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Development and Evaluation of Transdermal Drug Delivery System of Ketoprofen Drug with Chitosan for Treatment of Arthritis

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Abstract: Transdermal drug delivery system has numerous advantages over the more traditional drug delivery route. This includes high bioavailability, absence of first pass hepatic metabolism effect, steady drug plasma concentration and the fact that therapy is non-invasive. A Transdermal Patch is an adhesive patch that has a coating of medicine (drug) that is placed on the skin to deliver specific dose of the medicine (drug) into the bloodstream over a period of time. At the present research focused on Development of Transdermal Drug Delivery System of Ketoprofen drug With Chitosan Polymer for Treatment of Arthritis. Arthritis is a form of joint disorder that involves inflammation of one or more joints. The most common form, osteoarthritis (degenerative joint disease) is a result of trauma to the joint, infection of the joint. Ketoprofen is prescribed for arthritis-related inflammatory pains. Ketoprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Chitosan polysaccharide of animal origin is obtained from waste material of sea food industries. It is a Hydrophilic, non toxic, Poly cationic nature, Biocompatible, biodegradability, mucoadhesive, transdermal, permeation polymers for biomedical and pharmaceutical application. Preformulation testing of the active substances may provide useful information. It may be necessary to consider the physicochemical characteristics of the active substances. Solvent costing method is used for the formulation of transdermal film with modification of chitosan (chemically).

Key words: Transdermal Drug Delivery System · Arthritis · Ketoprofen · Modified Chitosan

INTRODUCTION

"A 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."

This approach to drug delivery offers many advantages over traditional methods. As a substitute for the oral route, transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced pharmacological dosaging due to the shortened metabolization pathway of the transdermal route versus the gastrointestinal pathway. The patch also permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medications [1, 2].

Ketoprofen (3-benzoylphenyl)- propionic acid (chemical formula $C_{16}H_{14}O_3$) is one of the propionic acid class of non-steroidal anti-inflammatory drug (NSAID). Its anti-inflammatory effects are believed to be due to inhibition of both cylooxygenase-1 (COX-1) and cylooxygenase-2 (COX-2) which leads to the inhibition of prostaglandin synthesis. It's have Plasma C_{max} -1-2 hour, Protein binding -98%, Half life -2 hours, It is highly plasma protein bound (99%). Ketoprofen is prescribed for arthritis-related inflammatory pains [3-5].

Chitosan a polysaccharide of animal origin is obtained from waste material of sea food industries. It occurs in the skeletal material of crustaceans such as crabs, lobsters, shrimps, prawns and crayfish. Crustacean shells are the usual row material of chitin. Chitosan is deacetylated product formed by treatment of chitin with concentrated (50%) caustic alkali. Chitosan is insoluble in neutral and alkaline pH, but dissolves in organic and

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inorganic acids e.g. acetic acid, formic acid, Glutamic acid, lactic acid, Hydrochloric acid. Viscosity of chitosan solution is increasing with degree of deacetylation. Solvent costing method is used for the formulation of transdermal film [6, 7].

Arthritis is a form of joint disorder that involves inflammation of one or more joints. The most common form, osteoarthritis (degenerative joint disease) is a result of trauma to the joint, infection of the joint. Ketoprofen is prescribed for arthritis-related inflammatory pains.

The transdermal anti-inflammatory film containing Ketoprofen, different polymers, permeation enhancers, were prepared and evaluated for different parameters. The formulations were also evaluated for Weight variation, Thickness, Folding Endurance, Drug Content, Moisture content, *In vitro* permeation studies. All eight formulations were evaluated for *in vitro* release study. Study was carried for 24 hrs.

The transdermal films of ketoprofen were subjected to accelerated stability study at (40°C/75% RH) conditions for 90 days as there was no change in color, odor, drug content, Moisture content, Weight variation, Thickness, Folding Endurance. Thus it may conclude that formulation were physically and chemically stable.

MATERIALS AND METHODS

Ketoprofen and Chitosan were received as a gift sample from Ranbaxy Lab Ltd Dewas (M.P.) and India sea food Cochin, India. Acetaldehyde and Propionaldehyde were procured from CDH Pvt. Ltd., Delhi and Merck Pvt. Ltd. Delhi. Glycerine, HPMC, procured from SDFCL. Pvt. Ltd, India.

