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Selexipag Loaded-Nanoparticulate Transdermal Patches:A Novel Approch for Pulmonary Hypertension Management

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Abstract: A revolutionary drug delivery method called transdermal delivery eliminates a number of obstacles in drug therapy, including the requirement for assistance, intermediate dosage, and painful administration. In comparison to traditional drug delivery methods, transdermal distribution has various benefits, including the avoidance of hepatic first pass metabolism, a potential reduction in side effects, and an increase in patient compliance. In the present study, the focus was on the development of Selexipag nanoparticle loaded transdermal patch by using solvent displacement technique or nanoprecipitation method using HPMC K-100M, PVP and PEG 400 of different ratios. The results indicated that the strategy adopted, viz, preparation of Selexipag polymeric nanoparticles and incorporation of these prepared nanoparticles into a transdermal patch, was successfully enhancing the permeation of drug nanoparticles. As the concentration of the polymerincreased, there was an increase in the thickness of the patch.

Keywords: Transdermal Patch, Selexipag, Nanoparticles, Nano precipitation method.

I. INTRODUCTION

Currently, the most widely used drug delivery method is the oral route due to its convenient administration. But it also has significant drawbacks, such as low bioavailability because of first pass effect and a tendency to result in dose-frequency variations in plasma drug levels, which can be prohibitively expensive and cumbersome.[2]

Continuous intravenously (I.V.) infusion is a viable form of systemic drug delivery that can keep medication levels constant and sustained within the therapeutic range for a considerable amount of time throughout the course of treatment. However, this technique of medication delivery includes considerable health hazards, including the potential for pain and needle sticks, especially for people who need many injections each day. As a result, it's critical to stay in a hospital while receiving medical attention. Subsequent studies indicated that medicine delivered by skin might very well match the advantages of intravenous infusion without any of its drawbacks. This is referred to as transdermal administration, and the drug therapy

delivery methods include transdermal therapeutic systems, transdermal drug delivery systems, or simply transdermal patches.[3]

Currently, the transdermal route has emerged as one of the most productive and innovative areas of focus for drug delivery research, with around 40% of medication candidates undergoing clinical evaluation connected to transdermal or dermal systems.[5]

The present research work was planned with the main aim of developing Selexipag Nanoparticles loaded transdermal patches which will be used to treat the symptoms of pulmonary arterial hypertension.

II. MATERIALS AND METHODS

Selexipag was received as a gift sample from Vama Pharma; Nagpur. The rest of the substances and components were all of the analytical or therapeutic variety.

2.1 Method of Preparation of Selexipag Nanoparticles

Table 1 shows composition for six batches of selexipag loaded nanoparticles. Eudragit RL 100 was used to create polymeric NPs of Selexipag using the solvent displacement method. In order to create the organic phase, the polymer (1-3 mg) and Selexipag (1 mg) were dissolved in 0.2 ml of a 3:1 acetone to methanol mixture. This organic phase was introduced into an aqueous medium (0.04 ml) containing PVA (1-2%) (hydrophilic surfactant) as a stabilizer while being moderately stirred by magnetism (1000 rpm) through a 0.22 µm aperture at a rate of 1 ml/minute at atmospheric pressure. Stirring was maintained at the same speed for an hour following the addition of the organic phase. To get the right particle size, it was sonicated for two minutes after an hour. Later, the colloidal dispersion was subjected to heating under reduced pressure at 58 ^{o}C to remove acetone and methanol (solvents) and the solution was concentrated.

Table 1 : Composition of Selexipag loaded Nanoparticles

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Selexipag (mg)	1	1	1	1	1	1
EudragitRL100 (mg)	1	1	2	2	3	3
Acetone:Methanol (ml)	3:1	3:1	3:1	3:1	3:1	3:1

Polyvinyl Alcoho l(%)	1	2	1	**2**	1	2
Water (ml) upto	0.2	0.2	0.2	0.2	0.2	0.2

2.2 Evaluation of Nanoparticles[7,8]

Prepared nanoparticles were evaluated for various parameters like Particle Size Analysis, Surface charge, Drug entrapment, Drug Content, In vitro Drug Release Study, Scanning Electron Microscopy.

