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Formulation and Physicochemical Evaluation of Theophylline Nanoparticles Transdermal Patch

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Abstract

The objectives of this research were to formulate theophylline nanoparticles matrix transdermal patch with different ratios of hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) polymers with ratio 90%:10% (F1), 80%:20% (F2), 70%:30% (F3), 60%:40% (F4), and 50%:50% (F5), and to evaluate the physicochemical characteristic of the resulted matrix patch. Preparation of matrix patch was conducted by the solvent evaporation casting method. Physicochemical characteristics of the patch, including physical appearance, weight uniformity, thickness uniformity, pH, moisture content, tensile strength, and profile release, were evaluated. Permeation of drugs into the skin was assessed using a modified Franz diffusion cell. Observations of the physical appearance showed that matrix patches were transparent, smooth, and dry. Weight uniformity ranges were from 0.69 g to 0.77 g with thickness 0.14 mm to 0.22 mm. Moisture content ranges were 0.49% to 2.14%, and pH values were from 5.0 to 6.0. Tensile strength ranged between 1.19 and 3.41 N/mm^2. Theophylline release of F1-F5 formulation was varied from 14.46% to 18.62% at 360 minutes, and all patches were capable of permeating through the rat skin membrane. Physicochemical evaluation of matrix patches showed that all patches fulfil the requirements of acceptable patches for transdermal administration.

Keywords: Formulation; theophylline nanoparticles; matrix transdermal patch; physicochemical evaluation.

1. Introduction

Theophylline is a methylxanthine derivative that has been used in the treatment of asthma. However, the oral route of theophylline is not completely satisfactory because of bitter taste and side effects, nausea and vomiting due to an increase in gastric acid secretion, which causes an uncomfortable feeling and poor intestinal absorption of theophylline. Additionally, theophylline has a relatively short half-life and a narrow therapeutic index of 10-15 µg/ml [1]. A transdermal drug delivery system may be an alternative to address these problems.

Transdermal drug delivery is applied for delivering drugs to the systemic circulation through the skin. Transdermal drug delivery system is an alternative route of administration of systematically acting drugs since this route of administration has the advantage of avoiding the first-pass metabolism, minimizing the side effects, and improving the physiological and pharmacological response of the drugs and most importantly, it gives patient compliance [2]. Transdermal has advantages over the conventional route, notably reduction of side effects and avoidance of the first-pass metabolism. The drugs can be delivered at a predetermined rate and maintain therapeutic drug concentration for a prolonged time [3][4].

The use of transdermal patches has been limited because only a few drugs can penetrate through the skin due to impermeability. The nanoparticles is one of the methods tried to enhance penetration of the drug through the skin.

The nanoparticles are a promising carrier to improve the bioavailability of biomolecules as they can diffusion and better penetration [5]. Particle size reduction can enhance penetration into the skin's stratum corneum [6]. The nanoparticles can be used to improve the therapeutic efficiency of the drugs. As nanoparticles can be used as a vehicle in drug transportation, this technique may be helpful in the targeted drug delivery system [7]. One of the methods to prepare nanoparticles uses natural polymers, such as chitosan. The ionic gelation technique can prepare chitosan nanoparticles [9]. In previous work, curcumin

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nanoparticles were formulated by the ionic gelation technique. Theophylline nanoparticles were developed using biodegradable and biocompatible polymers, chitosan and tripolyphosphates, as polyanion [9].

Because oral delivery of theophylline has limitations, a new method is urgently needed for the delivery of theophylline. Therefore, we developed and characterized a transdermal patch containing theophylline nanoparticles to provide an alternative method for theophylline formulation.

2. Materials and Methods

Theophylline (Intraco®), chitosan with corresponding viscosity average MW (Mv) of $3.05x10^5$ Dalton, was obtained from Physical Chemistry Laboratory, Faculty of Math and Science, Halu Oleo University. The molecular weight (MW) of chitosan was determined using the Mark Houwink equation. Tripolyphosphate (TPP) (Brataco®), acetic acid solution (Intraco®), Hydroxypropyl methylcellulose (HPMC) (Shinetsu, Japan), Ethyl Cellulose (EC) N10 (Hercules), Polyethylene glycol 400 (PG) (Merck), Ethanol 96% (Intraco®), Chloroform (Merck), dichloromethane (Sigma-Aldrich), menthol, distilled water, were obtained from the laboratory of pharmacy, Faculty of Pharmacy, Halu Oleo University.

