ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 11, Issue 8, 2018

Online - 2455-3891
Print - 0974-2441

Research Article

FORMULATION AND EVALUATION OF *IN VITRO* TRANSDERMAL PATCH DICLOFENAC SODIUM USING CHITOSAN POLYMER AND POLYVINYL ALCOHOL CROSS-LINKED TRIPOLYPHOSPHATE SODIUM

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Received: 06 February 2018, Revised and Accepted: 24 April 2018

ABSTRACT

Objective: The aim of this study was to investigate diclofenac sodium patches using chitosan (Ch) and polyvinyl (PVA) alcohol cross-linked tripolyphosphate sodium (TPP) to increased transdermal permeation of the drug from the matrix system across rabbit skin.

Materials and Methods: The chemical characterization of diclofenac sodium was done by ultraviolet-visible spectrophotometry. Formulation of diclofenac sodium patches using solvent evaporation method with cross-link technique. Evaluation of physical character of the film includes organoleptic observation, weight test, thickness, % moisture absorption, fold resistance, interaction between materials used Fourier transform infrared (FTIR), and active substance levels. The drug release was determined using Franz diffusion cells in phosphate buffer (pH 7.4).

Results: The result of physiochemical parameters of the transdermal patch were found satisfactory. Formula F1, F2, F3, and F4 produce patches with fine texture, F5 and F6 formulas produce patches with coarse texture. Formula F1, F2, F5, and F6 are flexible and fulfill the multiplier test requirements, while the F3 and F4 formulas are not flexible and do not meet the multiplier test requirements. The patch weight, thickness, and drug content were uniform. The release of patches with following the zero-order release. The optimal formula with the total sodium diclofenac released as much as 17.89 µg, the release flux of 89.42 µg/cm^2/h of permeation time of 10 h and the moisture absorption rate of 1.07±0.193. The FTIR data of rabbit skin indicated Ch and PVA alcohol cross-linked TPP increase transdermal permeation of diclofenac sodium in the stratum corneum.

Conclusion: The diclofenac sodium can be prepared by cross-linked method, resulted in a better discharge profile.

Key words: Diclofenac sodium, Chitosan, Polyvinyl alcohol, Tripolyphosphate sodium, Glycerin, Release kinetics.

 DOI: http://dx.doi.org/10.22159/ajpcr.2018.v11i8.25145

INTRODUCTION

The transdermal patch is designed to be able to deliver the drug in a controlled manner directly to the blood vessels [1]. The transdermal advantages such as to avoid absorption problem in the gastrointestinal tract, prevent the first cross effect, may be the choice for drugs not to be orally administered, may control the drug [29]. Transdermal can be formulated in ointment, cream, gel emulsion, and patch form [5]. The controlled delivery of drugs in the blood vessels can be achieved through the matrix system [36]. The basic components of the matrix system consist of polymers [7], drugs, enhancers, and other excipients [34]. Variations of polymer compositions, enhancers, and plasticizers will result in different release and permeation profiles [37]. The polymer in the matrix system will control the release rate of the drug from the patch matrix [3].

This study used diclofenac sodium as a test model of *in vitro* release and permeation using rabbit skin [33]. Diclofenac sodium includes non-steroidal anti-inflammatory drugs that act by inhibiting cyclooxygenase in a non-selective manner, resulting in inhibition of prostaglandin synthesis, which is a pain mediator [2]. The diclofenac sodium has a half-life of 1–2 h so that it is orally administered in a few times, leading to adverse side effects on the stomach and reducing patient compliance [4]. Stratum corneum is a limiting factor in the speed of percutaneous drug taking [23]. The diclofenac sodium has a fairly high lipophilicity with a low partition coefficient value, octanol/water log P at 25°C that is 4.17 causing low diclofenac sodium permeability [46].