2.3 Preparation of the Polymeric Nanoparticles Loaded Selexipag Transdermal Patches

Table 2 : Composition of selexipag Nanoparticles loaded transdermal patches

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Nanoparticles (Selexipag equivalent to1mg)	1	1	1	1	1	1
Hydroxy propyl methyl cellulose K100M (mg)	0.5	1	2	0.5	1	2
Polyvinylpyrrolidone (mg)	0.5	1	2	1	2	4
Polyethyleneglycol 400 (%)	0.5	1	2	0.5	1	2
Methanol: water (2:1) (ml)	2:1	2:1	2:1	2:1	2:1	2:1

The composition of selexipag loaded transdermal patches were given in Table 2. Boiling water was used to dissolve different amounts of HPMC K100M and PVP to create transdermal patches. Using a magnetic bead and a magnetic stirrer, a homogeneous solution was created. The necessary quantity of dried selexipag nanoparticles was dissolved in a mixture of methanol and water. After adding this solution to the homogenous mixture mentioned above, it was agitated until a homogenous suspension was achieved. Next, plasticizers (0.5, 1%, and 2%

solutions of PEG 400) were added in accordance with the formula. One percent of the films contained drugs. The patches were prepared using the solvent casting technique. A specially made stainless steel spherical assembly made up of two stainless steel plates with an interior diameter of 7.9 cm (area 48.99 cm^2) was filled with the solution combination. The solvent was allowed to evaporate at a temperature of 37 ± 0.5 °C and at a relative humidity of 40 ± 5%. An inverted funnel was placed over the metallic assembly to prevent rapid evaporation of the solvent. All patches were separated from the casting assembly with the help of a sharp blade and were then stored in the desiccators for further use.

2.4 Evaluation of Prepared Selexipag Nanoparticles Loaded Transdermal Patch[11]

Determination of the Thickness - Using a micrometer, the thickness of the produced films was determined. Each film's thickness was measured five times, and the average values were computed.

Tensile Strength - A tensiometer was used to assess the patch's tensile strength. There are two load cell grips in it. While the top one was adjustable, the lower one was fixed. Two-by-two-centimeter film strips were positioned in between these cell grips, and force was applied progressively until the film snapped. The dial reading in kg was used to determine the tensile strength directly.

Folding Endurance Measurement - The purpose of this test was to determine how brittle the produced films were. The films were repeatedly folded in the same spot until they completely broke down. It was established how many folds were needed to break the films.

Flatness - The prepared medicated film will be sliced into longitudinal strips, with each strip's length measured. Next, the length variation brought on by the unevenness in flatness will be quantified. The strips' constriction will be measured in order to determine flatness; a constriction of 0% is equivalent to 100% flatness.

$$\text{Constriction (\%)} = S1 - S2 / S1 \times 100$$

Where, S1-initial length of strip S2-final length of strip

Moisture Uptake - The films were weighed (Wi) using a Shimandzu digital balance after being placed in a desiccator filled with silica gel for a full day. After that, the films were moved to another desiccator that held a saturated NaCl solution at a temperature of 25°C and a relative humidity of 75% until a consistent weight was reached. The patches were removed and weighed once equilibrium was reached (Wf). Moisture uptake capacity was calculated according to the following equation:

$$\text{Moisture uptake capacity} = \frac{Wf - Wi}{Wi} \times 100$$

Moisture Content - The produced patches were weighed (Wi) and stored at 25℃ in desiccators with silica gel until their weight (Wd) exhibited a consistent value. The moisture content was calculated according to the following equation:

$$\text{Moisture content (\%)} = \frac{Wi - Wd \times 100}{Wd}$$

Where, W_d is the weight of the dried polymer film

W_i denotes the initial weight of the film.

Mechanical Properties - Using a Chatillon apparatus for force measurement, the mechanical properties were assessed. The space between the upper and lower jaws was filled with rectangular patch strips that were fixed in length and breadth. One millimeter per second was used to move the lower jaw downward. Curves of load against displacement were corded until the film broke. The mechanical properties were determined as follows:

$$\text{Tensile Strength} = \frac{\text{Breaking Force (Kg)}}{\text{Area of the Patch (cm}^2\text{)}}$$