2.1. Nanoparticles Preparation

Chitosan was dissolved in an acetic acid solution at concentration of 0.04% w/v and theophylline was dissolved in hot distilled water at concentration of 0.02 % w/v. Tripolyphosphate (TPP) was dissolved in distilled water at concentration of 0.02 % w/v. Theophylline nanoparticles were then prepared using the ionic gelation method. About 3 mL of theophylline solution was added to chitosan solution and stirred at 1250 rpm for 5 minutes. 3 mL of TPP solution was added to this mixture and then re-stirred for 5 minutes [8]. Nanoparticles were then frozen dry and characterized (Figure 1).

Figure 1. Freeze-dried theophylline nanoparticles

2.2. Nanoparticles Characterizations

2.2.1. Entrapment Efficiency

The nanoparticles solution was centrifuged (Boeco Sentrifuge S-8, Germany) at 6000 rpm for 45 minutes. The clear supernatant solution was measured by a Double Beam UV-Vis spectrophotometer (Jenway, UK) at 270 nm. The percentage of theophylline entrapment efficiency was calculated using the following equation [10]:

Entrapment efficiency (%) =

$$\frac{\text{Total theophylline weight-free theophylline weight}}{\text{total theophylline weight}} \text{ x } 100\%$$

2.2.2. Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR spectra of chitosan and theophylline nanoparticles were obtained on FTIR Jasco-4200 type A (Deutschland). The samples were placed on a sodium chloride window. The spectra were scanned on wave numbers 4000 to 400 cm^{-1}.

2.2.3. Transmission Electron Microscope (TEM)

Theophylline nanoparticles morphology and size were observed using Transmission Electron Microscope (TEM). A drop of theophylline nanoparticles was placed over the carbon coater (JOEL JEC-560, Japan) and allowed to air dry for 24 hours at room temperature. Once the nanoparticles samples dried, they were coated again with carbon before being loaded in the microscope. The image was visualized at 40,000x magnification and 120kv. The diameter of particles was measured using the Image J program.

2.2.4. Particles Size and Zeta Potential

Particle size and zeta potential of theophylline nanoparticles were determined using nanoparticles analyzer Horiba scientific nanopartica SZ-100 (Japan). The sample was analyzed, and the process parameters were set as scattering angle 90, the temperature of 24.8°C, and viscosity of 0.898 mPa.s.

2.2.5. Matrix Patch Formulation

A drug-loaded matrix nanoparticles theophylline transdermal patch was formulated using the solvent evaporation method [11]. Five formulas were prepared with the variation in concentration of polymers (HPMC and EC). Polyethylene glycol (PEG-400) was used as a plasticizer, and menthol was used as a permeation enhancer. Compositions of different formulations are shown in Table 1. HPMC was accurately weighed and dissolved in 15 mL of dichloromethane and ethanol (1:1) using a stirrer to form a clear solution. EC solution was made by dissolving EC in 2 mL of chloroform. EC solution was added to HPMC solution and then homogenized using stirrer for 5 minutes. To the prepared solution, polyethylene glycol (PEG-400) solution which was accurately weighed at 30% of total weigh of patch and menthol were added. Fifteen milligrams of theophylline nanoparticles were added to the solution and stirred for 5 minutes to form a dope solution. The resulted solution was poured to the plate and dried at

30°C in the hot air oven for 24 hours. After 24 hours, the dried matrix film was taken and placed into desiccators for further studies (Figure 2).

Table 1. Theophylline nanoparticles Patch's Formulation

Formulations	F1	F2	F3	F4	F5
Theophylline Nanoparticles (mg)	15	15	15	15	15
HPMC (mg)	450	400	350	300	250
EC (mg)	50	100	150	200	250
PEG (%)	30	30	30	30	30
Menthol (%)	5	5	5	5	5

2.3. Physicochemical Evaluation

2.3.1. Organoleptic

All the prepared patches were evaluated for physical appearance, including texture, color, odor, and consistency.

2.3.2. Weight Uniformity

For each formula, each of the three patches was weighed, and the average weight was calculated [4].

2.3.3. Thickness

The thickness uniformity of the patch was evaluated using a digital micrometer at three different points of the patch. The average thickness of the three points was calculated [12].

2.3.4. pH

The pH of the patch was measured using a universal pH indicator. A strip of film (1 x 1) cm were cut and immersed in 1 ml of water for 2 hours at room temperature. A universal pH indicator was then placed on the surface of the patch for 1 minute, and pH was measured [13].

2.3.5. Moisture Content

The prepared patches were weighed one by one and then kept in desiccators containing silica gels for 24 hours at room temperature. The patches were then reweighed, and the percentage of moisture content was calculated using the formula [13].