Experiment

Chemical modification of chitosan

Preparation of Polymer a: Chemical modification of chitosan, in which the chitosan solution was prepared by dissolving the polymer in 1% acetic acid solution (1% acetic acid solution was prepared in 99 ml of water). The solution was string continuously with Acetaldehyde for 3 hours at 60°c. Acetone was added to the above polymer solution to precipitate the chemically modified chitosan A.

Preparation of Polymer b: Chemical modification of chitosan, in which the chitosan solution was prepared by dissolving by, dissolves the polymer in 1% acetic acid solution (1% acetic acid solution preparing in 99 ml of water). The solution was string continuously with propionaldehyde for 3 hours at 60°. After that, acetone was added to above polymer solution to precipitate the chemically modified chitosan [8].

Fabrication of Blank Transdermal Patches: Solution of polymer A, polymer B, plan chitosan and chitosan/ HPMC blend were prepared by dissolve 1.0% W/V acetic acid solution, respectively. The above solution (15ml) was poured into a petridish precoated with polyureathane and kept in an oven at 40° for complete drying. Films produced were with 50% ethanol to remove surface bound traces of acid. The dried films were removed from the petridish and stored in a desicator [9].

Fabrication of Drug Transdermal Patches: Solution of polymer A, polymer B, plan chitosan and chitosan/HPMC blend were prepared by dissolve polymer in 100 ml of 1.0% W/V acetic acid solution. To the above prepared polymeric solution, 20% V/W (with respect to dry weight of polymer) of glycerol followed by 20% W/W (with respect to dry weight polymer) of ketoprofen was added and stirred for 30 min. drug containing polymeric solution (22 ml) poured into a petridish (44.15 cm^2), precoated with polyureatane and kept in an oven at 40° for complete drying. Film produced was washed with 50% ethanol to remove surface bound traces of acid. The film was removed from the petridish and stored in a desicator [9].

Evaluation Parameters

Drug Content: The uniformity of drug content of the Transdermal film was determined, based on dry weight of drugs and polymers used by means of a UV Spectrophotometer method. Different Formulations were cut into pieces dissolved separately in 10 ml of Phosphate buffer pH 7.4 and stirred for 30 minutes. Appropriate dilutions were made with methanol. The resulting solutions were filtered with whatman filter paper No: 1 and analyzed for content at 258 nm in UV spectrophotometer. The average reading of three films was taken as the content of drug in one formulation.

***In-vitro* Permeation Studies:** The aim of *in vitro* experimentation in Transdermal drug delivery was to understand or predict the delivery and permeation of a molecule from the skin surface into the body. This was achieved by using a modified Keshary- Chien cell (K-C cell).

Preparation of Human Cadaver Skin: The human cadaver skin obtained from cadaver at Index Medical College and Research Center was utilized for the study. After taking consent of H.O.D of the Department, the skin from the cadaver was taken in sealed evacuated plastic bag containing formalin. The samples were stored in the evacuated plastic bag in the deep freezer at –20°C until use. Skin was taken from male cadaver in the age group of 20 to 60 years. Before use, the skin was allowed to thaw at room temperature, following which all subcutaneous fat was removed with the scalpel. The hairs were removed with the help of pair of scissors.

Epidermal layers were separated from the remaining skin by immersing each skin section in water at 60°C for 30 seconds. The epidermis was teased from the dermis using forceps, the separated epidermal layer was used as such for the skin permeation studies. At the time of use, the epidermis was spread on the cell and allowed to equilibrate with receptor fluid for 15 minutes before commencing the experiment.

Permeation Cell: A modified K-C cell was used for evaluating drug permeation profiles across excised human cadaver skin. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4 containing 20% (V/V) ethanol to ensure sink condition. Care was taken to remove any bubbles the underside of the skin. The solution in the receptor compartment stirred by the use of the Teflon coated bead on a magnetic stirrer. The upper part of the cell has pair of flange between which was placed the skin for release studies. The film was placed over the skin, the flanges held in place were tightened for the cell setup. The whole assembly was kept on the magnetic stirrer and the temperature was maintained at 37±1°C with the water jacket. The withdrawal port was covered with the cork. Measures were taken to prevent air entrapment and also proper filling of the cell to the position of the horizontal membrane. The upper portion of the cell is the donor compartment which was open and the top to maintain the exposure of the system to the ambient conditions. The amount of drug permeated into the receptor solution was determined by removing samples (1ml) at hourly intervals for 7 hrs and then at 24 hours. The withdrawn volume was replaced with an equal volume of fresh solution. The drug permeated was determined by analyzing the samples at 258nm.

