UV spectrophotometer instrument at λ = 255 nm. Stages of testing the ketoprofen content, include:
1. Making the standard curve in ethanol solvent
   The standard curves created with five variations concentration of ketoprofen in ethanol 96%, i.e. 4, 6, 8, 10, and 12 ppm. Based on the measurement results of of the linear regression equation obtained y = 0.0646x + 0.0033 with r value = 1 at maximum wavelength 255 nm.
2. Dosage uniformity test of ketoprofen in patch preparations
   Uniformity rates of ketoprofen was done by measuring the levels of four different patches. The calculation results of the percent variation coefficient (% VC) for the sixth formula was < 2%. This indicates that the levels of ketoprofen patch in preparations on a batch were uniforms and already qualified, < 2%.[27,28]
3. Dosage homogeneity test of ketoprofen in patch preparations
   Its homogeneity test levels of ketoprofen was done to ensure the equitable distribution of the drugs level in

dosage patch and become one of the factors that affect the control of drug release. Testing was done by cutting the four parts of the same great patch to make sure that the patches have the same levels of ketoprofen. The calculation results of the percent variation coefficient (% VC) for the sixth formula was < 2%, this indicated that the levels of ketoprofen in a patch already homogeneous and qualify, < 2%.[27,28] Results from total content of patches on each formula, seen that the percentage ketoprofen recovery in the patch preparation meets the criteria, the range at 85%-105%.[29] On formula with higher concentration of chitosan, recovery percentage of ketoprofen becomes lower. It is influenced by the pore and the distance from the channels that bypassed by solvent.[30]

4. Ketoprofen content test during storage

In addition, the test levels during storage also performed for two months to see the storage stability of ketoprofen in the patch preparations. As a result, the sixth formula get decrease content every month during storage. This situation was suspected because of ketoprofen degraded by light and oxygen also. Ketoprofen undergoes oxidation through the formation of free radicals that the reaction rate is accelerated by oxygen. This causes ketoprofen changed form and degraded.[31] In addition, the instability of ketoprofen in preparations made patch can be caused due to the limitations of the less packaging containers to the patch preparations. In general the patch material is packed in a container with a vacuum system.[32]

Table 4. Content Uniformity Test Results of Ketoprofen Patch Preparations

Formula	Ketoprofen mass per mg *patch* (mg)	Mean ± SD(mg)	CV (%)
F1	0,340 0,307 0,279 0,268	0,298±0,032	0,11
F2	0,110 0,136 0,119 0,121	0,121±0,011	0,09
F3	0,079 0,093 0,071 0,081	0,081±0,009	0,11
F4	0,403 0,246 0,257 0,312	0,304±0,072	0,24
F5	0,092 0,113 0,100 0,101	0,102±0,009	0,09
F6	0,073 0,071 0,081 0,067	0,073±0,006	0,08

Table 5. Content Homogeneity Test Results of Ketoprofen Patch Preparations

Formula	Ketoprofen mass per mg *patch*(mg)	Total content (mg)	*Recovery*(%)	CV(%)
F1	0,281 0,238 0,270 0,269	111,85	103,58	0,07
F2	0,131 0,135 0,120 0,126	96,93	89,76	0,05
F3	0,088 0,106 0,082 0,089	92,06	85,25	0,11
F4	0,298 0,403 0,264 0,312	109,97	101,84	0,19
F5	0,100 0,234 0,133 0,149	95,69	88,62	0,37
F6	0,073 0,140 0,141 0,101	93,53	86,62	0,29

Table 6. Results of Ketoprofen Content Test During Storage

Formula	Ketoprofen content in patch (%)		
	Day 0	Day 30	Day 60
F1	103,58	90,97	85,62
F2	89,76	87,90	80,68
F3	85,25	77,34	69,61
F4	101,84	80,12	74,00
F5	88,62	76,58	69,44
F6	86,62	70,88	69,33

Permeation Test Results of Ketoprofen Patch Preparations

Permeation test preparation of ketoprofen patch on in vitro was performed using Franz diffusion cell method. The receptor medium used was phosphate buffer pH 7.4 with $37 \pm 0.5^{o}C$ in accordance with the conditions of human body fluid.[33] The patch was cut with a size of 2 x 2 cm and affixed to the membrane diffusion. Permeation tests to be performed for 24 h. Stages of testing that was conducted, covering the creation of curves with ketoprofen standard in buffer phosphate pH 7.4, permeation test of ketoprofen from patch preparations, and statistical analysis for permeation data results.

