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Formulation and Evaluation of Transdermal Patches of Anti Hypertensive Drug Irbesartan

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ABSTRACT

Irbesartan is an angiotensin receptor blocker (ARB) used mainly for the treatment of hypertension. Angiotensin2 the principal pressor agent of the rennin angiotensin system is responsible for effects such as vasoconstriction stimulation of synthesis and release of aldosterone. Irbesartan containing transdermal patch was prepared to utilize the solvent casting method. The casting solution was prepared by dissolving weighed quantities of HPMC (350, 400, and 450mg) and ethylcellulose, Eudragit RSPO (50, 100, and 150mg) and Eudragit RLPO (50, 100 and 150mg) in 10 mL of methanol and chloroform and water mixture in ratio 1:1. A total of nine formulations were prepared and evaluated for Thickness, Percent moisture content, Percent moisture uptake, Folding endurance, Tensile Strength, Drug Content, and *in-vitro* skin permeation study. Based on the *in-vitro* drug release and drug content result, formulation F4 was concluded as an optimized formulation, which shows its higher percentage of drug release.

INTRODUCTION:

Transdermal drug administration generally refers to the topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. Transdermal Patch offers many advantages over the traditional dosage forms or controlled release oral systems. The transdermal patch provides constant blood levels, avoids first-pass metabolism, increased patient compliance, and avoids dose dumping [1,2]. The application of transdermal delivery to a wider range of medicine is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum corneum layer of the epidermis. The formulation on the skin can be classified into two categories according to the target site of the action. One has systemic action after drug uptake from the cutaneous microvascular network and the other exhibits local effects in the skin. Transdermal drug delivery can closely mimic the slow intravenous infusion without its potential hazards and also offer another most vital advantage in allowing the patient to terminate the drug therapy by simply removing the patch at the desired time if toxicity develops [3].

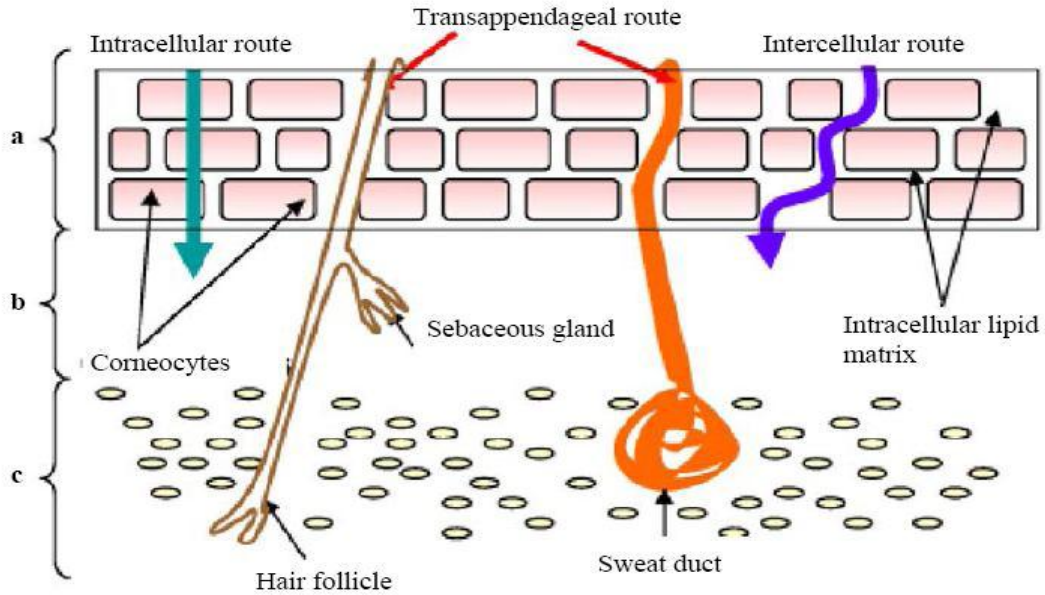

Figure No. 1: Pathways through the skin: a) Epidermis b) Dermis c) Subcutaneous layer

Transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin[4]. Transdermal drug delivery has many advantages over the oral route of

administration like improving patient compliance in long term therapy, bypassing the first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intrapatient variability and making it possible to interrupt or terminate treatment when necessary[5,6].

