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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF SELECTED PIOGLITAZONE HYDROCHLORIDE FOR ANTI-HYPERGLYCEMIC TREATMENT

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ABSTRACT

The present study aimed to develop matrix type transdermal drug delivery system for selected anti-hyperglycemic agent of Pioglitazone Hydrochloride. Preliminary studies were done to determine the solubility, pH, partition coefficient and steady state flux and permeability coefficient. The steady state flux and the permeability coefficient values obtained from *in vitro* diffusion studies across Wistar rat skin suggested the need of penetration enhancers in view to achieve the desired flux so as to maintain the therapeutic concentrations. It shows good permeation for the selected drugs. Different ratio batches of drug loaded films were for each drug using a combination of excipient in different ratios by solvent casting technique. Based on the physicochemical properties and drug diffusion profile of the films, it could be concluded that PVP and PVA in ratio of 1:2 were better suited than the other polymer combinations for the development of transdermal drug delivery systems of Pioglitazone Hydrochloride. Drug-Polymer interaction studies were carried out using FT-IR and DSC techniques. The Pharmacodynamic data indicated that the therapeutic action starts at 1 h and sustains up to 24 h, suggesting that the systems developed could be beneficial in the management of diabetic.

KEYWORDS

Anti-hyperglycemic agent, Pioglitazone Hydrochloride and Transdermal drug delivery system.

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INTRODUCTION

For thousands of years, human civilization has applied substances to the skin as cosmetic and medicinal ingredients. TDDS delivers drugs through the skin as an alternative to traditional routes such as oral, intravascular, subcutaneous and transmucosal. Transdermal drug delivery systems (TDDS), or transdermal patches, are flexible,

flexible patches of various sizes containing one or more drug substancesthatare applied to intact skin to maintain systemic circulation and maintain plasma levels. Defined as a multi-layered medicinal product[1-3].

It is usually formulated with a pressure sensitive adhesive that ensures adhesion of the formulation to the skin. In the current scenario, there are very few transdermal patches on the market. Academic and industrial activity in percutaneous research has grown significantly over the past two decades. This route of administration remains limited by the number of suitable drug candidates available, but nevertheless attracts considerable interest worldwide. A comprehensive literature search was conducted and compiled to focus on these developments[4-6].

The potential application of drug delivery to the skin has been recognized for several years, as evidenced by the development of medicated patches in China and Japan. Perhaps this practice may have sparked interest in studying the skin as an entry point for drug administration for the effects of drugs on the systemic circulation. Excellent uniformity[7-10]. Transdermal drug delivery systems are designed to bypass first-pass hepatic metabolism and improve patient compliance[11-13]. Most transdermal systems are designed to release active ingredients at a zero-order rate for hours to days after application to the skin. Remember that this will allow the patient to become accustomed to traditional oral medicines and take them several times a day.

The possible useful polymers for transdermal device are:

Natural polymers: chitosan, cellulose derivatives, zein, gelatin, shellac, waxes, proteins, gums and their derivatives, natural rubber, starch etc.

Synthetic elastomers: polybutadine, hydrin rubber, polysiloxane, silicon rubber, nitrile, acrylonitrile, butyl rubber, styrene butadiene rubber, neoprene etc.

Synthetic polymers: Polyvinylalcohal, polyvinyl chloride, polyethylene, polyacrylate, polyamide, polyuria, polyvinyl pyrrollidone, polymethylmethacrylate, epoxy etc.

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentrations (hyperglycemia) caused by insulin deficiency, often combined with insulin resistance. Pioglitazone hydrochloride is an important diabetes drug currently on the market for the treatment of hyperglycemia associated with non-insulin dependent diabetes mellitus (NIDDM). However, it is associated with severe, sometimes fatal hypoglycemia and gastric disturbances such as nausea, vomiting, heartburn, anorexia, and increased appetite after oral treatment. Patient compliance is also very important because these drugs are usually intended to be taken for a long period of time.

However, the current scenario is to use antihyperglycemic activity to treat diabetics to lower blood sugar levels. Conventional oral therapy for type I and type II diabetes requires long-term treatment with frequent dosing schedules. Therefore, there is a growing need for alternative routes of drug delivery that are better released at lower doses and over longer treatment periods. The transdermal drug delivery system "TDDS" has the above desirable properties[14-17].