This study used chitosan (Ch) polymer excipients, tripolyphosphate sodium (TPP), alcohol polyvinyl (PVA), and glycerol plasticizer [35]. Ch is widely used because it has the characteristics of biocompatibility, non-toxic, and antimicrobial [13]. Ch and alcohol PVA that are hydrophilic will increase patch permeability and drug diffusion [12,32]. Ch with alcohol PVA produces cross-linking hydrogels with good swelling activity. The combination of Ch and alcohol PVA anhydrous maleic cross-links by alprazolam model resulted in patches with physical characteristics, permeability, and release profiles [29]. Penetration test of Ch cross-linked tripolyphosphate sodium (TPP) with diclofenac diethylamine model showed 30-min cross-link time yielding the best permeation through mouse skin membrane [39]. The combination of Ch and alcohol PVA cross-linked tripolyphosphate sodium using bovine serum albumin produced a controlled release film that could be characterized by Fourier transform infrared spectroscopy (FTIR), scanning electron microscope (SEM), and release test. Studies on the use of glycerin plasticizer using Ch - alcohol PVA polymer resulted in a controlled patch [52].

MATERIALS AND METHODS

Materials

Chemicals

The materials used in this study were diclofenac sodium (Kimia Farma, Indonesia), PVA alcohol, TPP, Ch, glycerin, acetic acid, hydrogen phosphate sodium, bromide potassium, and chloride potassium (Merck).

Animals

Adult male New Zealand albino rabbits (1.5–2 kg) were supplied by the Animal House of Pharmacology, Laboratory of Pharmacy Department at Universitas Sumatera Utara was inhabited under standard laboratory condition with proper diet. The animal were accepted after the proposed

study was approved by the Animal Research Ethics Committees (Komite Etik Penelitian Hewan FMIPA, Universitas Sumatera Utara), Government of Indonesia bearing the number 530/KEPH-FMIPA/2017.

Methods

Procedure for preparation patch of natrium diclofenac

The transdermal patch of diclofenac sodium is prepared by solvent evaporation technique, using a combination of Ch-PVA-TPP polymer and glycerine plasticizer [27]. The formula prepared by mixing an 8% PVA solution and 2% Ch with ratio that has been determined, adding a diclofenac sodium and glycerin solution, stirring with a magnetic stirrer until a composite film is formed, the film is cast into the mold, then dried in a 40°C oven for 48 h. To make the cross-linked film membrane formed soaked in 1% sodium tripolyphosphate solution with time 10 and 20 min, the film was then dried in a 40°C oven for 24 h. The finished film is transferred to plaster [26].

Transdermal patch formulation

The composition of transdermal patch formulation can be seen on Table 1.

Evaluation of transdermal patch characteristics

Physical appearance

The quality of transdermal patches can be physically evaluated for color, clarity, and texture of the surface.[11,21,44]

Uniformity of weight

The test of matrix weight of each formula is done by weighing the matrix of each formula, then calculated the average weight [14].

Thickness uniformity

The thick patch measurements employed a slider and were performed on three different sides of the matrix on each matrix patch formulas [14].

Percentage moisture uptake

The weighed patch is then inserted in the desiccator at 30°C for 24 h. Furthermore, the patch is taken out from the desiccator and weighed again. Percent of moisture absorption is calculated using the following formula % power [11].

Folding endurance

This test is performed to determine the elasticity and fragility of transdermal patches [7]. Testing of resistance to folding is done by folding the patch repeatedly in the same position until the patch is broken. The number of folds is considered to be the value of resistance to folding [11].

Observation of patch morphology

Ch - PVA-TPP solution containing diclofenac sodium is disonified for 1 min to produce a good particle disperse [32]. One drop of the solution is dispersed into carbon-coated copper gird which is then dried at room temperature for SEM photography analysis. The SEM-5800 LV instrument was used to study the surface morphology of the diclofenac sodium patches with high vacuum and a high voltage of 15.00 kv condition [31].