The major problem related to the dermal delivery system is that the excellent barrier property of the skin (Fig.1). This resides in the outermost layer, the stratum corneum. This unique membrane is only some 20 μm thick but has evolved to provide a layer that prevents us from losing excessive amounts of water and limits the ingress of chemicals with which we come into contact[7,8]. The precise mechanisms by which drugs permeate the stratum corneum are still under debate but there's substantial evidence that the route of permeation is a tortuous one following the intercellular channels. The diffusional path length is between 300 and 500 μm rather than the 20μm suggested by the thickness of the stratum corneum. However, the tortuosity alone cannot account for the impermeability of the skin. The intercellular channels contain a complex milieu of lipids that are structured into ordered bilayer arrays. It is the combination of the nature of these and the tortuous route that is responsible. A diffusing drug has got to cross, sequentially, repeated bilayers and thus encounters a series of lipophilic and hydrophilic domains. The physicochemical properties of permeants are therefore crucial in dictating the overall rate of delivery. A hydrophilic molecule is going to be held back by the lipophilic acyl chains of the lipids and conversely, a lipophilic permeant won't penetrate well through the hydrophilic headgroup regions of the lipids. Furthermore, the lipids appear to compress very effectively, creating regions within the alkyl chains close to the head groups that have a high microviscosity. This creates multiple layers in which diffusion is comparatively slow[9].

Irbesartan is an angiotensin receptor blocker (ARB) used mainly for the treatment of hypertension. It competes with angiotensin II for binding at the AT1 receptor subtype. Unlike ACE inhibitors, ARBs don't have the adverse effect of dry cough. The use of ARBs is pending revision due to findings from several clinical trials suggesting that this class of drugs could also be associated with a small increased risk of cancer. Hypertension, cardiovascular diseases account for a large proportion of all deaths and disabilities worldwide. Global Burden of Disease study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries. Transdermal systems are ideally suited for diseases that demand

chronic treatment. Despite the suitability of TDDS within the treatment of chronic diseases like hypertension, the high cost of antihypertensive patches than conventional products made the target patients think twice. Despite the high cost of transdermal patches for hypertension treatment, antihypertensive patches with the established dosage forms reduced the occurrence of hospitalization and diagnostic costs [10].

MATERIALS AND METHODS:

MATERIALS:

Irbesartan was received as a gift sample from Avanscure Lifesciences PVT. LTD., India. Hydroxyl poly methylcellulose (HPMC) andEudragit RL/RS 100 was a generous gift from Mission Pharma Ltd, Indore, India. Other materials used in the study (chloroform, methanol, dichloromethane, glycerol, potassium dihydrogen phosphate, Ethylcellulose, propylene glycol, etc.) were of analytical grade. Double-distilled water was used throughout the study.

METHODS:

Matrix-type transdermal patches containing Irbesartan were prepared by the solvent evaporation technique using the composition as given in Table 1. The casting solution was prepared by dissolving weighed quantities of HPMC (350, 400, and 450mg) and ethylcellulose, Eudragit RSPO (50, 100, and 150mg) and Eudragit RLPO (50, 100 and 150mg) in 10 mL of methanol and chloroform and water mixture in ratio 1:1. To the resulting solution, 0.5% w/w of propylene glycol as a plasticizer and 10% w/w penetration enhancer was added in this solution. Then drug (10 mg) was added and mixed thoroughly to form a homogeneous mixture. The casting solution was then poured into a glass mold/Petri dish specially designed to seize the contents. The glass mold containing the casting solution was dried at room temperature for 24 hours in a vacuum oven. The patch was removed by peeling and cut into 2.5x2.5 cm^2. These patches were kept in desiccators for 2 days for further drying and enclose in aluminum foil and then packed in self-sealing cover.

Table No. 1: Different Formulation used for Optimization TDDS

Formulation Code	Drug (mg)	HPMC (mg)	Eudragit RSPO (mg)	Eudragit RLPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Propylene glycol (Plasticizer) % w/w	Permeation Enhancer % w/w
F1	900	450	-	-	50	500	0.5	10
F2	900	400	-	-	100	500	0.5	10
F3	900	350	-	-	150	500	0.5	10
F4	900	450	50	-	-	500	0.5	10
F5	900	400	100	-	-	500	0.5	10
F6	900	350	150	-	-	500	0.5	10
F7	900	450	-	50	-	500	0.5	10
F8	900	400	-	100	-	500	0.5	10
F9	900	350	-	150	-	500	0.5	10

Evaluation and Characterization of Transdermal Patches:

A) Thickness: The thickness of the formulated film was measured at 3 different points employing a digital caliper and the average thickness of three readings was calculated [11].