MATERIALS AND METHODS

Name of the Materials/Chemicals

Pioglitazone Hydrochloride, Polyvinyl Alcohol (PVA), Polyvinyl Pyrrollidone (PVP), Ethyl Cellulose (EC), Hydroxy Propyl Methyl Cellulose (HPME), Potassium dihydrogenortho Phosphate, Dibutyl phthalate, Methanol, Ethanol, Dimethyl Sulfoxide, Potassium dihydro Phosphate, Sodium Hydroxide, Surgical Sprit.

Name of Equipment's/Instruments

Electrical balance (V-Tech), Vernier caliper (Mitutoya), Hydrolic press hardness tester (Dharma scientific products), Dissolution apparatus (Lab India), Sonicator (bath) (Remi equipment pvt Ltd), Dryer (Techno- Tray dryer), Micro centrifugator (Remi Rsearch Centrifugur), Hot air ovan (NSW India), Cyclo mixer (Rapid),U.V double beam spectrometer (Systronics), pH meter (Elico India), Screw Gauze (Linker, India), Venire caliper

(Linker, India), Scanning Electron Microscope (JEOL Tokyo, Japan), Differential Scanning Calorimeter (DSC Q 200 Shimadzu Corporation, Japan), Blood Glucose Monitoring System (ACCU-CHEK, Roche Diagnostic, Mannheim, Germany), Magnetic Stirrer with hot plate (M.C. Dalal and Co).

RESULTS AND DISCUSSION

Formulation design (Preparation of Transdermal patches)

Different methods are employed for the preparation of transdermal patches/films, which Includes: Below molding, Injection below molding, Extrusion below molding, Stretch below molding, Calendaring, Casting, etc.

Casting (Solvent)

Casting is process where a liquid or molten form of polymer solution is poured into molds of desired shape and allowed to set, cure or harden to form a right object that represents the shape of the mold.

Continuous casting process

In the process the liquid is poured between two parallel, continuously conveying, endless, highly polished conveyor belts. As the solvent evaporates, a continuous film of consistent thickness is obtained.

Cell casting

It is a batch process in which the liquid is poured into a confined area formed by the boundary of the mold and process or allowed to cool or harden. Cell casting method was chosen as the method for the formulation of film in the present study because of its small-scale laboratory feasibility and suitability for aqueous as well as non-aqueous polymeric solutions.

Selection of Polymeric and Solvent Systems

The polymers and solvents are selected as per the trial and error method and were here used for the polymers in the present studies are represented in Table No.1.

Pre-formulation Studies

Determination of λmax and construction of UV calibration curves

The Drug solution having a concentration of 10µg/ml was prepared in phosphate buffer of 7.4. These solutions were scanned in the wavelength ranging from 200 to 400nm against phosphate buffer as a blank in double beam UV spectrophotometer. The absorption maxima (λmax) values were noted for each drug from the respective plots of absorbance v/s wavelength.

Extraction of Pioglitazone from diffusion blood samples by Solid Phase Extraction Techniques

Extraction procedure for Pioglitazone Hydrochloride (PGZ)

1ml of PGZ serum standard or sample was diluted with 2ml of 0.1M HCL and vortexes. The diluted samples were then passed through previously conditioned SPE cartridges under gravity. The cartridges were subsequently washed with 3ml of 0.1M HCL and 3ml of chloroform. After washing, a low vacuum was applied to remove the traces of chloroform before elution of PGZ with 2ml of methanol. Methanol was evaporated at 40ºC and the residue was reconstituted with 1ml of 0.05M ammonium formate buffer of pH 3.5. The samples were filtered through a 0.45µg/ml nylon syringe filter and the absorption of drug taken by UV Double Beam Spectroscopy and the ʎ-max is 225nm. A result of calibration curve was showed in Table No.2 and Figure No.1.

Permeability studies

Preparation of the skin barrier

The fresh full thickness (70-80-mcm) male wistar rat skin was used for these studies. The skin was immersed in water at 60ºC for a period of 5 minutes. The epidermis was peeled from the dermis. The isolated epidermis (25 ± 5mcm thick) was rapidly rinsed with hexane to remove surface lipids, rinsed with water and used immediately.