Examination with FTIR [45]

The diclofenac sodium patch is made in the form of a KBr pellet. How, matrix patch containing diclofenac sodium and without diclofenac sodium mixed with 10 mg KBr in the mortar, then crushed to homogeneous [44]. The mixture is forged with hydraulic pressure so that a transparent disc is obtained. The spectrum was measured using IR spectroscopy at a wavelength of 400–4000 cm^{-1} [43].

Rabbit skin preparation and *in vitro* permeation study

Permeation study [21]

Preparation of standard solution

100 mg diclofenac sodium was weighed, then put into a 100 ml flask, then dissolved in phosphate buffer pH 7.4 to 100 ml with sonification aid obtained 1000 µg/ml standard solution (LIB I). Standard standard solution of 1000 µg/ml 10 ml dipipet then put 100 ml papier flask added phosphate buffer solution pH 7.4 to 100 ml so obtained 100 µg/ml concentration (LIB II). The solutions were aspirated by pipette, respectively, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 ml were then inserted into the flask 10 ml and inserted phosphate buffer to obtain concentration 2–20 µg/ml. The absorption is measured at the maximum wavelength obtained.

Drug content uniformity

The 1.5 cm film was cut into small pieces, then put into a 100 ml buffer (pH 7,4) and shaken with a magnetic bar for 5 h then it was ultrasonified for 15 min then filtration. The result of filtration measured the content of active substance with spectrophotometer at λ 228 nm [14].

Preparation phosphate-buffered saline (PBS) solution

PBS solution was made from KCl of 0.1 g, KH2PO4 of 0.1 g, NaCl of 4 g, and $Na_2HPO_4.H_2O$ of 1.08 g. The materials were dissolved in 250 ml of CO_2-free distilled water and homogenized using a magnetic stirrer in a 500 ml glass. The pH of the solution is adjusted to reach 7.4 with 1 M NaOH solution using pH meter. The solution was then transferred to a 500 ml measuring flask and a CO_2-free aquadest was added to the limit marker.

Rabbit skin preparation

Rabbits used in the study were male rabbits weighing 1.5–2 kg. Rabbits are sacrificed with diethyl ether, and then, the hair on the skin of the back is cut with a shaver without damaging the stratum corneum layer. The rabbit's skin is separated; the fatty layers still attached are removed and then circled in accordance with the size of the diffusion cell. The skin used was measured in thickness, and before use, it was immersed in phosphate buffer pH 7.4 for 1 h and stored at 4°C. Leather can be used within 24 h.

Preparation of sample solution

The transport test was carried out using a modified vertical type Franz diffusion cell. The donor portion contains a transdermal patch of diclofenac sodium [6]. The donor and acceptor compartment separator membrane is the rabbit's skin. The membrane is placed between the donor compartment and the acceptor compartment with the dermis side facing the acceptor compartment. The acceptor compartment contains a PBS of pH 6.8 of 15 mL and stirred with a continuous magnetic stirrer at 37±1°C. The observation was conducted for 24 h and the samples were taken at hour to 1, 2, 4, 6, 8, 10, 12, and 24 every 1 mL sampling was done by adding phosphate buffer pH 6.8 as much as 1 mL. Samples were stored in closed flaccon containers and diclofenac sodium content was determined by ultraviolet-visible spectrometric instrument and determined drug release kinetics [14,16].

RESULTS AND DISCUSSION

Evaluation of transdermal patches

The observed results of various physicochemical parameter of diclofenac sodium transdermal patches are shown in Table 2. The values of weight, thickness, and drug content were found to be uniform having an almost low value of standard deviation [8]. The result of evaluation of folding endurance was indicated F1, F2, F5, and F6 patch were the ability to withstand rupture and qualified the multiplier test.

Scanning electron microscope

The homogeneity of patch surface was determined using scanning electron microscope [53]. The cross-linked produced a smooth patch with different levels of density and homogeneity. The result of evaluation of patch morphology can be seen at Fig. 1.