% moisture content = (Initial weight – final weight)/(Initial weight) x 100%

2.3.6. Tensile Strength

The tensile strength of the patch was measured using a tensile tester (Shimadzu Autograph AG-X, Japan), which consists of two load cell grips. The lower one was fixed, and the upper one was movable. The test film of size (4 × 1) cm^2 was placed between these cell grips, and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows [4].

Tensile strength = (Tensile load at break)/(Cross-section area)

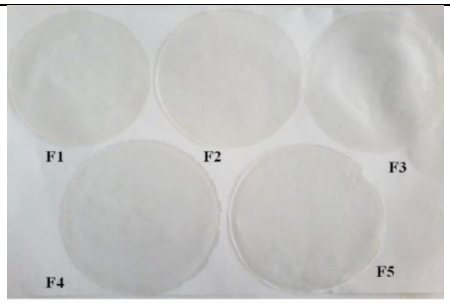

Figure 2. Matrix patches of theophylline nanoparticles with various ratios of HPMC and EC; 450:50 (F1), 400:100 (F2), 350:150 (F3), 300:200 (F4) and 250:250 (F5)

2.3.7. Drug Release Study

A dissolution tester (Erweka DT 820, Germany) was used to evaluate theophylline release from patches. Paddle over disk method was used. Phosphate buffered saline (PBS; 500 mL, pH; 7.4) was used as receptor fluid. The matrix patch was placed in an aluminum disk. The receptor fluid was agitated at 50 rpm. The temperature of the receptor fluid was maintained at 37±0.5°C during drug release evaluation. Five milliliters of samples were collected at minutes 0, 5, 10, 15, 20, 30, 60, 120, 240, 360 and were replaced with fresh receptor fluid in equal volume. Theophylline was determined by using spectrophotometer UV VIS at λ 270 nm (Jenway, UK). The test was carried out in triplicate.

2.3.8. In-Vitro Skin Permeation Study

In vitro skin permeation studies used Wistar rat skin were performed using a modified Franz diffusion cell. Ethical approval for handling animal experiments was obtained from The Ethical Committee Research LPPM UHO. The approval number was 1922/UN29.10/PPM/2017. The male Wistar rat skin was excised. The hair and fat were removed. The clean skin was set up in a Franz diffusion cell between the donor and receptor compartment (Binarjo and Nugroho, 2019). Fifty milliliters of Phosphate buffered saline pH 7.4 was used as a diffusion medium. The temperature of the medium was maintained at 37 ± 0.5 °C. The patches were placed between the donor and receptor compartment, facing the matrix to the skin. The donor and receptor compartment was held together with a clip with a firm grip. The diffusion medium

was stirred magnetically to maintain the distribution of the drug. Three milliliters of the sample were withdrawn in an interval of time and replaced with the same volume of fresh medium. The permeated drugs were analyzed by spectrophotometer UV VIS (Jenway, UK) at λ 270 nm.

3. Result and Discussion

In the preparation of theophylline nanoparticles, ionic gelation technique was used. In this study, theophylline nanoparticles were developed by using biodegradable polymer chitosan and tripolyphosphate as polyanion [9]. The principal of ionic gelation technique is interaction between chitosan and polyanion. The NH_2 group of chitosan was protonated in acid conditions and became NH^{3+}. Sodium tripolyphosphate dissolved in water yielding phosphoric ions [14]. The NH^{3+} sites interacted with oxygen atoms from polyanion (TPP) and formed nanoparticles spontaneously[9]. Theophylline became entrapped in nanoparticles. pH plays an essential role in forming cross-linked chitosan nanoparticles [14].

We observed satisfactory entrapment efficiency which was affected by the ratio of chitosan/TPP. The entrapment efficiency of theophylline in nanoparticles was range 75-78%. The entrapment of theophylline into nanoparticles was caused by the form of cross-linking between chitosan and tripolyphosphate as polyanion [9]. The more formation of cross-linking resulting in the stronger the matrix of nanoparticles increases the entrapment efficiency of nanoparticles. Previous research showed that the encapsulation efficiency decreased as the chitosan-TPP mass ratio increased [16].

From the observed FTIR spectra of theophylline nanoparticles on Figure 3, we conclude that theophylline nanoparticles consist of chitosan, TPP, and theophylline. The peak around 3390 cm^{-1}showed the O-H group, while the peak around 3900 cm^{-1} showed C-H streching (aromatic). This data confirmed the presence of chitosan in theophylline nanoparticles. The C=O streching group showed the peak at 1700 cm^{-1} in chitosan spectra and becoming sharper in theophylline nanoparticles spectra provided adequate proof of the presence of theophylline in nanoparticles. The peak around 1100 cm^{-1} confirmed the presence of tripolyphosphate (TPP).

