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Research Article

Preparation and Characterization of Maleic Anhydride Cross-Linked Chitosan-Polyvinyl Alcohol Hydrogel Matrix Transdermal Patch

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Abstract

Transdermal drug delivery systems are polymeric patches containing dissolved or dispersed drugs that deliver therapeutic agents at a constant rate to the human body. Matrix type transdermal patches were prepared using alprazolam as a model drug and employing the combinations of chitosan-polyvinyl alcohol (CS-PVA) cross linked with Maleic anhydride. The transdermal patches were evaluated for their physicochemical properties like thickness, tensile strength, folding endurance, drug content, swellability, surface pH, water vapour transmission, in vitro permeation and skin irritation studies. FTIR study indicated no interaction between drug and polymers. The permeability of alprazolam was increased with increase in PVA content. The in vitro drug permeation followed Higuchi kinetics as its coefficient of correlation value predominates over zero order and first order kinetics. Also the diffusion coefficient of release profiles had a value of nearly 0.5, which indicated Fickian transport diffusion. The patches were found to be free of any skin irritation.

Keywords: Transdermal patches, alprazolam, polyvinyl alcohol, in-vitro skin permeation

Introduction

Transdermal drug delivery system (TDDS) has been used for the drug administration via the skin for both local therapeutic effects as well as for systemic delivery. The skin as a site of drug delivery has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy, provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with injections.[1] The present work is aimed at developing Maleic anhydride cross-linked chitosan-Poly vinyl alcohol(PVA) hydrogel matrix dispersion type transdermal drug delivery of alprozolam to ensure satisfactory drug release with the use of optimum polymer and prolong duration of action. Alprazolam, which is a highly potent short-acting drug of the benzodiazepine class, used here as a model drug. It is primarily used to treat moderate to severe anxiety disorders (e.g., Social anxiety disorder) and panic attacks, and is used as an adjunctive treatment for anxiety associated with moderate depression. Alprazolam possesses anxiolytic, sedative, hypnotic, , and muscle relaxant properties. Chitosan is used as a carrier material for drug delivery because of its biodegradable and nontoxic in nature.[2] It is a linear polysaccharide composed of α-1,4-linked 2 - amino- 2-deoxy- α- D-glucose (N-acetyl glucosamine). It is obtained from the N-deacetylation of chitin with a strong alkali.[3-4] Generally PVA hydrogels are excellent candidates for biomaterials as they exhibit a high degree of swelling in water, a rubbery elastic nature are non-toxic, non-carcinogenic and can be readily accepted in the body.[5-6]

Materials and Methods

Materials

Alprazolam was received as a gift sample from Drackt Pharmaceutical Pvt. Ltd., Gujarat, India. Chitosan was purchased from Everest Edward, Cochin, India. PVA was obtained from SD fine-Chem. Ltd., Mumbai, India. Polyethylene glycol 400 was obtained from Merck Specialities Private Ltd., Mumbai, India. Maleic anhydride was obtained from Loba chemie Pvt. Ltd., Mumbai, India. All other chemicals used were of analytical grade.

Preparation of transdermal patch

Matrix type transdermal patches composed of different concentrations of PVA, chitosan and drug were prepared by solvent evaporation method. A petridish with a total area of 44.15cm^2 was used. PVA were accurately weighed and dissolved in 10ml of hot water. Drug was dissolved in the above solution and mixed until clear solution was obtained. Chitosan solution added to the different formulation and blended well. Maleic anhydride solution added drop wise .Then the entire mixture stirred well for

30 min. Simultaneously 2 to 3 drops of concentrated sulphuric acid was added. Polyethylene glycol was used as plasticizer. The resulted uniform solution was cast on the petridish, which was lubricated with glycerin and dried at room temperature for 24h. An inverted funnel was placed over the petridish to prevent fast evaporation of the solvent. After 24h, the dried patches were taken out and stored in desiccators for further studies. The composition of transdermal patches is shown in Table 1.

Characterization of transdermal patches

Folding endurance

A strip of specific area (4 cm^2) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance.[7]

Moisture absorption study

The films were weighed accurately and placed in a desiccator containing 100 ml of saturated solution of aluminium chloride (75% RH). After 3 days, the films were taken out and weighed, the percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.[8]

Moisture content

The patches were weighed and kept in a desiccator containing calcium chloride at 40°C for 24h. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to initial weight.