Drug excipient compatibility study

FTIR spectroscopy

The diclofenac sodium spectrum shows the spectral peaks in regions 3402.43 and 3248.13 cm^{-1} in the presence of the NH group, as can be seen in Fig. 2 and Table 3 A Ch spectrum, producing a peak spectrum at

Table 1: The composition of the diclofenac sodium patch

Formula	Cross-linked time	Glycerin (%)	TPP (%)	Ch-PVA (2 and 8%)	Diclofenac sodium (mg)
F1	10	5	1	30:70	20
F2	20	5	1	30:70	20
F3	10	5	1	50:50	20
F4	20	5	1	50:50	20
F5	10	5	1	70:30	20
F6	20	5	1	7030	20

TPP: Tripolyphosphate sodium, Ch: Chitosan, PVA: Polyvinyl

Table 2: Drug content and physical parameters of different formulation of patch

Formulation code	Uniformity of weight (mg)	Film thickness (mm)	Folding endurance	% Drug content
F1	172±0.574	0.253±0.0010	631	95.08±0.626
F2	177±0.812	0.262±0.0066	631	96.37±0.102
F3	184±0.812	0.274±0.0014	8	97.54±0.376
F4	181±1.000	0.266±0.0016	8	95.74±0.359
F5	184±0.812	0.266±0.0016	724	97.54±0.376
F6	185±1.153	0.267±0.0010	722	97.46±0.343

Table 3: *In vitro* cumulative percentage of diclofenac sodium release

No	Time	F1	F2	F3	F4	F5	F6
1	10	4.99	3.53	4.25	1.17	5.42	1.48
2	20	10.11	7.58	10.49	2.4	11.43	3.16
3	30	15.52	12.21	15.63	5.31	17.7	5.96
4	60	21.83	17.22	21.9	8.2	24.57	7.51
5	120	27.72	23.46	28.73	11.31	31.81	10.09
6	180	34.6	30.37	35.97	14.78	39.3	12.9
7	240	42.27	37.82	43.78	18.2	47.07	16.34
8	300	50.35	45.62	52.23	21.21	55.47	19.11
9	360	58.81	54.06	62.82	23.1	64.01	22.89
10	420	68.12	63.97	70.22	25.68	73.24	26.93
11	480	77.62	74.88	77.99	28.69	82.64	31.13
12	540	85.94	84.24	87.91	30.15	91.8	34.36
13	600	94.07	92.82	95.76	32.69	99.81	37.24

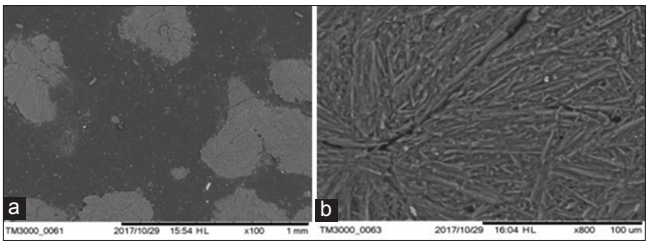

Fig. 1: The morphology of patch sodium natrium diclofenac at ×100 (a) and ×800 (b)

3437.15/cm in the presence of the NH_2 and OH groups in the 1600.92/cm, 1666.50/cm region in the presence of C=0.

Observation of FTIR PVA shows peak spectrum at 3375.43/cm region with the presence of OH group. FTIR observations of TPP showed peak spectrum at 3430.03/cm, 3383.14/cm, 3217.27/cm, and 1157.29/cm. Ch interaction TPP resulted in a shift of absorption peak at 1549.02/cm, 1481.33/cm, and 1134/cm. Peak at 3549.02/cm indicated no interaction between sodium diclofenac and the excipient polymer.

