# DEVELOPMENT AND EVALUATION OF MACITENTAN LOADED NANOPARTICULATE TRANSDERMAL PATCHES

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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 Macitentan nanoparticle loaded transdermal patch by using solvent displacement technique or nano precipitation method.
Particle size and distribution were two important factors influencing the drug's penetration. The drug content, entrapment efficiency, zeta potential, particle size, and in vitro diffusion experiments were used to characterize the produced nanoparticles. The mean size of all six formulations was modest, which is appropriate for a transdermal administration technique. Transdermal patches loaded with macitentan nanoparticles were made using Eudragit RS 100, and varying percentages of ethyl cellulose.
The results indicated that the strategy adopted, viz, preparation of Macitentan polymeric nanoparticles and incorporation of these prepared nanoparticles into a transdermal patch, will successful in enhancing the permeation of drug nanoparticles. As the concentration of the polymer increased, there was an increase in the thickness of the patch.

**Keywords:** Transdermal Patch, Macitentan, Nano precipitation method, Eudragit RS 100.

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## I. INTRODUCTION

Due to its simplicity of use, oral medication distribution is currently the most used approach. However, it also has a number of serious disadvantages, including limited bioavailability due to first pass digestion and a propensity to induce dose-frequency fluctuations in plasma drug levels, which can be extremely costly and time-consuming.[2]

Research showed that medication applied topically could very well match the benefits of intravenous infusion while excluding all of its disadvantages. This process is known as transdermal delivery. Among the methods for delivering pharmacological therapy are transdermal patches, transdermal therapeutic systems, and transdermal drug delivery systems.[3]

As of right now, drug delivery research is focusing a great deal of energy and creativity on the transdermal route; around 40% of drug candidates going via clinical review are associated with transdermal or dermal systems.[5]

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

## II. MATERIALS AND METHODS

Macitentan 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.

### 1. Pre-Formulation Study

Pre-formulation testing is the first stage in the systematic development of a pharmacological substance's dosage forms. Pre-formulation study is a method that maximizes drug delivery by determining the physicochemical properties of the excipients that may affect the performance of the treatment and the creation of a safe, stable, and effective dosage form. It provides a dosage form structure for the drug combination that contains pharmaceutical excipients. It was done to measure organoleptic qualities like color, odor, and taste, melting point, solubility studies, determination of absorbance maximum, calibration curve, FTIR Studies.

### 2. Method of Preparation of Macitentan Nanoparticle

**Table No.1: Composition of Macitentan loaded Nanoparticles**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Macitentan (mg) | 10 | 10 | 10 | 10 | 10 | 10 |
| PEG-PLGA (mg) | 10 | 10 | 20 | 20 | 30 | 30 |
| Acetonitrile (ml) | 2 | 2 | 2 | 2 | 2 | 2 |
| Polyvinyl Alcohol (%) | 1 | 2 | 1 | 2 | 1 | 2 |
| Water (ml) upto | 2 | 2 | 2 | 2 | 2 | 2 |

By using the solvent displacement approach, PEG-PLGA was used to create Macitentan polymeric NPs. Table no. 1 shows Composition of Macitentan loaded Nanoparticles. The organic phase was created by dissolving the polymer (10–30 mg) and Macitentan (10 mg) in 2 milliliters of acetonitrile solvent. With a modest amount of stirring by magnetism (1000 rpm) via a 0.22 µm aperture, this organic phase was added to an aqueous medium (2 ml) containing PVA (1-2%) (hydrophilic surfactant) as a stabilizer at a rate of 1 ml/minute at atmospheric pressure. After adding the organic phase, stirring was continued at the same pace for an hour. After an hour, it was sonicated for two minutes to get the desired particle size. Subsequently, acetonitrile and polyvinyl alcohol (solvents) were eliminated from the colloidal dispersion by heating it at 58°C under decreased pressure, and the solution was concentrated.