B) Percent moisture content: The prepared films were marked, then weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hrs. The films were weighed again and again individually until it showed a constant weight. The percentage of moisture content was calculated as a difference between the initial and final weight concerning final weight [12].

$$\%\text{moisture} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Determination of moisture uptake: A weighed film kept in a desiccator at normal room temperature for 24 hrs, was taken out and exposed to 84% relative humidity (saturated solution of potassium chloride) during a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight concerning initial weight [12].

$$\%\text{moisture} = \frac{\text{final weight} - \text{initial weight}}{\text{final weight}} \times 100$$

C) Folding endurance: The folding endurance was measured manually for the prepared films. A strip of film (2 x 2 cm) was cut and repeatedly folded at the identical place till it broke. The no. of times the film could be folded at the identical place without breaking/cracking gave the value of folding endurance [13].

D) Tensile strength: Tensile strength is that the maximum stress applied to a degree at which the film breaks. rectangular patch strips of 25.4mm X 50mm were fixed between the jaws of the instrument. The load on the strip was gradually increased to a maximum at a speed of 50mm/min. & also the change within the length of the strips that occurred with increasing stress was measured. Tensile strength and percent elongation of three patches of every batch was measured [14].

$$\text{Tensile Streanght}(s) = \frac{\text{Applied force}(m * g)}{\text{Cross sectional}\ (b * t)}$$

E) Drug content: A specified area of patch was dissolved in a phosphate buffer solution. The content was stirred to dissolve the film. The content was transferred to a volumetric flask. The absorbance of the solution was measured at wavelength 284nm and determines the drug content [15].

F) *In-vitro* skin permeation study: The *in-vitro* skin permeation study was allotted by employing a Franz diffusion cell (receptor compartment capacity: 80 ml: area: 2.5*2.5 cm^2 (Equivalent to 75 mg of drug). The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the center of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in a position such that the surface of the membrane just touches the receptor fluid surface. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed within the diffusion cell. The temperature of the receptor compartment was maintained at 32±0.5ºC. The samples were

withdrawn at different time intervals and analyzed for drug content. At the same time receptor phase was replaced with an equal volume of buffer solution at each time interval.

Release Kinetics Studies:

➢ **Zero-order kinetics-** Drug dissolution from pharmaceutical dosage forms that don't disaggregate and release the drug slowly (assuming that area doesn't change and no equilibrium conditions are obtained) can be represented by the following equation;

$$Q_t = Q_o + k_o t$$

Where, Q_t= amount of drug released in time't', Q_o= initial amount of drug within the solution, k_t= zero-order release constant.

The pharmaceutical dosage forms following this profile, release an equivalent amount of drug by the unit of time and it's the ideal method of drug release to achieve a pharmacological prolonged action. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as within the case of some transdermal system, as well as matrix tablets with low soluble drugs coated form, osmotic systems, etc.

➢ **First-order kinetics -** The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967). The following relation can express this model:

$$\text{L og } Q_t = \text{Log } Q_o + k_t t/2.303$$

Where, Q_t= amount of drug released in time't', Q_o= initial amount of drug within the solution, k_t= first-order release constant.

The pharmaceutical dosage forms following this dissolution profile, like those containing water-soluble drugs in porous matrices, release the drug during a way that's proportional to the quantity of drug remaining in its interior, in such way, that the amount of drug released by a unit of time diminishes.

➢ **Korsmeyer-Peppas model -** Korsmeyer et al., (1983) developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time (t);

$$f_t = at^n$$

Where, a = constant incorporating structural and geometric characteristics of the drug dosage form, n = release exponent, $f_t = M_t/M_\infty$ = fraction release of the drug.

The objectives of the developments of in-vitro diffusion study are to show the release rates and extent of drug release from the dosage form. The study was carried out for 24 hr duration which was represented graphically.

RESULTS AND DISCUSSION:

Table No. 2: Evaluation and Characterization of Transdermal Patches of Irbesartan

Formulation Code	Thickness (mm)	% Moisture content (w/w)	% Moisture uptake (w/w)	Folding endurance	Tensile strength (kg/cm^2)	Drug content (mg)
F1	45±2	1.65±0.02	3.25±0.52	155±5	3.4±0.7	93.75±0.25
F2	48±4	1.23±0.45	3.65±0.45	159±8	3.7±0.3	94.53±0.32
F3	50±3	1.41±0.25	3.45±0.32	166±7	4.3±0.5	91.65±0.33
F4	49±5	1.25±0.36	3.22±0.14	185±6	2.9±0.3	96.36±0.42
F5	48±2	1.69±0.25	3.98±0.25	147±8	3.4±0.5	93.92±0.48
F6	46±3	1.45±0.15	3.65±0.26	123±5	3.6±0.2	95.45±0.41
F7	45±4	1.09±0.22	2.65±0.21	198±4	3.5±0.2	94.25±0.32
F8	49±5	1.33±0.32	3.74±0.15	165±6	3.2±0.4	93.12±0.41
F9	47±3	1.65±0.14	3.52±0.45	174±8	3.4±0.1	94.74±0.47