Manufacture of Standard Curve Ketoprofen in Buffer Phosphate pH 7.4

The standard curves created with five variations concentration of ketoprofen in buffer phosphate pH 7.4, i.e. 4, 6, 8, 10, and 12 ppm. Based on the measurement results of of the linear regression equation obtained $y = 0.0644x -$

0.0013 with r value = 0.9999 at maximum wavelength 260 nm.

Permeation Test of Ketoprofen Patch Preparations

Ketoprofen permeation test from patch done for 24 h against formula F1, F2, F3, and F4 using diffusion cells Franz, while F5 and F6 permeation test was not done. At the time of the making of F4, F5, formula and F6 formed vapour as well as the appearance of the organoleptic patch when dry, there were white spots. The increasing concentration of chitosan cause more clots that formed during the manufacture, then to represent the permeation test, formula F4 has been choosen. Permeation test results was analyzed using UV-Vis spectrophotometer.

Based on the results of permeation test, the concentration of matrix influence against the release of ketoprofen in the patch. F1 (formula with chitosan 1%) provide the best release profiles and active substances that permeated through diffusion process for 24 h reach 99.15%. At F2 (formula with chitosan 2%) the amount of release was 86.91%, while F3 (formula with chitosan 3%) was 9.08%. The increase in the concentration of chitosan as a matrix for patch preparation can lower the release profile of ketoprofen, views on the release profile of F1, F2, and F3. This can occur because of the higher concentration of chitosan, then the distance between molecular chitosan would close and interrupt the molecular ketoprofen for penetrated through the membrane.[34] Other factors that influence is swelling index of chitosan that give influence on the release of drug. Chitosan has high swelling index so the swelling can occur quickly and is quite fragile mechanical as well as easy to crack. On a formula with a higher concentration of chitosan, chitosan molecules become inflexible and troublesome solvent for penetrated so the active substance permeation is lower.[35]

It can be seen also from the release profiles of ketoprofen patch preparations, the use of tween 80 as enhancer into the formula gives a better release effect when compared with no use of penetration enhancer. F1 (formula with the penetration enhancer) produces percent permeation for 24 h of testing 99.15%. While F4 (formula without penetration enhancer) was 6.18%. This indicated that the penetration enhancer has a fairly important role in formula preparation to increase the release profiles of active substances. Tween 80 is the penetration enhancer that comes from the nonionic surfactants. In terms of their effectiveness, penetration of the cationic surfactants can potentially have a much higher effectiveness to improve the penetration of active substances. However, the nonionic surfactant more often used as penetration enhancer because nonionic surfactants has analogous structure to stratum corneum so tend to have a potential low irritation effect. Meanwhile, the use of cationic and anionic surfactants is often accompanied by irritation effects because it has a charge. In addition, the effect of increased penetration by tween 80 occurs due to its interaction with keratin on the skin.[22]
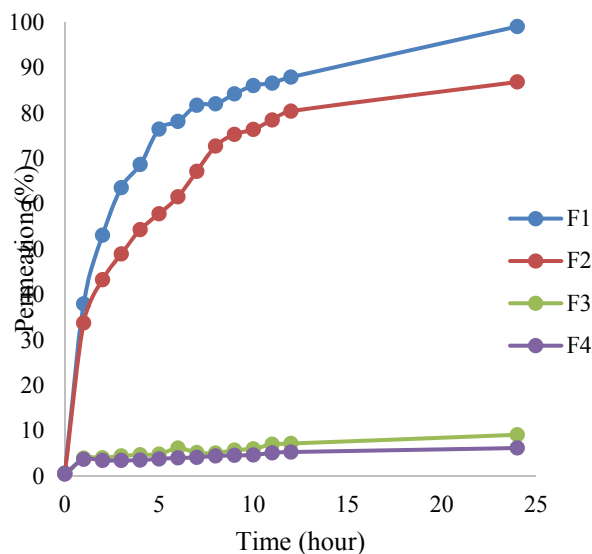