Permeation study

All the six formulations were subjected to *in vitro* permeation studies across rabbit skin for establishing the permeation parameters [15,19]. The results of permeation study were shown on Table 3 and Fig. 3. According to the penetration test, cumulative value of penetrated sodium diclofenac was found highest in F5 (cumulative % 99.81 time

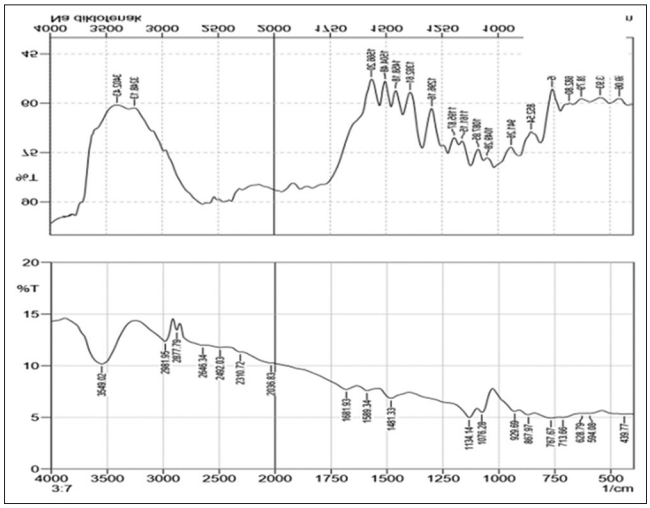

Fig. 2: Infrared spectra of pure of sodium diclofenac and patch sodium diclofenac

10 h), followed by F3, F1, and F2. Cumulative value of penetrated sodium diclofenac was found lowest in F6 and F4 with cross-linked time 20 min. The release of patches with formulas was following zero-order release (Table 4). Permeation study was showed F1, F3, and F5 with cross-linked time 10 min has bigger % cumulative and better release than F2, F4, and F6 with cross-linked time 20 min.

CONCLUSION

In the present study, various formulation of transdermal sodium diclofenac patches were prepared using cross-linked method of Ch polymer, polyvinyl alcohol, and tripolyphosphate sodium. This research showed that the formulation of transdermal diclofenac sodium patches using cross-linked method with cross-linked time of 10 min has better profile release than cross-linked time of 20 min. Formulation of transdermal sodium diclofenac patches using cross-linked method needed optimal drying to make good characteristic and profile release.

AUTHOR'S CONTRIBUTION

The first author has carried out the research and provided study conception. The second and third authors have provided study conception, the design of work, drafting of the manuscript, and critical revision.

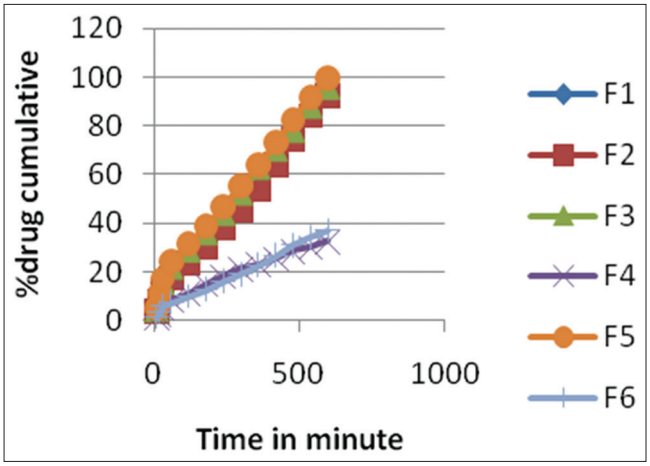

Fig. 3: In vitro profile permeation of various patches

Table 4: R^2 value from of zero order, Higuchi and Korsmeyer plot

	F1	F2	F3	F4	F5	F6
Orde nol	0.994	0.994	0.993	0.973	0.991	0.994
Korsmeyer–Peppas	0.982	0.982	0.977	0.973	0.979	0.974
Higuchi	0.965	0.95	0.971	0.996	0.973	0.959

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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