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Formulation and evaluation of transdermal patches of Irbesartan

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ABSTRACT

The purpose of the research was to develop matrix type transdermal therapeutic system containing irbesartan with different ratios of hydrophilic and hydrophobic polymeric concentration by the solvent evaporation technique. The prepared patched showed satisfactory physiochemical characteristics of weight uniformity, thickness, folding endurance, moisture absorption for stability of the formulation and drug content were uniform in all patches. In vitro study done by using Franz diffusion cell having cellophane membrane to determine the amount of drug present in the formulated patch. In different formulation on the basis of present study formulation F5 show satisfactory drug release pattern.

1. INTRODUCTION

With the advent new era of pharmaceutical dosage forms (TDDS) established itself as an integral part novel drug delivery systems .Transdermal drug delivery is the non in-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body-through its layers, to the circulatory system. BASIC Components used for transdermal drug delivery system: Polymer matrix, Drug, Permeation enhancer, Adhesive and backing membrane

Polymer matrix: Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix a prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and pressure sensitive adhesive (PSAs). Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status.

Natural polymers: Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Gums, Natural Rubber and Chitosan.

Synthetic elastomers: Polybutadiene, Hydrin rubber, Polyisobutlylene, silicon rubber nitrile, Acrylonitrile, Neoprene, Butyl rubber etc.

Synthetic polymers: polyvinyl alcohol, polyvinyl chloride, poly ethylene, polyacrylate, polyamide, poly urea, poly vinyl pyrrolidone, polymethymethacrylate etc. The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, poly vinyl pyorrolidone and hydroxyl propyl methyl cellulose are used as matrix former for TDDS.

- The polymer should be chemically non-reactive or it should be inert drug carrier.
- The polymer must not decompose on storage or during the life of device.
- The polymer and its decomposed product should be non-toxic.
- The polymer must be easy to manufacture and fabricate in to the desired product.

Drug: Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half-life which causes noncompliance due to frequent dosing .The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery.

Permeation enhancers: Permeation enhancers controls the release of the drug. E.g. Terpene, terpenoids, pyrrolidones. Solvents like alcohol, ethanol, and methanol. Surfactants like sodium lauryl sulfate, pluronic F127, pluronic F68.

Adhesives: Polysobutylenes, Acrylic and Silicons.

Backing membrane: Vinyl, Poly Ethylene, Polyester Films, Cellulose Derivatives, Polyvinyl Alcohol, and Polypropylene Silicon Rubber.

Drug profile: Irbesartan is an angiotensin receptor blocker (ARB) used mainly for the treatment of hypertension. Angiotensin2 the principal pressor agent of rennin angiotensin system is responsible for effects such as vasoconstriction stimulation of synthesis and release of aldosterone. Cardiac stimulation and renal reabsorption of sodium. Irbesartan is a specific competitive antagonist of AT1 receptor with much greater affinity for the AT2 receptor than for the AT2 receptor and no agonist activity. Irbesartan's inhibition of angiotensin 2 binding to the AT1 receptor leads to multiple effect including vasodilation, reduction in the secretion of vasopressin, and reduction in the production and secretion of aldosterone. The resulting effect is a decrease in blood pressure. Irbesartan effectively lowers BP in patients with hypertension without effecting heart rate.

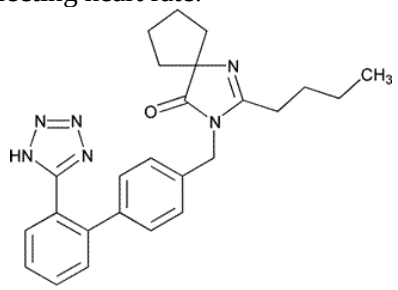

Figure.1.Molecular structure of Irbesartan

2. MATERIALS AND METHODS

Preparation of drug containing polymer matrix: Drug loaded polymer patches were prepared by solvent evaporation technique. The matrix was prepared by PVP:EC in different ratio. The polymer in different ratios was dissolved in chloroform. Irbesartan dissolved in ethanol and slowly added in polymer solution and mixed thoroughly to obtain a uniform solution, PEG-400 as a plasticizer was added and mixed. Films were casted by placing this solution on desired size flat Teflon plates allow to evaporate the solvent for 24 hours.