Thickness

Patch thickness was measured using micrometer screw gauge at three different places of each patch and the mean value was calculated and reported.[9]

Tensile strength

The tensile strength of the patch was evaluated by using the tensiometer. It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 4 cm2 were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.[10]

Swellability

The patches of 2.5 cm^2 was weighed and put in a petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed.

The degree of swelling (S) was calculated using the formula

$$S(\%) = W_t - W_o / W_o \times 100$$

where S is percent swelling, W_t is the weight of patch at time t and W_o is the weight of patch at time zero.[11]

Surface pH

The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1h in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 min.[12]

Water vapor transmission

Water vapor transmission studies glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried to constant weight in an oven. Fused calcium chloride (1g) as a desiccant was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape. These pre-weighed vials were stored in a humidity chamber at an RH of 80% with the temperature set to 30ºC for a period of 24h. The weight gain was determined every hour up to a period of 24 h.

Water vapor transmission (Q) usually expressed as number of grams of moisture gain per 24h per square centimeter, was calculated using the equation[13]

$$Q = WL/S$$

where W is g of water transmitted /24 h; L is patch thickness in cm; S is surface area in square cm.

Fourier transform infrared (FT-IR) spectroscopy

Fourier transform infrared (FT-IR) spectrum was recorded on Perkin Elmer (USA) FT-IR spectrophotometer (Spectrum Rx-1). Sample were prepared as KBr pellet and scanned against a blank KBr pellet background at wave number range 4000-400cm^{-1}. The drug-excipient compatibility study was done by FT-IR analysis.

Drug entrapment efficiency

Specified area of patch (4 cm2) was dissolved in 100 ml saline phosphate buffer pH 7.4 and shaken continuously for 24h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometrically at wavelength of 221nm and determined the drug content.

Drug permeation study

Drug permeation study was carried out with saline phosphate buffer (pH 7.4) using Franz diffusion cells. The skin permeation study permission was obtained from Institutional Animal Ethics Committee. Full thickness abdominal skin of male Wister rat weighing 200 to 250g was used. Hair from the abdominal region was removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrate for an hour in saline phosphate buffer pH 7.4 The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. The whole assembly was kept on magnetic stirrer, which thermostatically controlled at 37°C at 50 rpm. Samples were withdrawn at pre set

time interval from the receiving compartment and analyzed at 221nm using UV-visible spectrophotometer (Spectronic, England, model-UV1). The fresh buffer in receiving compartment was replaced after each withdrawal. The permeation studies continued for period of 6 h and calculated as cumulative percent drug permeated (CAP %). Cumulative amounts of drug permeated [Q] in µg/cm^2 were calculated and plotted against time. Drug flux [J] (µg min^{-1}cm^{-2}) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface (2.54cm^2).[14]

Primary skin irritation test

Primary skin irritation and corrosion are evaluated most often by modification described by Draize and his colleagues in 1994, which is based on scoring method. Scores as assigned from 0 to 4 based on the severity of erythema or edema formation. The safety of the patch decreases with increase in scoring. The skin irritation study permission was obtained from Institutional Animal Ethics Committee. The hair on the dorsal side of Wister albino rats was removed 1day before the initiation of this study. The rats were divided into three groups. Group I served as the control, group II received transdermal patch, and group III received a 0.8 % (v/v) aqueous solution of formalin as a standard irritant. A new patch or new formalin was applied daily for 7 days. Finally the application sites were graded always by the same investigator.[15]

Table 1. Composition of transdermal patches

Formulation code	Drug (mg)	PVA (%w/v)	Chitosan (%w/v)	Maleic anhydride(%w/v)	Propylene glycol (%v/v)
F1	10	-	0.5	1.5	2
F2	10	2	0.5	1.5	2
F3	10	2.5	0.5	1.5	2
F4	10	3	0.5	1.5	2