Table No. 3: *In-vitro* cumulative % drug release from an optimized batch of transdermal patches F3

Sr. No.	Time (Hrs.)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	0.5	0.707	-0.301	29.56±0.24	1.471	70.44	1.848
2	1	1.000	0.000	33.36±0.14	1.523	66.64	1.824
3	2	1.414	0.301	55.65±0.19	1.745	44.35	1.647
4	4	2.000	0.602	69.98±0.21	1.845	30.02	1.477
5	6	2.449	0.778	78.98±0.24	1.898	21.02	1.323
6	8	2.828	0.903	85.65±0.16	1.933	14.35	1.157
7	10	3.162	1.000	85.65±0.32	1.933	14.35	1.157
8	12	3.464	1.079	90.23±0.41	1.955	9.77	0.990

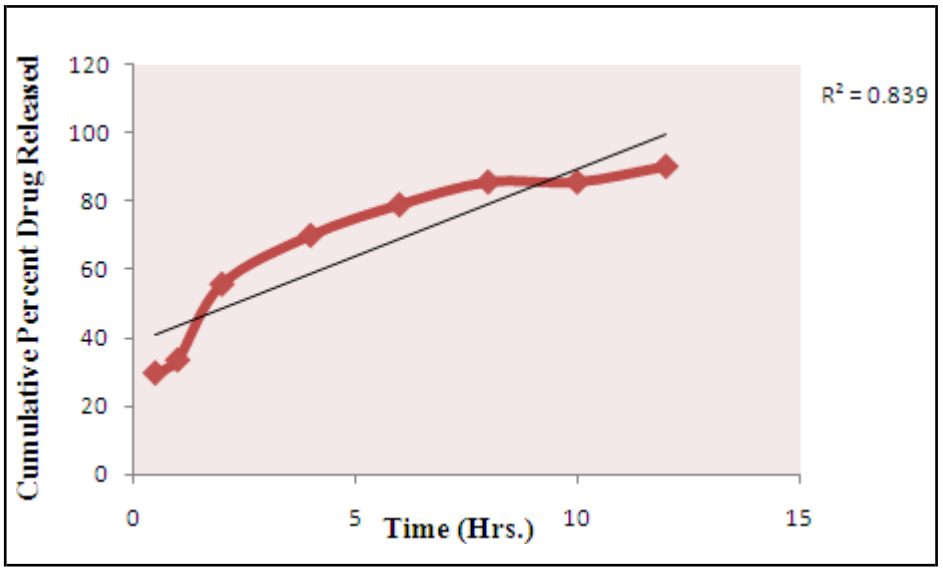

Figure No. 2: Cumulative Percent Drug Released Vs Time (Zero Order Plots)

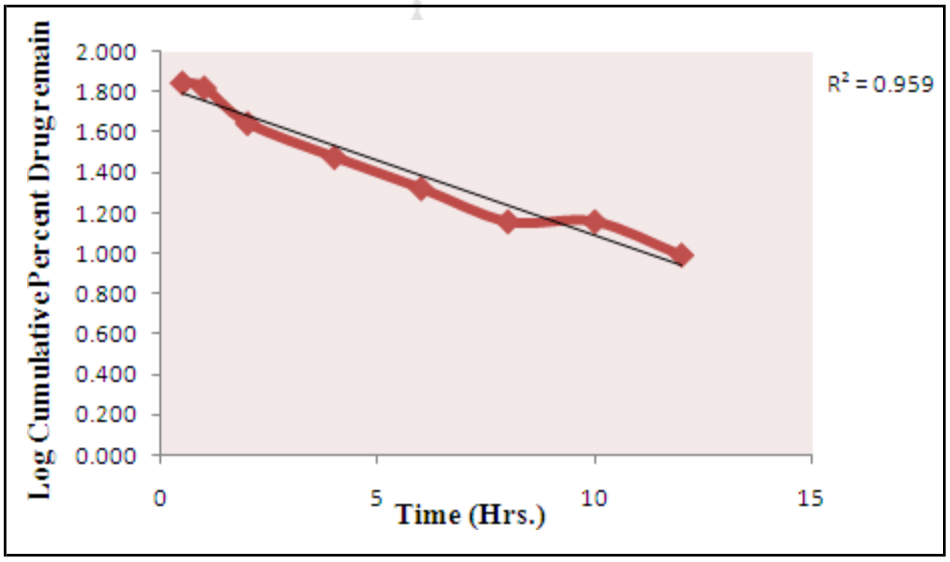

Figure No. 3: Log Cumulative Percent Drug Remaining Vs Time (First Order Plots)