In-vitro Permeation Study - The Franz diffusion cell, with a 25 ml capacity, was used for the in vitro permeation evaluation of the patches. A dialysis membrane was used to keep the donor and receptor compartments apart. Cut into equal sections (2.5 cm x 2.5 cm), the dialysis membrane (thickness 0.025 mm) was soaked in distilled water for 12 hours before to use. The dialysis membrane utilized in the investigation has a molecular weight of 50 K Daltons. The drug release experiments were conducted in 10 milliliters of phosphate buffer (pH 7.4 saline), maintained at 37± 2℃ using a magnetic stirrer and continuous heating apparatus. In the receptor compartment, a sample of two milliliters of transdermal patch suspension was added. One milliliter aliquot samples were taken out at regular intervals and replaced with an equal volume of brand-new buffer. When necessary, fresh medium was added to the aliquots. A UV-Visible spectrophotometer operating at 270 nm, was used to measure the amount of Selexipag medication that diffused across the membrane in comparison to a saline phosphate buffer with a pH of 7.4 as blank.

Stability Study - Stability testing is done to determine a drug product's shelf life and suggest storage conditions by demonstrating how the quality of a drug substance or drug product changes over time under the influence of various environmental factors like temperature, humidity, and light. Three months were dedicated to conducting stability studies on specific formulations in accordance with ICH recommendations, namely ICHQ1AR: "Stability testing of new drug substances and products." 5% RH ± 5% and 25°C ± 2℃/60% RH Frequency of testing: Samples were assessed every 0, 1, 2, and 3 months. Evaluation: The drug content,

folding endurance, tensile strength, and drug release studies of the sampled formulations were assessed.

III. RESULTS AND DISCUSSION

3.1 Evaluation of Selexipag Nanoparticles –

Table 3 shows results for various evaluation parameters like particle size, zeta potential, entrapment efficiency, drug content and Figure 1 shows graphical representation of zeta potential. Among all the formulation, F4 gave high entrapment efficiency, high drug content and it releases drug in a gradual and complete drug release until 12 hours. The F4 formulation contains drug: polymer in the ratio of 1:2 with 2 % PVA. This product was considered as optimized. In order to create dry nanoparticles for use in the creation of a transdermal patch loaded with nanoparticles, the produced nanosuspension of F4 underwent additional lyophilization.

Table 3 : Evaluation data of prepared Selexipag Nanoparticles

Formulation Batches	Particle Size (nm)	Zeta Potential	Entrapment Efficiency (%)	Drug Content (%)
F1	351.7±0.61	21.1±1.34	69.76±5.16	94.75±0.62
F2	330.6±0.87	16.0±2.51	75.65±4.49	96.52±0.65
F3	200.2±0.74	15.4±2.32	79.13±2.86	98.63±0.79
F4	190.2± 0.42	18.6±2.31	86.07±3.97	99.66±0.33
F5	300.9±0.43	14.6±2.22	76.18±3.20	98.25±0.55
F6	291.8±0.53	13.4±1.42	78.25±0.93	97.06±0.34

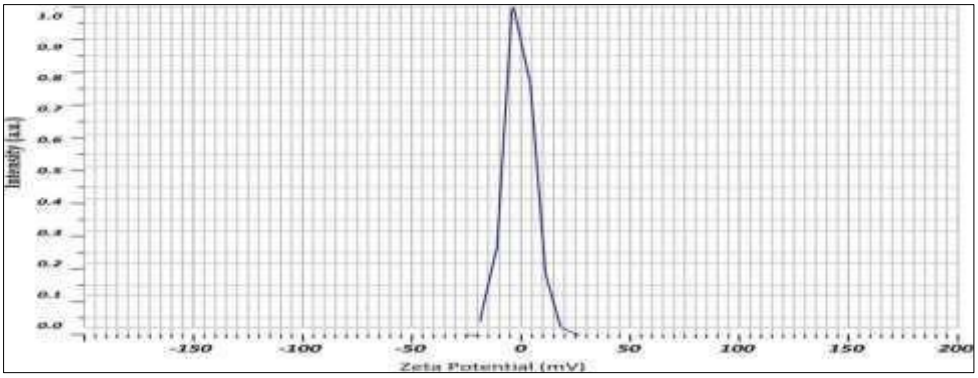

Figure 1 : Zeta Potential

In-Vitro Drug Release Study of Selexipag loaded Nanoparticle - The rate of drug release and the duration of drug release are outcomes that are determined by the interaction of various factors, including the drug's polymer, particle size, solubility, and properties of the nanoparticles, such as the formation of the polymer network and the facilitation of diffusion. The Selexipag nanoparticle in vitro drug release investigation was conducted over the course of 12 hours using the membrane diffusion method. Since formulation F4 exhibits the highest entrapment efficiency, batch F4 is subjected to in vitro drug release. With an increase in polymer content, 97% of the drug was released within 12 hours which is depicted in Figure 2.