### 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 and Scanning Electron Microscopy.

### 3. Preparation of the Polymeric Nanoparticles Loaded Macitentan Transdermal Patch

**Table No. 2: Composition of Macitentan nanoparticle loaded transdermal patch**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Nanoparticles (Macitentanequivalent to 10 mg) | 10 | 10 | 10 | 10 | 10 | 10 |
| Eudragit RS 100(mg) | 5 | 10 | 20 | 5 | 10 | 20 |
| Ethyl Cellulose(mg) | 5 | 10 | 20 | 10 | 20 | 40 |
| Polyethylene glycol 400(%) | 0.5 | 1 | 2 | 0.5 | 1 | 2 |
| Ethanol : water (1:1) | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 |

Boiling water was used to dissolve different amounts of ethyl cellulose and Eudragit RS 100 to create transdermal patches. A magnetic bead and a magnetic stirrer were used to create a homogenous solution. Dried Macitentan nanoparticles in the required amount were dissolved in a solution of ethanol and water. After adding this solution to the homogenous mixture mentioned above, it was agitated until a homogenous suspension was achieved. Plasticizers (PEG400 solutions at 0.5, 1%, and 2% concentrations) were then added using the formula. There was drug content in 10 percent of the movies. The patches were created using the solvent casting technique. Inside a specially-built spherical assembly made of two stainless steel plates with an inner diameter of 7.9 cm (area 48.99 cm2), the solution combination was inserted. The solvent was allowed to evaporate at 37 0.5°C with a relative humidity of 40 ± 5%. To prevent the solvent from evaporating too quickly, an inverted funnel was placed above the metallic assembly. Using a sharp knife, each patch was taken off the casting assembly and preserved in the desiccators for later use. Different batches were prepared and composition for the same is depicted in table no. 2.

**Evaluation of Prepared Macitentan Nanoparticles Loaded Transdermal Patch**

**a. 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.

**b. Tensile Strength**

The tensile strength of the patch was evaluated using a tensiometer. It has two load cell grips. While the top one was adjustable, the lower one was immovable. Between these cell grips, two-by-two-centimeter film strips were positioned, and strain was exerted progressively until the film snapped. The dial reading in kg was used to determine the tensile strength.

**c. Folding Endurance Measurement**

The purpose of this test was to determine how brittle the produced films were. The films were folded in the same area over and over until they finally fell apart. It was established how many folds were needed to break the films.

**d. 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 flatness of the strips will be ascertained by measuring their constriction; a constriction of 0% corresponds to 100% flatness.

Constriction (%) = S1 − S2 /S1 × 100

Where, S1- initial length of strip

S2 - final length of strip

**e. Moisture Uptake**

The films were weighted (Wi) on a Shimandzu digital balance after being dried for one entire day in a desiccator using silica gel. After that, the films were moved to another desiccator that held a saturated NaCl solution. This desiccator was maintained at 25°C and 75% relative humidity until the films reached a stable weight. Upon reaching balance, the patches were removed and weighed (Wf). The moisture uptake capacity was calculated using the following equation:

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

**f. Moisture Content**

The resulting patches were weighed (Wi) and kept in silica gel-filled desiccators at 25°C until their weight (Wd) showed a stable value. The moisture content was calculated using the formula below:

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

Where, $W_d$ is the weight of the dried polymer film $W_i$ denotes the initial weight of the film.

**g. Mechanical Properties**

Using a Chatillon apparatus for force measurement, the mechanical properties were assessed. Rectangular patch strips, fixed in length and width, filled the area between the lower and upper jaws. 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 characteristics are ascertained as follows:

$$\text{Tensile strength} = \frac{\text{Breaking force (kg)}}{\text{Area of the patch (cm2)}}$$

**h. *In-vitro* Permeation Study**

The Franz diffusion cell, with a 25 ml capacity, was used to examine the in vitro penetration of the patches. A dialysis membrane was used to keep the donor and receptor compartments apart. The dialysis membrane (thickness 0.025 mm) was cut into equal parts and left to soak in distilled water for 12 hours prior to use. The dialysis membrane used in the experiment has a molecular weight of 50 K Daltons. The drug release experiments were conducted in 10 milliliters of phosphate buffer

(pH 7.4 saline), which was heated to 37± 2°C continuously and mixed with a magnetic stirrer. A sample of two milliliters of transdermal patch suspension was introduced to the receptor compartment. At regular intervals, one milliliter aliquot samples were removed and replaced with an equivalent volume of fresh buffer. New media was introduced to the aliquots as needed. The amount of Macitentan medicine that diffused across the membrane was measured using a UV-visible spectrophotometer operating 258 nm, in comparison to a saline phosphate buffer with a pH of 7.4 as a blank.