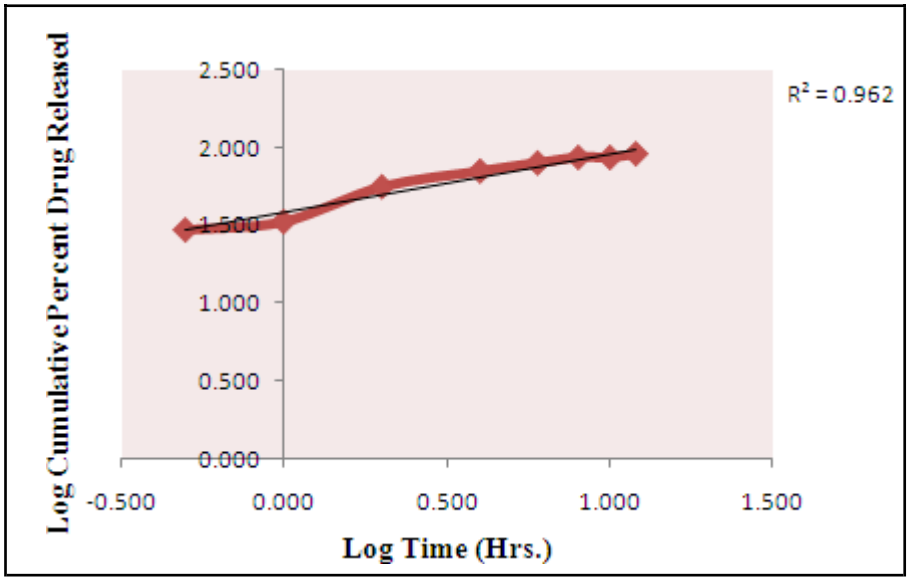

Figure No. 4: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plots)

Table No. 4: Regression Analysis Data of Formulation F4

Formulation	Zero-order	First-order	Pappas plot
F3	$R^2 = 0.839$	$R^2 = 0.959$	$R^2 = 0.962$

The present investigation deals with the preparation of matrix transdermal patches by using a combination of applicable polymers. Total Nine formulations were prepared and evaluated for Thickness, Percent moisture content, Percent moisture uptake, Folding endurance, Tensile Strength, Drug Content, and *in-vitro* skin permeation study. All the formulation show lowest moisture content i.e. less than 2%. Moisture in this value is required to provide strength and flexibility to the patches. Formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9 were found to be contains 1.65±0.02, 1.23±0.45, 1.41±0.25,1.25±0.36, 1.69±0.25, 1.45±0.15, 1.09±0.22, 1.33±0.32 and 1.65±0.14% of moisture content respectively. In all formulations formulation, F7 contains minimum moisture contain 1.25±0.36. This was determined by repeatedly folding one film at the same place until it broke. The no. of times the film might be folded at an equivalent place without breaking / cracking gave the worth of folding endurance. The maximum folding endurance was found 185±6 in formulation F4.

Transdermal patch preparations were observed for any change in appearance or color for 3 weeks. There was no change in appearance in formulation throughout the study.

CONCLUSION:

Irbesartan is an angiotensin receptor blocker (ARB) used mainly for the treatment of hypertension (Cardiovascular disease). Angiotensin2 the principal pressure agent of the rennin angiotensin system is responsible for effects such as vasoconstriction stimulation of synthesis and release of aldosterone. Cardiac stimulation and urinary reabsorption of sodium. Irbesartan is a specific competitive antagonist of the AT1 receptor with a 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 results in multiple effects including vasodilation, reduction in the secretion of vasopressin, and reduction in the production and secretion of aldosterone. The effect may be a decrease in blood pressure. Irbesartan effectively lowers BP in patients with hypertension without effecting heart rate.

The prepared transdermal drug delivery system of Irbesartan using different ratios of polymers such as RLPO and RSPO had shown good promising results for all the evaluated parameters. Based on the *in-vitro* drug release & drug content result, formulation F4 was concluded as an optimized formulation, which shows its higher percentage of drug release.

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