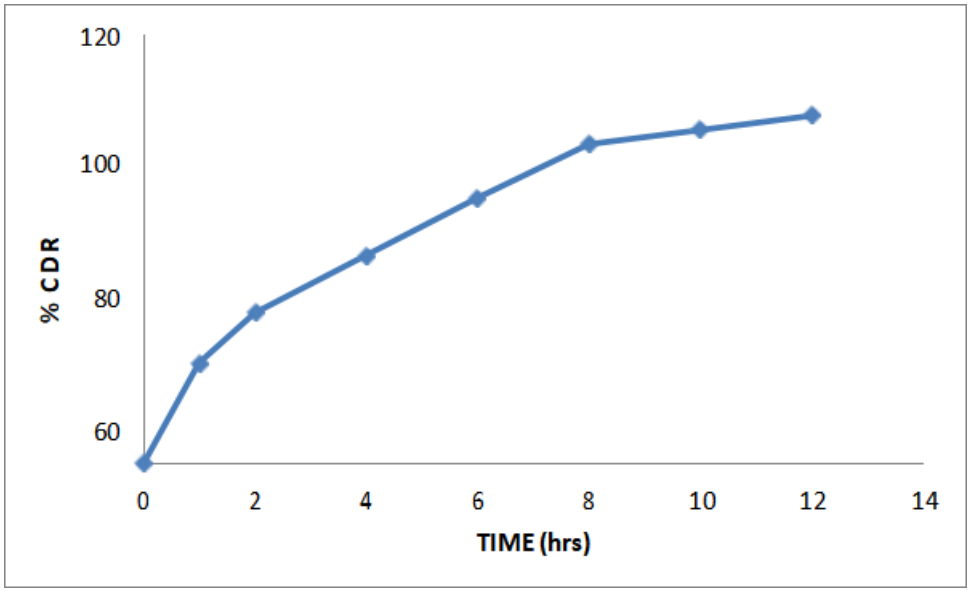

Figure 2 : In Vitro Drug Release for Formulation F4

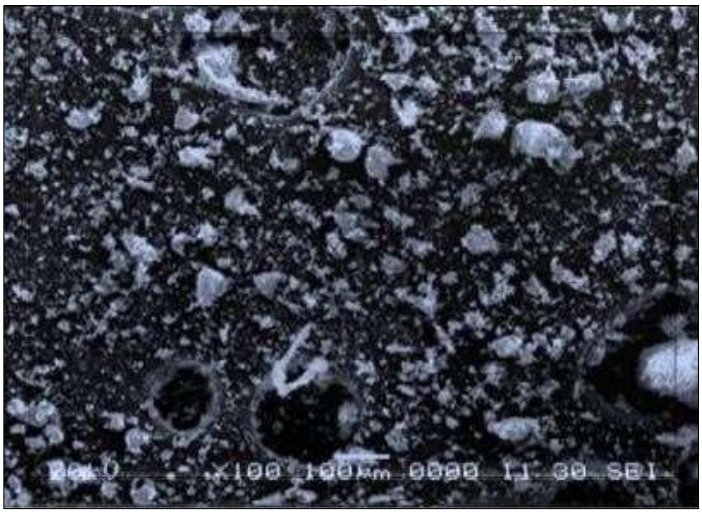

Figure 3 : SEM Images of Selexipag Nanoparticles

The nanoparticles were tiny, spherical, and porous by nature, as demonstrated by SEM showed in Figure 3. The powder Selexipag looked as crystalline powder on the SEM picture. On the other hand, the transformed solid nanoparticles had smooth surfaces, indicating that the Eudragit RL-100 polymer had completely bonded to them.