According to the Transmission Electron Microscope image, the shape of theophylline nanoparticles was spherical with an unsmooth surface (Figure 4). The diameter of the particle on the photograph was 57.04 nm.

The average size of the particle was 367.2±105,1 nm, and the zeta potential value was +15.5 mV. The polydispersity index (PI) of theophylline nanoparticles was 0.415 (Figures 5 and 6).

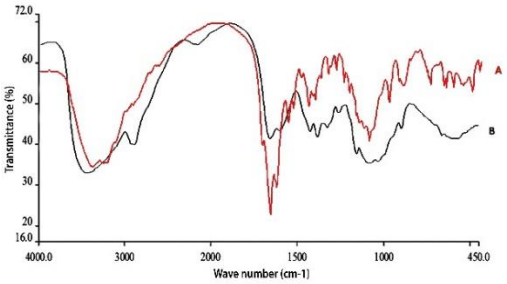

Figure 3.Spectras of chitosan (A), theophylline nanoparticles (B)

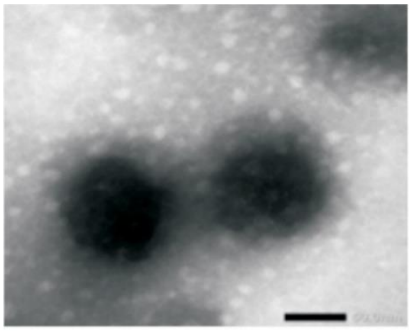

Figure 4. Morphology of theophylline nanoparticles

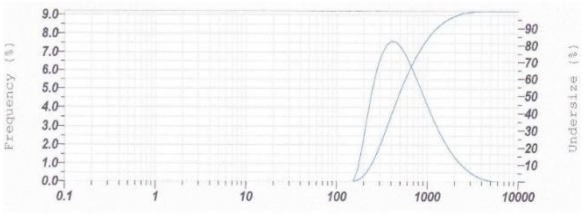

Figure 5.Distribution of particle size

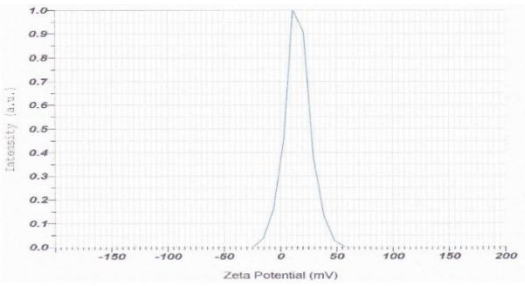

Figure 6. Zeta potential value of theophylline nanoparticles

The results of the physicochemical evaluation matrix transdermal patch are shown in Table 2, including weight, thickness, pH, percentage moisture content, tensile strength, and percentage elongation. The transdermal patches were dry, smooth, and transparent. All patches had a characteristic odor of menthol.

The theophylline release from patches was studied in vitro condition by using a dissolution tester. Theophylline release of F1-F5 formulation was varied from 14.46% to 18.62% at 360 minutes. Figure 7 shows that theophylline release of F2 formulation was higher than other formulas.

The evaluation result of in vitro skin permeation studies are shown in Figure 8, and the calculated flux values are tabulated in Table 3. The graph shows that the cumulative drug permeation increases as time increases.

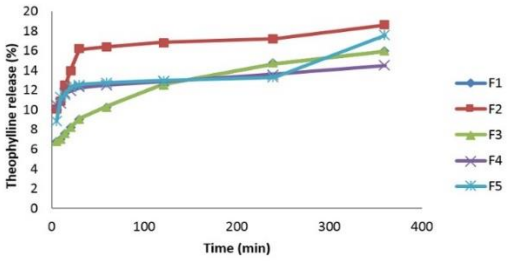

Figure 7. Profile of theophylline dissolution from matrix transdermal patches with various ratios of HPMC and EC; 450:50 (F1), 400:100 (F2), 350:150 (F3), 300:200 (F4) and 250:250 (F5)

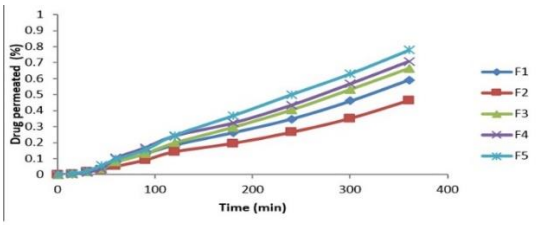

Figure 8. In vitro skin permeation studies with various ratios of HPMC and EC; 450:50 (F1), 400:100 (F2), 350:150 (F3), 300:200 (F4) and 250:250 (F5)