% Moisture Content: The prepared films are to be weighed individually and to be kept in a desicator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films were weighed and the percentage of moisture content was determined from the below mentioned formula.

Percentage moisture content = [Initial weight- Final weight / Final weight] ×100.

Weight Variation: Uniformity of weights were determined by weighing five matrices of each formulation. After each film unit was weighed individually on a digital balance, the average weight of film was taken as the weight of the film.

Thickness of Patch: The thickness of the patch was determined by measuring the thickness at five sites on three films of each formulations using digital verniercalipher (Ocean premium) and the average was calculated.

Folding Endurance: The folding endurance is expressed as the number of folds (Number of times the film folded at the same place), either to break the specimen or to develop visible cracks. This test is performed to check the suitability of sample to withstand folding and brittleness. Three patchs of each formulation of size were cut by using sharp blade. Folding endurance was determined by repeatedly folding one film at the same place till it break. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Stability Studies: The transdermal films of ketoprofen were subjected to accelerated stability study at (40°C/75% RH) conditions for 90 days, The films were packed in aluminum foil and kept at accelerated conditions. The films were analyzed for drug content at 0, 30, 60 and 90 days respectively by a UV spectrophotometer method.

RESULT

Any drug for its permeation through skin should be potent, must be lipophilic as well as hydrophilic in nature, optimum partition coefficient etc, this prompted us to carry out the present study. The pre formulation study for the drug was conducted. The ë max of ketoprofen was

found at 258 nm, which is comparatively same as given in I.P. This shows that the drug is pure. By the determination of organoleptic properties, it was observed that the ketoprofen is a white colored, crystalline powder, bitter in taste and odorless drug. Results of qualitative solubility studies show that the ketoprofen is soluble in organic solvent and insoluble in water. So it is hydrophobic in nature. Quantitative solubility studies shown that ketoprofen is more soluble in methanol as compared to other solvents.

The partition coefficient was found to be 3.85, which is suitable for transdermal drug delivery, the obtained value of partition coefficient of ketoprofen was more than 1 which showed that the ketoprofen is lipophilic in nature. The average particle size of ketoprofen was measured by microscopy method was found to be 3.73 micrometer. The melting point was observed at 94°C and this range is nearly same as reported in I.P. it shows the drug is crystalline & pure. The standard curve of ketoprofen was prepared in methanol, the r^2 values was obtained 0.997 respectively, which shows linearity of absorbance between the range of 2-16 microgram per ml. The preformulation study of ketoprofen showed satisfactorily results to select the drug for transdermal drug delivery system.

The transdermal anti-inflammatory film containing Ketoprofen, different polymers, permeation enhancers, were prepared and evaluated for different parameters. The formulations were also evaluated for Weight variation, Thickness, Folding Endurance, Drug Content, Moisture content, *In-vitro* permeation studies. All eight formulations were evaluated for *in- vitro* release study. Study were carried for 24 hrs formulation D-6 was also evaluated for drug release without addition of ketoprofen but the former gives better results in terms of all the evaluating parameters.

The transdermal films of ketoprofen were subjected to accelerated stability study at (40°C/75% RH) conditions for 90 days as there was no change in color, odor, drug content, Moisture content, Weight variation, Thickness, Folding Endurance. Thus it may conclude that formulation were physically and chemically stable.

The results of evaluation studies are given in Table 3. All the formulations showed drug content in the range of 86.45 - 94.63%. The% Moisture content of all the formulations was found to be in the range 2.31 – 6.0%. The Folding endurance of all the formulations was in the range of 78- 84. The transdermal drug delivery is one of the promising route of drug delivery system, since it by passes the first pass metabolism, avoids inactivation of

Table 1: Formulation Composition of Blank Transdermal Patch

S. No.	Formulation code	Plan chitosan (g)	Polymer A (g)	Polymer B (g)	Chitosan / HPMC (g)
1.	F1	1.8%	-	-	-
2.	-	2.3%	-	-	-
3.	-	2.8%	-	-	-
4.	F2	-	1.8%	-	-
5.	-	-	2.3%	-	-
6.	-	-	2.8%	-	-
7.	F3	-	-	1.8%	-
8.	-	-	-	2.3%	-
9.	-	-	-	2.8%	-
10.	F4	-	-	-	1:1%
11.	-	-	-	-	2:1%
12.	-	-	-	-	1:2%

Table 2: Composition of various Drug Loaded Transdermal Patch:

S.No.	Formulation	Polymeric Polymers	Plasticizer ketoprofen	code solution (%) (Glycerol)	w/w% w/v%
1.	D1	2.3	Plain chitosan	15	20.0
2.	D2	2.3	Plain chitosan	25	20.0
3.	D3	2.3	Polymer A	15	20.0
4.	D4	2.3	Polymer A	25	20.0
5.	D5	2.3	Polymer B	15	20.0
6.	D6	2.3	Polymer B	25	20.0
7.	D7	2.3	Plain chitosan+ HPMC (75:25)	15	20.0
8.	D8	2.3	Plain chitosan+ HPMC (75:25)	25	20.0

Table 3: Drug Content, *In-Vitro* Permeation Studies,% Moisture Content, Weight Variation, Thickness of Patch, Folding Endurance of Transdermal Film of Ketoprofen Drug:

Formulation	Drug content	*In-vitro* permeation studies	% Moisture content	Weight variation	Thickness of path	Folding endurance
D1	87.76%	79.59%	2.31%	1.33	0.40	78
D2	86.45%	76.98%	2.93%	1.42	0.44	82
D3	94.21%	65.25%	4.15%	1.36	0.46	79
D4	93.7%	72.3%	5.6%	1.43	0.46	83
D5	94.16%	73.7%	3.7%	1.34	0.43	78
D6	90.48%	78.6%	3.73%	1.39	0.44	84
D7	92.57%	81.4%	5.6%	1.42	0.45	79
D8	94.63%	85.5%	6.0%	1.45	0.47	84

Table 4: Stability Studies of Transdermal Film of Ketoprofen Drug with Chitosan Polymer

	Drug content			
Formulation	Day(0)	Day(30)	Day(60)	Day(90)
D-1	83.21%	88.11%	83.76%	89.74%
D-2	81.41%	87.71%	81.53%	79.4%
D-3	90.20%	92.14%	87.31%	90.56%
D-4	85.8%	90.28%	93.72%	89.31%
D-5	88.3%	87.54%	90.1%	91.2%
D-6	91.1%	88.4%	90.2%	94.2%
D-7	90.20%	89.24%	90.35%	92.34%
D-8	91.23%	90.35%	92.34%	90.21%

drugs by pH effects and enzymes present in GI tract, provides a continuous mode of administration at rates approaching zero order similar to that provided by an intravenous infusion, increase the half life of the drug, the delivery is non-invasive, no hospitalization is required and improves patient compliance. Any drug for its permeation through skin should be potent, must be lipophilic as well as hydrophilic in nature, optimum partition coefficient etc, this prompted us to carry out the present study on ketoprofen. The transdermal anti-inflammatory film containing Ketoprofen & different polymers, were prepared and evaluated for different parameters. The formulations were also evaluated for Drug content, *In-vitro* Permeation studies,% Moisture content, Weight variation, Thickness of patch, folding endurance and results found were all satisfactory. All the formulations showed drug content in the range of 86.45-94.63% indicating uniform distribution of drug throughout the base. The% Moisture content of all the formulations was found to be in the range 2.31 – 6.0%. The Folding endurance of all the formulations was found in the range of 0.40 - 0.47. Stability study indicated that all the selected formulations (D_3, D_5, D_6 and D_7) were stable enough at different temperature conditions (40°C, 25°C, room temperature) for 90 days as there was no change. Accelerated stability studies were done on the basis of ICH guidelines shows that the formulation was stable.

DISCUSSION

As compared to the formulation prepared by singh S. *et al*. [10] in which polymers used for formulating the transdermal system were sodium carboxymethylcellulose, xanthan gum, poloxamer 407 and carbopol 934P as bioadhesive polymer with and without penetration enhancer (oleic acid), formulation prepared by chitosan were show more better results in respect of all the parameters. Chitosan as easily available, having less cost and less antigenic potential makes the formulation highly useful for the treatment of arthritic conditions.

CONCLUSION

Successful transdermal drug delivery requires numerous considerations owing to the nature and function of the site of application. This article provide an valuable information regarding the transdermal drug delivery systems with modified chitosan and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. Modified chitosan used as permeation polymers for biomedical and pharmaceutical application. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. It should always be kept in

mind, that the basic functions of the skin are protection and containment. As per these rulings, it would seem exceptionally difficult to cross the skin for systemic absorption. However, with continuous exploration of the structure, function and physicochemical propertties of the skin, more and more new drug products are being developed for transdermal delivery. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions and polymer are required.

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