Figure 1. Permeation test ketoprofen from patch preparations for 24 hours

Statistical Analysis for Permeation Test Data Results of Ketoprofen Patch

Permeation data for F1, F2, and F3 were then processed statistically using analysis of varians (ANOVA) with IBM SPSS Statistics version 20 software. On this analysis taken two hypotheses, there were:

H0 = there is no influence of variation of the concentration matrix against percent permeation of ketoprofen patch preparations.

H1 = there is influence of the variation of the concentrations of matrix against percent permeation of ketoprofen patch preparations.

Based on the results of the ANOVA confidence level 95% ($\alpha = 5\%$), obtained a value of $p < 0.05$ so H0 was rejected. This indicated the influence of matrix variation concentrations against ketoprofen patch percent permeation (H0 was rejected). Therefore, further testing was done using Tukey test to find out the formula that has the most significant influence towards ketoprofen percent permeation when compared with other formulas. A test result values were said to be significant if smaller than 0.05 ($\alpha = 5\%$). Based on Tukey test, formula F1 with chitosan concentration 1% gave the most significant results because it has the most massive percent permeation compared to other formulas.

Determination Reaction Kinetics of Ketoprofen Patch Preparations

Next, determination of release kinetics preparations against formula F1, F2, F3, and F4 base on correlation coefficients (r) through the linear equations for each order. Determination of release kinetics is aimed to knowing the drug release mechanism from patch preparations. Each formula will have correlation coefficient (r) value in accordance with the respective order.

Based on the correlation coefficient value obtained from the calculation of any reaction order results, then it can be determined dominant reaction kinetics in the patch preparations release. The most dominant reaction order is the reaction order with the most correlation coefficient value approaching a value of 1 (one).

The result of correlation coefficient (r) calculation indicates that the formula F1, F2, F3, and F4 release follows Higuchi kinetics order. The rate of drug release from the insoluble matrix generally followed Higuchi release. Higuchi kinetics order is kinetics order that are not constant at all times. The rate of drug release from matrix on Higuchi order is affected by matrix porosity and turtuosity. Porosity described the pores or channels that can be penetrated by the surrounding fluid, whereas the turtuosity takes the increased diffusion distance due to curvaceous pores. Turtuosity tend to reduce the amount of active substance apart from time to time during the occurrence of diffusion due to active substances need a longer time to release from the preparations.[30] Drug release kinetics from a transdermal patch dosage is influenced by the form of polymer matrix, both single or combination. The percentages and ratio use of polymer matrix in designing appropriate patch preparations can determine the desired drug release kinetics. Chitosan matrices are used in the manufacture of ketoprofen patch generates a tendency to follow Higuchi order from the four formulas that do diffusion testing.

Table 7. Value of Correlation Coefficient (r)

Formula	Correlation coefficient (r)		
	Zero order	One order	Higuchi order
F1	0,5549	0,2336	0,8530
F2	0,6299	0,2627	0,9304
F3	0,7436	0,4997	0,9043
F4	0,6326	0,4617	0,8425

CONCLUSION

Ketoprofen patch preparations can be created by using solvent evaporation method that, in general, produce a patch preparations as yellowish film coating. Formula that gave highest percent permeation was formula containing 1% chitosan and 0.3% tween 80 with percent permeation for 24 h reached 99.15%. Ketoprofen percent permeation from patch preparations was affected by variations concentration of chitosan matrix. The higher concentration of chitosan used as matrix, then the release of ketoprofen become stunted.

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