Permeability of the drug through male wistar rat skin

The permeability studies of the drug were carried out across the male wistar rat skin using a modified Franz diffusion cell. Saturated solution of the drug

along with a portion of suspended excess drug was taken in the donor compartment. The barrier was mounted between the donor and the receptor compartment. The receptor cell contained phosphate buffer of pH 7.4 as the medium. The medium was magnetically stirred for uniform drug distribution and was maintained at 37±1ºC. The samples withdrawn every hrs up to 12 hrs and estimated UV/ Spectrofluorometrically to determine the amount of drug diffused. The flux (mcg/cm2) was calculated from the slope of the plot of cumulative amount of the drug permeated per cm2 of skin at steady state against the time using linear regression analysis.

EVALUATION OF TRANSDERMAL PATCHES

The transdermal patches prepared were subjected for the following evaluation methods

Physicochemical parameters

The following Physicochemical parameters are evaluated and results has been showed in Table No.3.

Gross visual appearance

All the transdermal patches were visually inspected for colour, clarity, flexibility and smoothness.

Scanning Electron Microscopy (SEM)

The external morphology of the transdermal patches was analyzed using a Scanning electron microscope. The samples placed on the stabs were coated (platinum) finally with gold palladium. These coated films were observed under the microscope and photographs of suitable magnifications (1000X, 1500X) obtained.

Thickness Test

The thickness of the drug loaded polymeric films was measured at five different points using digital micrometer. The average and standard deviation of five reading was calculated for each batch of the drug-loaded film.

Flatness Test

Longitudinal strips were cut from the drug-loaded patches. The length of each strip was measured and then variation in the length due to non-uniformity flatness was recorded. Flatness was calculated by measuring constriction of strips using equation 12 and a 0% constriction was considered to be equal to 100% flatness.

Uniformity of weight

The films of different batches were dried at 60ºC for 4 h prior to the testing. Five patches from each batch were accurately weighed in a digital balance. The average weight and the standard deviation values were calculated from the individual weights. The individual weight should not deviate significantly from the average weight of films.

Moisture content

The film was weighed and kept in desiccator containing a anhydrous calcium chloride at 40ºC in a drier for 24 h repeatedly weighed until a constant weight was attained. The moisture content was obtained from the difference between the constant weight attained and the initial weight.

Drug-polymer interaction studies

Differential Scanning Calorimetry

Thermograms of drugs and transdermal patches of optimized batches were recorded using a differential scanning calorimeter and were compared. The samples were hermetically sealed in flat-bottomed aluminum pans and heated over a temperature range of 40-240ºC at a rate of10ºC/m in using alumina as a reference standard.

Measurement of blood glucose level

Experiments were performed using 6 rats per drug. Rats had their abdomen shaved using an electric shaver prior to examination. The rat was trained to enter the holder for at least 2 weeks and was repeated prior to the experiment. The patch was applied to the abdomen using a medical patch. Rats are observed for 24 hours. The ventral (back) side of the rat is shaved 12 hours prior to the start of the experiment. Approximately 2×2cm 2 of skin is shaved ventrally from each group of rats, except for the group treated with the commercial (suspension) formulation. Fast for 12 hours to monitor side effects.

Effect of pH on drug (PGZ) solubility

The solubility of PGZ was determine at different pH values from 4.0-8.0 in phosphate buffer. The solubility of drug was found to increase with an

increase in the pH value. The solubility profile of PGZ is shown in Table No.4.

Table No.1: Composition of pioglitazone HCL transdermal patches

S.No	Formulation Code	Polymeric Blend	Drug mg/cm2	Ratio (w/w)	Plasticizer Glycerol (30%w/w)	Permeation enhancer (DMSO	Solvent system
1	F1	PVA:PVP	1mg/cm2	1:2	30 %	1 %	Ethanol
2	F2	PVA:PVP	1mg/cm2	2:1	30 %	1 %	Ethanol
3	F3	PVA:PVP	1mg/cm2	2:2	30 %	1 %	Ethanol
4	F4	PVA:PVP	1mg/cm2	2:3	30 %	1 %	Ethanol
5	F5	PVA:PVP	1mg/cm2	3:2	30 %	1 %	Ethanol
6	F6	PVA:PVP	1mg/cm2	1:4	30 %	1 %	Ethanol
7	F7	PVA:PVP	1mg/cm2	4:1	30 %	1 %	Ethanol