3.2 Evaluation of Prepared Selexipag Nanoparticles Loaded Transdermal Patches –

The patch made with HPMC and PVP had a tensile strength of between 0.933 and 1.953 kg/cm2. It was discovered that as the concentration of PVP and HPMC climbed, the patch's tensile strength gradually increased. The test for folding endurance is essential in assessing the sample's ability to tolerate folding. This also offers proof of brittleness. The folding endurance value was determined to be between 194 to 252 folds, indicating good film property and being deemed satisfactory. Because the strip lengths were the same before and after the cuts, the flatness study indicated that every formulation showed 100% flatness. No constriction was visible, and each patch had a flat, smooth surface that could be maintained when the patch was placed on the skin. Patches with higher concentrations of the hydrophilic polymer hydroxyl propyl methyl cellulose absorb moisture more readily. It was found that the formulations' moisture content increased in response to increases in both PVP concentration and HPMC grade. The percentage of moisture absorbed by the patches varied from 9.18 ± 0.08 to 16.76 ± 0.63. Because of their lower moisture content, the compositions are more stable and solidify into a completely dry, brittle covering. Again, low moisture uptake protects the material from microbial contamination and bulkiness. Table 4 shows the detailed data of evaluation parameters like thickness, tensile strength, folding endurance, flatness, moisture uptake and moisture content.

Table 4 : Evaluation data of prepared Selexipag nanoparticles loaded transdermal patch

Formulation code	Thickness (mm)	Tensile strength (kg/cm^2)	Folding endurance	Flatness (%)	Moisture absorption /uptake (%)	Moisture Content (%)
F1	0.215±0.04	0.933±0.02	194±1.23	100	9.18±0.08	7.8±0.44
F2	0.228±0.02	1.023±0.06	252±2.14	100	11.23±0.98	6.4±0.53
F3	0.277±0.03	1.826±0.01	208±3.21	100	14.22±0.24	7.5±0.23
F4	0.216±0.04	1.433±0.07	218±2.29	100	14.26±0.08	6.7±0.77
F5	0.268±0.02	1.655±0.06	199±3.56	100	15.35±0.45	8.1±0.35
F6	0.274±0.02	1.953±0.12	221±2.43	100	16.76±0.63	8.4±0.97

For every formulation from F1 to F6, the medication released gradually, biphasically, and slowly. However, the drug leak continued for 12 hours, during which the entire maximum amount of medication from the F2 batch was released. The in vitro release data of selexipag nanoparticles loaded transdermal patches from F1-F6 batches was depicted in Figure 4.

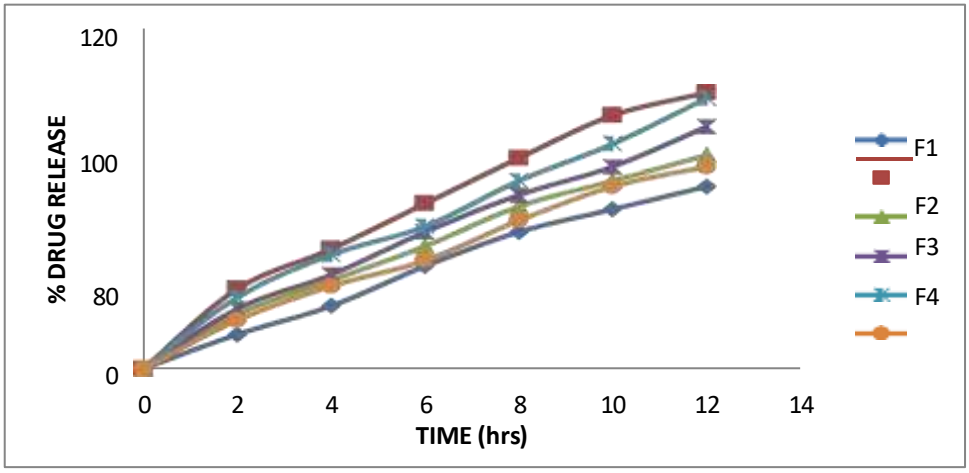

Figure 4 : In Vitro Drug Release Data of Selexipag Nanoparticles Loaded Transdermal Patches (F1-F6)

The formulation's stability studies demonstrated that the drug content, tensile strength, folding endurance, and drug release parameters that were chosen showed negligible fluctuation.

IV. CONCLUSION

The outcomes showed that the chosen strategy creating Selexipag polymeric nanoparticles and adding them to a transdermal patch was successful in boosting medication nanoparticle penetration.

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