***In vitro* drug permeation study with different formulation:** The *in vitro* permeation studies were conducted using fabricated Franz diffusion cell. The treated rat skin was cut into desired size and placed between the receptor and donor compartments the diffusion cell. The fabricated patch was placed over the membrane. The donor compartment was placed on the receptor compartment containing phosphate buffer PH 7.4 maintaining at 37+_ 0.5 C the entire assembly was kept on magnetic stirrer. The solution in the receiver compartment was continuously stirrer with magnetic beads with about 500rpm during the experiment.

The amount the drug permeated through membrane was determined by withdrawing 2ml of sample at predetermined time interval and replacing them with an equal volume of buffer. The withdrawal samples were diluted 10 times and filtered through filter paper (whatmanR 41). Absorbance of the sample was measured at 248 nm taking phosphate buffer as the blank. Drug absorbance were determined by the standard curve of Irbesartan in phosphate buffer PH (7.4). The amount of drug permeated per square centimeter at each time interval was calculated from the calibration curve. The mean cumulative percentage of the drug permeation through total patch area was plotted against time.

Table.1.Formulation of transdermal patches

Ingredient	F1	F2	F3	F4	F5
Irbesartan (mg)	30	30	30	30	30
Ethyl Cellulose (mg)	500	400	300	200	100
PVP K30 (mg)	100	200	300	400	500
Tween-80 (ml)	6	6	6	6	6
PEG 400 (ml)	0.3	0.3	0.3	0.3	0.3
Chloroform: Alcohol (ml)	10	10	10	10	10

3. RESULTS AND DISCUSSION

The present work efforts have been made to prepare transdermal drug delivery system of Irbesartan, EC and PVP, using poly ethylene glycol as a plasticizer by solvent casting technique. The selection of polymer combination produces clear, smooth, uniform, substantive, flexible and desired thickness film for the transdermal drug delivery system of Irbesartan. The prepared formulation were evaluated for different physic chemical characteristics such as thickness, folding endurance, drug content, percent moisture absorption, percentage moisture loss and weight uniformity. The release characteristics of the formulation were studied in vitro conditions. In vitro permission studies were carried out in phosphate buffer (PH 7.4) for 24 hours. The partition coefficient of Irbesartan was found to be 3.87 after 24 hours. 71.25% drug was permeated through skin.

The thickness of patches varied from 52 to 65µm. The minimum standard deviation values assumed that process used for preparing the drug delivery system is capable of giving reproducible result.

As the concentration of PVP and ethyl cellulose increase, moisture content of patches was also increased. Formulation F5 (1.481±0.24) absorbed highest amount of moisture which also revealed its high hydrophilicity and formulation F1 (1.096±0.14) absorb least amount of moisture.

The folding endurance was measured manually; films were folded 59times maximum in formulation F1 and if the film shows any cracks it was taken as end point. The folding endurance was better in F1 formulation. As the concentration of PVP and ethyl cellulose increase, moisture uptake of patches was also increase. The highest moisture absorption was found in the formulation F5 and lowest value of moisture absorption was found in the formulation F1.

The drug content uniformity of the prepared formulation have shown that the process used to prepare the transdermal film in the study was capable of giving film with uniform drug content. The result of drug content indicates that drug is uniformly dispersed in formulation.

In vitro drug permeation studies were carried out for the different formulations using Franz diffusion cell. The medicated films showed drug release study in % cumulative release. The relationship can be established as F5>F4>F2>F3>F1 thus, by varying amount of polymer in film, percent release can be varied. Drug-polymer affinity can be major factor that control release of drug from formulation.

Maximum percentage of drug release (i.e.90.28%) was observed with formulation F5 and the minimum (i.e.68.57%) was fond with formulation F1. The addition of hydrophilic components such as PVP into the formulation tends to enhance its release-rate constants.