Note: Content: 1mg/cm2, Plasticizer: Glycerol (30%w/w), Penetration chemical enhancer: DMSO (1%w/w)

Table No.2: Absorption of standard solution of PGZ in phosphate buffer pH 7.4 (n=5)

S.No	Concentration in µg/ml	Mean Absorbance	±SD
1	5	0.187	±0.0013
2	10	0.289	±0.0017
3	15	0.395	±0.0008
4	20	0.474	±0.0023
5	25	0.591	±0.0015

Table No.3: Results of physicochemical evaluation's

S.No	Duration	Thickness	Weight	Drug content	Moisture content	Moisture uptake
1	0 Week	0.22mm	25mg/cm2	98.60%	1.98	4.95(75% RH)
2	3 Month	0.23mm	25mg/cm2	98.53 %	2.13	5.86(75% RH)
3	6month	0.24mm	25mg/cm2	98.13 %	2.58	5.96(75% RH)

Table No.4: Effect of pH on drug (PGZ) solubility

pH	5.5	6.0	6.5	7.0	7.5
Solubility mg/ml	60.67	72.90	85.91	96.48	99.87

Table No.5: Effect on blood glucose level at different time intervals

S.No	Animal No	0 hr	2 hr	4 hr	8 hr	10 hr	12 hr	24 hr
1	AR_1	226	198	159	96	84	79	74
2	AR_2	227	196	157	99	83	77	71
3	AR_3	224	194	155	93	87	73	69
4	AR_4	222	190	158	90	81	76	72
5	AR_5	220	193	151	93	89	78	73
6	AR_6	229	189	150	97	86	74	69
7	Mean±SD	225	193	155	95	85	76	71

**P<0.000, when compared with 0 h (n=6)

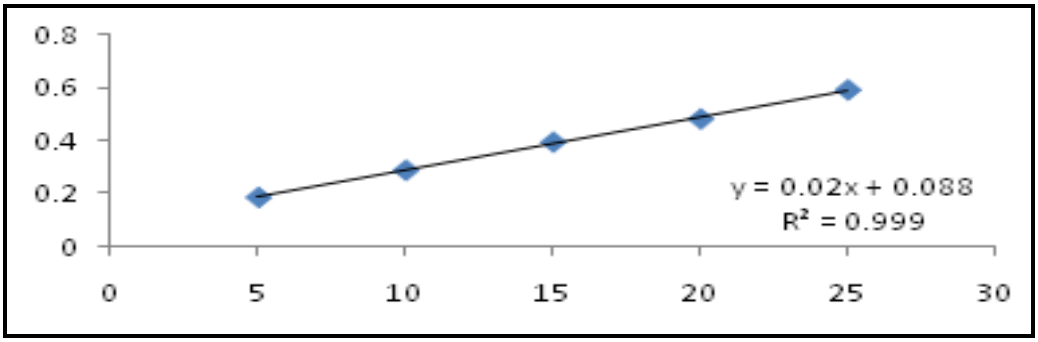

Figure No.1: Calibration curve of Pioglitazone

CONCLUSION

There are often compelling reasons for administering drugs by routes other than oral. Over the past decade, there has been a growing recognition that conventionally administered drugs are often highly toxic and sometimes inactive, so they have been introduced into the body as legumes and have had significant effects on drug concentrations in the bloodstream and in the body. Transdermal delivery is gaining increasing attention as it provides variability. The result is an unfavorable pattern of efficacy and toxicity. Fundamental research into skin physiology, its structure, and immunological properties has greatly helped formulators overcome the highly effective skin barrier properties attributed to the outermost layer of the skin, the stratum corneum. Irritation studies showed no evidence of edema or erythema on intact or abraded skin after patch application for 72 hours. Hyperglycemia requires continuous monitoring of blood glucose levels and repeated administration of drugs by the conventional oral route for effective treatment. In this context, transdermal drug delivery has emerged as a viable alternative to systemic drugs. The matrix type of transdermal drug delivery system for selected antihyperglycemic agents shows potential for further clinical use in effective treatment of diabetic patients.

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CONFLICT OF INTEREST

The entire author's declared as no conflict of interests.

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