## III. RESULTS AND DISCUSSION

### 1. Pre-Formulation Study

Results of preformulation studies indicated that the official numbers and the experimental results coincided well, proving the purity of the medicine powder used in the study. The physical mixture's FTIR peaks were compared to the original spectra. The absence of any molecular interaction between the drug and the polymer is indicated by the appearance of identical peaks. Hence at the end it can be concluded that the drug and selected excipients were compatible with each other.

### 2. Evaluation of Macitentan Nanoparticles

**Table No. 3: Evaluation data of Macitentan Nanoparticles**

| Formulation Batches | Particle Size (nm) | Zeta Potential | Entrapment Efficiency (%) | Drug Content (%) |
|---|---|---|---|---|
| **F1** | 78.5±0.30 | -0.80±0.02 | 88.60±1.2 | 98.28±1.1 |
| **F2** | 84.10±0.51 | -0.92±0.03 | 80.23±0.9 | 94.60±1.2 |
| **F3** | 208.63±0.20 | 2.12±0.04 | 72.88±1.2 | 90.34±1.3 |
| **F4** | 117.91±1.20 | 1.12±0.05 | 71.34±1.3 | 94.56±0.8 |
| **F5** | 101.30±1.0 | -0.96±0.03 | 70.00±1.3 | 93.23±0.9 |
| **F6** | 80.83±0.68 | -0.87±0.04 | 84.91±1.1 | 96.91±1.4 |

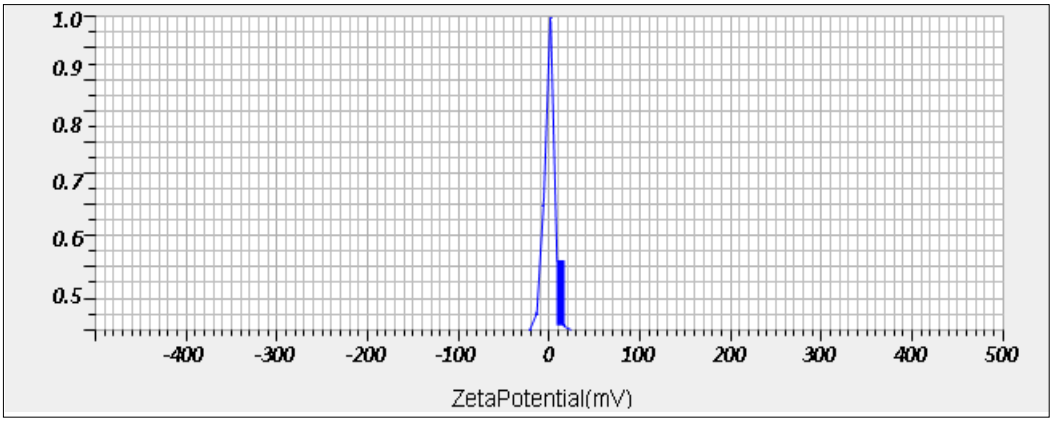


**Figure No.1: Zeta Potential**

Transdermal drug delivery is the intended usage of the created Macitentan nanoparticles. Therefore, the zeta potential and particle size are essential factors for the medicine to permeate the body safely and effectively. Table no. 3 shows results for various evaluation parameters of Macitentan nanoparticles. The mean sizes of all the formulations were moderate, making them appropriate for transdermal administration. The data indicates that the particle sizes range from 78.5 to 208.63 nm. Over 70% of the formulations exhibited signs of drug entrapment. Nevertheless, formulation F1 had a higher drug entrapment efficiency of 88.60% in comparison to all other formulations. All of the formulations that were created had drug contents higher than
90%. The statistics for drug content and drug entrapment efficiency are consistent among formulation batches, as indicated by the low standard deviation values. The F1 formulation was chosen out of all of the formulations due to its small particle size and good drug entrapment efficiency.

### *In-Vitro* Drug Release Study of Macitentan loaded Nanoparticles

The drug polymer's, particle size, solubility, and characteristics of the nanoparticles, such as the formation of the polymer network and the facilitation of diffusion, interact to determine the rate and duration of drug release. Using the membrane diffusion approach, the Macitentan nanoparticle in vitro drug release study was carried out during a 12-hour period.