Table 2. Physico-chemical evaluation of transdermal films of alprazolam

Code	Folding Endurance	Tensile Strength (kg cm^{-2})	Water vapour transmission (gm-cm/cm^2 24h)	Moisture content (%)
F1	211±0.31	2.64±0.76	3.82*10^{-4}	1.22±0.12
F2	209±0.44	2.75±0.66	4.21*10^{-4}	1.26±0.24
F3	209±0.86	2.87±0.54	4.67*10^{-4}	1.28±0.32
F4	212±0.73	2.98±0.89	5.12*10^{-4}	1.31±0.16

Table 3. Physico-chemical evaluation of transdermal films of alprazolam

Code	%moisture absorption	Thickness (mm)	Swellability (%)	Surface pH
F1	14.48±0.57	0.33±0.01	15.97±0.44	7.3± 0.14
F2	14.56±0.86	0.31±0.03	17.34±0.38	7.4±0.22
F3	15.59±0.64	0.32±0.01	18.78±0.52	7.4±0.08
F4	16.65±0.46	0.34±0.02	20.56±0.58	7.4±0.12

Table 4. Data of cumulative percentage of drug permeated, Q value, drug flux and percentage drug content of different formulations

Formulation code	Cumulative % of drug permeated after 6 h.	Q value ($\mu g/cm^2$)	Drug flux ($\mu g/cm^2/h$)	% drug content
F1	22.92	0.4052	0.00112	88.21
F2	38.39	0.7200	0.00200	91.11
F3	46.87	0.9350	0.00259	92.82
F4	54.02	1.0410	0.00289	93.36

Table 5. Various kinetic models for TDDS of alprazolam

Code	Zero order		First order		Higuchi model		Korsmeyer Model	
	R^2	K (mg h^{-1})	R^2	K (h^{-1})	R^2	K (mg $h^{-1/2}$)	R^2	*n*
F1	0.881	0.069	0.865	1.112	0.959	1.105	0.922	0.508
F2	0.897	0.107	0.876	1.234	0.954	1.650	0.932	0.506
F3	0.918	0.133	0.912	1.356	0.940	2.085	0.914	0.502
F4	0.854	0.149	0.953	1.654	0.998	2.261	0.982	0.501

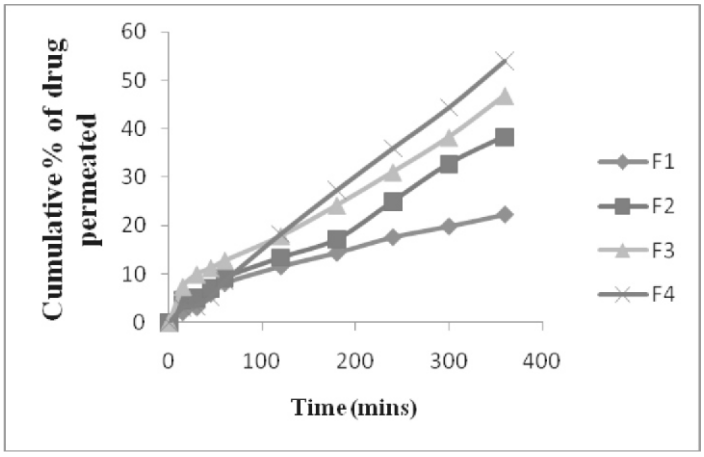

Fig. 1: Results of permeation study for F1, F2, F3 and F4 formulations

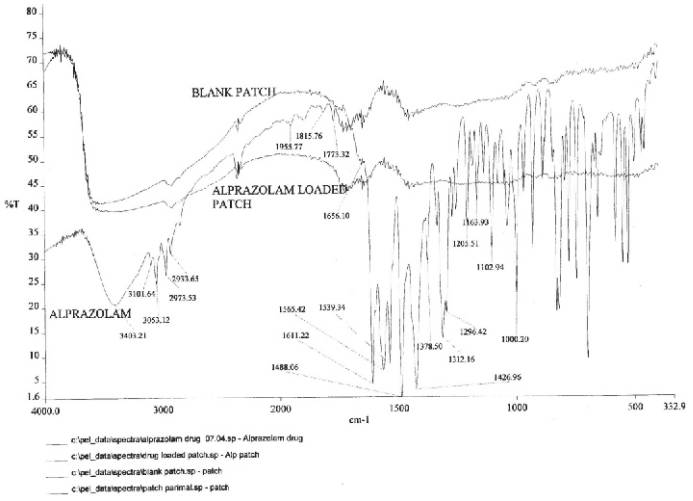

Fig. 2: FT-IR study results of pure alprazolam, blank patch and alprazolam loaded patch