This outcome can be attributed to the leaching of the soluble component, which leads to the formation of pores and thus a decrease in the mean diffusion path length of drug molecules to release into the dissolution medium the result is higher dissolution rates. Substances such as PVP act as antinucleating agents that retards the crystallization of a drug. Thus they play a significant role in improving the solubility of a drug in the matrix by sustaining the drug in an amorphous form so that it undergoes rapid solubilization by penetration of the dissolution medium.

Table.2.Physiochemical characterization of transdermal patches

Parameter	F1	F2	F3	F4	F5
Thickness(µm)	52±10	61±10	54±10	65±10	55±15
Weight variation (mg)	115±2.13	105±3.06	111±2.53	109±3.05	95±2.07
Folding Endurance	59±2.8	55±3.6	41±4.4	49±3.2	45±2.8
Percentage Moisture Content (%)	1.035±0.32	1.113±0.35	1.096±0.14	1.252 ±0.22	1.481±0.24
Percentage Moisture Uptake (%)	1.112±0.25	0.994±0.15	1.028±0.27	1.118±0.22	1.124±0.23
Drug Content	89.21±0.24	84.61±0.19	79.44±0.34	88.92±0.16	94.21±0.21
Percentage Elongation break (%)	92.4	92.3	85.5	87. 1	113.1
Percentage cumulative amt. permeation (%)	68.57	74.19	69.86	84.92	90.28

Table.3.Cumulative percentage drug release

Time (Hours)	Cumulative percentage drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
4	8.64	11.62	12.66	14.02	18.23
8	17.55	18.21	22.14	24.15	33.46
12	28.45	26.34	31.45	38.12	46.28
16	36.12	44.27	43.18	51.45	64.25
20	52.45	57.5	57.64	72.66	78.59
24	68.57	74.19	69.86	84.92	90.28

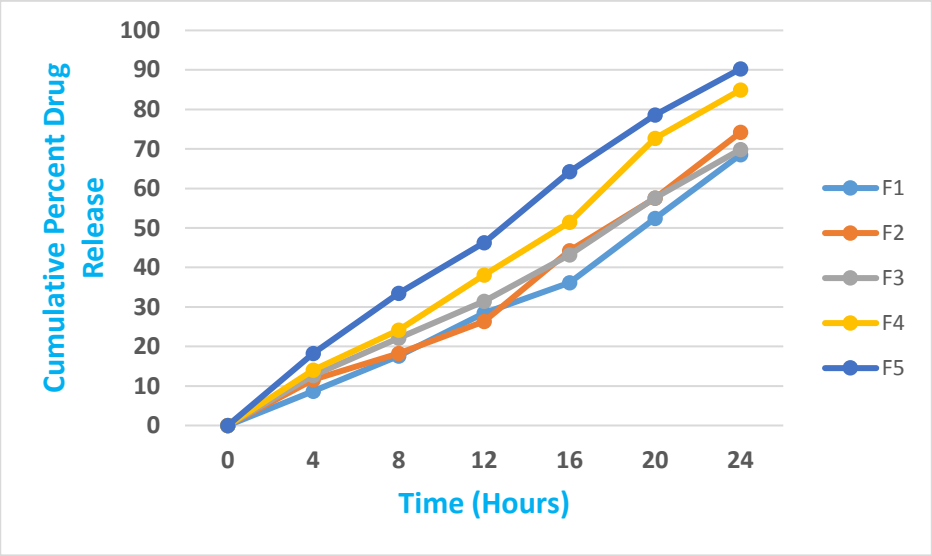

Figure.2. Cumulative percentage drug release

4. CONCLUSION

The prepared transdermal drug delivery system of Irbesartan using different ratios of polymers such as EC and PVP had shown good promising results for all the evaluated parameters. Based on the *in vitro* drug release and drug content result, formulation F5 was concluded as an optimized formulation, which shows its higher percentage of drug release.

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