According to results from a previous study [17], the mean size of zeta potential value has depended on the molecular weight of chitosan. The lower the molecular weight of chitosan, the smaller the size of the chitosan nanoparticles and the higher the zeta potential were observed. In other research [16], the chitosan-TPP ratio has also been shown to affect nanoparticle size and distribution. The particle size exhibited a negative relationship with the chitosan-TPP ratio. Besides, chitosan-TPP nanoparticles were mainly characterized by positive zeta potential. A polydispersity index (PI) was used to indicate the size distribution of nanoparticles. The higher the PI value gets, the higher the size distribution of nanoparticles. A PI value higher than 0.5 tends to form aggregate nanoparticles [18]. The polydispersity index (PI) for theophylline nanoparticles indicates an acceptable particle size distribution (< 0.5) and more than 0.1 [17].

Table 2. Physicochemical Properties of Transdermal Patchs

Formulation Code	Weight (g)	Thickness (mm)	pH	Moisture content (%)	Tensile strength (N/mm^2)	Elongation (%)
F1	0.7716 ± 0.0025	0.1733 ± 0.012	6 ± 0.000	2.149 ± 0.45	1.57	180
F2	0.7322 ± 0.006	0.2200 ± 0.000	6 ± 0.000	1.947 ± 0.68	3.41	180
F3	0.7053 ± 0.004	0.1400 ± 0.000	5.33 ± 0.0577	1.651 ± 0.90	2.86	160
F4	0.7041 ± 0.009	0.1767 ± 0.006	5.33 ± 0.0577	0.583 ± 0.21	2.12	180
F5	0.6931 ± 0.008	0.2133 ± 0.006	5 ± 0.000	0.494 ± 0.15	1.19	200

Two polymers were combined to prepare matrix transdermal patches to control transdermal patches drug release and mechanical characteristics [19]. Hydroxypropyl methylcellulose (HPMC) is a hydrophilic polymer widely used to form matrix patches. Ethylcellulose (EC) is a hydrophobic polymer. HPMC and EC are commonly-used polymers compatible with several drugs [20].

Table 3. Flux Values of Transdermal Patches

Formulation Code	Flux value ($\mu g/cm^2$)
F1	6.003
F2	4.643
F3	6.879
F4	7.303
F5	8.140

Similar weights indicate the uniformity of matrix patches. An increase in HPMC indicates an increase in the weight of the matrix patch due to HPMC's capability to absorb moisture from the environment [21]. The low standard deviation of thickness value ensured uniformity of the patches and observed pH values occurring within the range of normal skin pH values. Moisture loss from the patches increased with increasing the concentration of hydrophilic polymers [20]. As the concentration of hydrophilic polymer increased, there was also an increase in tensile strength. The elasticity of the matrix transdermal patch was performed by percentage elongation, which indicated that matrix transdermal patches have high elasticity.

In vitro permeation studies were conducted using Franz Diffusion Cell Apparatus (Figure 8). The theophylline permeated at 6 h from all patches for F1, F2, F3, F4 and F5 were 0.591, 0.462, 0.664, 0.706, 0.777 %, respectively. These data show that all patches

successfully release the drug (Theophylline) and permeate through the rat skin membrane. All patches containing theophylline nanoparticles which consist of tripolyphosphate (TPP) and chitosan, may affect the stratum corneum and reduce the diffusional barrier by acting as a permeation enhancer. The permeation rate of theophylline nanoparticles is shown in Table 3 as flux value. The flux value ranged from 4.643 to 8.140 $\mu g/cm^2$.

The permeation rate of the patches might attribute to several factors. Firstly, the concentration of theophylline in nanoparticles resulted in a high concentration gradient, which might be the primary permeation mechanism of theophylline through the skin from these nanoparticles. Secondly, due to small particle size, some particles may settle down to close contact with the skin. The use of chitosan also affects the permeation rate. Chitosan acts as a penetration enhancer by opening the tight junction of the epithelium. Chitosan facilitates both paracellular and transcellular transport of drugs [22].

4. Conclusion

We successfully developed a new formulation of transdermal patches using theophylline nanoparticles as the active agent. These patches potentially alleviate the need for oral delivery of theophylline in treating asthma, which has some limitations, including a bitter taste. The use of a transdermal patch may encourage people with asthma to take medication more regularly. Future research should evaluate the capacity for penetration of theophylline through the skin via the transdermal route in vivo.

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