Batch F1 is the most effective at trapping, hence this formulation is evaluated in vitro for drug release. When the polymer concentration was increased, 98% of the medicine was released within 12 hours.

Out of all the formulations, F1 had the highest drug concentration, the highest entrapment efficiency, and the slowest, most thorough drug release over a 12-hour period. The F1 formulation contains 1% PVA along with a 1:1 ratio of drug to polymer. It was thought that this product was optimized. The resulting nanosuspension of F1 underwent additional lyophilization to produce dry nanoparticles that could be used to fill a transdermal patch.

**Scanning Electron Microscopy of Macitentan nanoparticles**

The nanoparticles were tiny, spherical, and porous by nature, as demonstrated by SEM. The Macitentan powder's SEM scan showed an amorphous powder. However, the converted solid nanoparticles indicate complete adsorption of PEG-PLGA polymer. Figure no. 2 shows SEM Image of Macitentan nanoparticles.

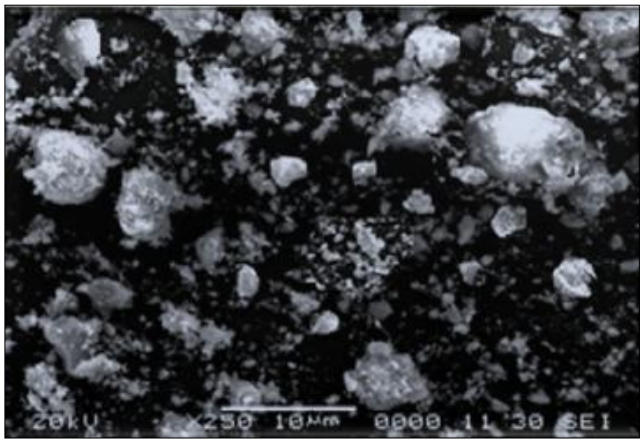


**Figure No. 2: SEM image of Macitentan nanoparticles**

**3. Evaluation of Prepared Macitentan Nanoparticles Loaded Transdermal Patch**

**Table No. 4: Evaluation data of prepared Macitentan nanoparticles loaded transdermal patch**

| Formulation code | Thickness (mm) | Tensilestrength (kg/cm$^2$) | Folding endurance | Flatness (%) | Moisture absorption/uptake (%) | Moisture content(%) |
|---|---|---|---|---|---|---|
| F1 | 0.38±0.03 | 0.394 ± 0.06 | 187±2.23 | 100 | 11.67±0.33 | 8.88±0.05 |
| F2 | 0.49±0.03 | 0.361 ± 0.06 | 196±3.14 | 100 | 12.29±0.39 | 7.96±0.04 |
| F3 | 0.46±0.04 | 0.348 ± 0.10 | 184±4.21 | 100 | 13.64±0.41 | 6.74±0.04 |
| F4 | 0.43±0.02 | 0.371 ± 0.07 | 190±3.29 | 100 | 10.98±0.50 | 7.7±0.77 |
| F5 | 0.53±0.04 | 0.318 ± 0.09 | 199±4.56 | 100 | 14.01±0.44 | 6.11±0.03 |
| F6 | 0.33±0.03 | 0.297 ± 0.06 | 192±2.43 | 100 | 13.99±0.29 | 9.97±0.02 |

The evaluation data for prepared Macitentan nanoparticles loaded transdermal patch was summarized in table no. 4. The patch composed of ethyl cellulose and Eudragit RS 100 had a tensile strength ranging from 0.297 to 0.394 kg/cm2. It was shown that the tensile strength of the patch rose gradually with the quantity of ethyl cellulose and Eudragit RS 100. Determining the sample's folding resistance requires the folding endurance test. This also offers proof of brittleness. It was found that the folding endurance value ranged from 184 to 199 folds, which is considered adequate and indicates good film property. The flatness investigation demonstrated that every formulation exhibited 100% flatness since the strip lengths were the same before and after the cuts. Each patch had a smooth, level surface that could be maintained when it was applied to the skin; no constriction was apparent. Moisture is more easily absorbed by patches that contain larger concentrations of the hydrophilic polymer Eudragit RS 100. The range of the moisture content is 6.11±0.03 to 9.97±0.02. Raising the formulations' moisture content was shown to increase the ethyl cellulose concentration and the eudragit RS 100 grade. The patches moisture uptake values ranged from 10.98±0.50 to 14.01±0.44%. The formulations moisture level keeps them stable and prevents them from drying out entirely and brittlely.