Results and Discussion

In the present study, efforts have been made to prepare Alprazolam Transdermal patches using solvent evaporation technique. The films were prepared by using different hydrophilic polymers such as PVA and Chitosan in presence of Maleic Anhydride and Propylene glycol. The physicochemical evaluation data in Table 2-3 reveals that all formulations measured thickness with low standard deviation values. The thickness of the films varied from 0.31 to 0.34 mm. The minimum Standard deviation values assured that the process used for preparing the delivery system is capable of giving reproducible results.

The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The values in the range of 209 to 212 were observed. The result indicated that the patches would not break and would maintain their integrity with general skin folding when used.

The surface pH of all the formulations was in the range of 7.3 -7.4 and hence no skin irritation was expected. The tensile strength of the patches was found to vary with the nature of polymer and plasticizer. Formulation F4 (3 % w/v PVA, 0.5 % w/v chitosan) showed highest tensile strength of 2.98 ± 0.89 kg/cm^2.

Data of percentage moisture absorption indicates that the formulation F4 (3 % w/v PVA, 0.5% w/v chitosan) has shown highest maximum absorption than the other formulations. This may be due to the presence of hydrophilicity of PVA. The same patch showed more pronounced swelling as compared to other patches. It varied between 15.97 to 20.56%. The swellability varied with nature and composition of patches. Increasing the concentration of PVA showed considerable increase in swelling, as it increased the surface wettability and consequently water penetration within the matrix.

Release of the drug from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains. Table 4 indicates the cumulative percent of drug permeated from formulations F1, F2, F3 and F4 were found to be 22.92, 38.39, 46.87 and 54.02 % respectively after 6 h. The increase of release with increase of PVA content in the patch may be due to the leaching of PVA and pore formation. This leads to an increase in the external film area exposed to the solvent, increased internal porosity and decreased the tortuosity. Also PVA has antinucleating effect that converts crystalline drug into high energy amorphous state with improved solubility. The enhancement in solubility of drug increases thermodynamic activity that facilitates permeation of drug across the skin. Drug flux (μg/cm^2/h) of F4 was also higher than other formulations. The possible mechanism of enhancement of skin flux with increase of PVA in the patches may be due to its co enhancing property in aqueous vehicle system. The initial burst effect due to the incorporation of PVA was because of the rapid dissolution of the surface hydrophilic drug. The rapid leaching of hydrophilic fraction of polymers resulted in the formation of pores and thus leads to the decrease of mean diffusional path length of the drug molecules to permeate into dissolution medium.

The percentage of drug content of different patches varied between 88.21 to 93.36% and it indicated that the patches had good drug containing capability. Fig.1 shows the results of permeation study of different formulations. The *in vitro* skin permeation data were fit to different equations and kinetic models to explain permeation profiles (Table 5). The coefficient of correlation of each of the kinetics was calculated and compared.

The *in vitro* permeation profiles of all the different formulations of transdermal patches did not fit to zero order behavior truly and they could be best expressed by Higuchi's equation for the release of drug from a homogeneous polymer matrix type delivery system that depends mostly on diffusion characteristic. The data was further treated as per Korsmeyer's equation. The slope (*n*) values obtained by this equation indicated that the drug released by Fickian diffusion predominated with all formulations. The FT-IR study indicated that there was no interaction between the drug and polymers (Fig. 2).

The skin irritation study indicated that neither the polymer nor the drug caused any noticeable irritation or inflammation on or around the patch area, either during the period of study or after removal of the patch.

Conclusion

Transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc is that it provides a controlled release of the medicament into the patient. From the evaluation studies of the transdermal patches, it may be concluded that transdermal drug delivery system of alprazolam can be formulated, which provides better compliance than conventional drug delivery system. The formulation which contains highest concentration of PVA showed greater tensile strength and swellability. Permeation results of optimized formulation revealed Higuchi model release pattern. The Higuchi's plot was shown the highest regression value which indicated that diffusion might be one of the prominent mechanisms influencing the drug release. Hence this combination of polymers can be successfully manipulated to attain desired

efficacy of drug with minimum fluctuations in plasma levels.

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