***In-Vitro* Permeation Study of Macitentan Transdermal Patch**

**Table No. 5 : Cumulative percent drug diffused from Macitentan nanoparticle loaded transdermal patch.**

| Time (hrs) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| **1** | 19 ±1.21 | 14 ±1.39 | 20 ±1.76 | 16 ±0.69 | 13 ± 0.79 | 16 ± 1.26 |
| **2** | 25 ±0.96 | 23 ±0.69 | 27 ±0.46 | 21 ±2.07 | 25 ± 1.35 | 29 ± 0.58 |
| **4** | 37 ±0.46 | 39 ±0.62 | 40 ±0.78 | 42 ±1.41 | 39 ± 1.18 | 52 ± 0.58 |
| **6** | 60 ±0.87 | 57 ±0.96 | 62 ±1.65 | 64 ±0.62 | 66 ± 0.95 | 63 ± 1.08 |
| **10** | 78 ±1.23 | 75 ±0.78 | 76 ±0.62 | 79 ±0.53 | 75 ± 1.13 | 78 ± 1.16 |
| **12** | 90 ±0.89 | 93 ±0.79 | 88 ±0.70 | 92 ±1.12 | 95 ± 1.04 | 94 ± 0.89 |

In-vitro drug release is carried out for each batch. For F5, the proportion of drug release within a 12-hour period rose by 95% as the polymer concentration increased.

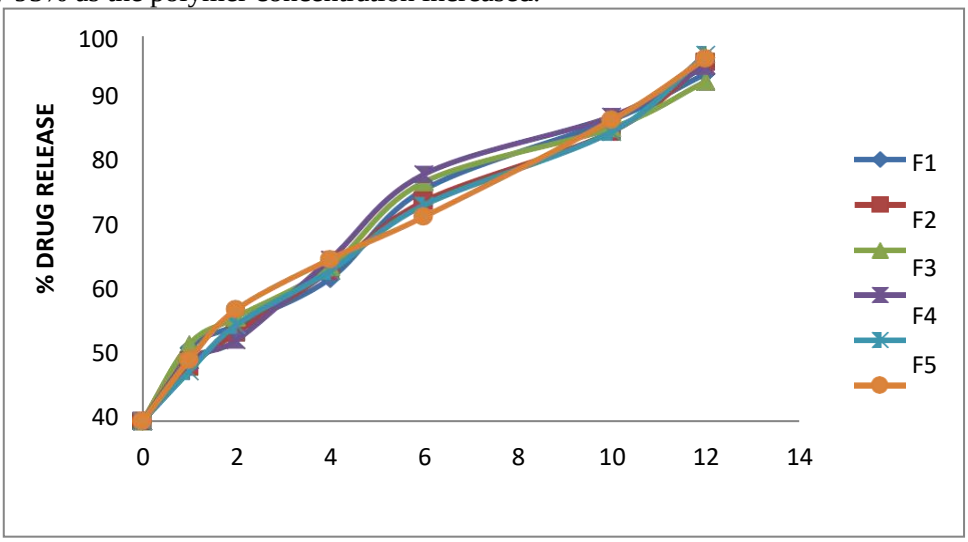


**Figure No. 3: In vitro drug release data of Macitentan Nanoparticles Loaded Transdermal Patch (F1-F6)**

For every formulation from F1 to F6, the medication released gradually, biphasically, and slowly as shown in figure no. 3. However, the drug release lasted for 12 hours, with the F5 batch producing the most drug release. The models of the Zero order, First order, and Higuchi and Peppas equations were used to assess the release data.

## IV. CONCLUSION

A transdermal patch containing Macitentan nanoparticles provides a step-by-step delivery of the drug. It also exemplifies the advantages of a long-lasting effect, ease of administration, and the assurance that it can be stopped once it is no longer required. Because the medication is included in the patch as nanoparticles, it can easily pass past the skin's barriers. This is an innovative approach.

The outcomes showed that the chosen strategy creating Macitentan polymeric nanoparticles and adding them to a transdermal patch was successful.

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