Design and Optimization of Telmisartan Nanosuspension for Improved Drug Delivery

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Abstract

This research paper presents the design and optimization of a nanosuspension formulation for Telmisartan, an antihypertensive drug with poor solubility and bioavailability. The nanosuspension was prepared using a solvent evaporation technique with Poloxamer 188 as surfactants and Sodium lauryl sulfate (SLS) as a stabilizer. The formulation was optimized using a Design of Experiment (DoE) approach. The optimized nanosuspension showed a particle size of 73 nm, a polydispersity index (PDI) of 0.183, and a zeta potential of -22.2 mV. Differential scanning calorimetry (DSC) of drug exhibited a change in crystalline form to amorphous. The *in vitro* drug release studies demonstrated a significant improvement in drug dissolution, with a dissolution rate of optimized nanosuspension formulation (F3) 97.34% in 40 minutes. The developed nanosuspension showed a significant improvement in drug solubility and dissolution making it a promising drug delivery system for Telmisartan with potential clinical applications.

Keywords: Telmisartan, nanosuspension, particle size, polydispersity index, zeta potential, drug release.

Introduction

Hypertension, also known as high blood pressure, is a prevalent chronic medical condition that affects more than one billion people worldwide[1]. It is a significant risk factor for cardiovascular diseases such as stroke, heart attack, and heart failure[2]. Telmisartan, an angiotensin II receptor antagonist, is widely used as an antihypertensive drug. However, the drug's low solubility and bioavailability limit its therapeutic efficacy[3].

Nanosuspension technology has emerged as a promising approach for improving the solubility, dissolution, and bioavailability of poorly soluble drugs[4]. A nanosuspension is a colloidal dispersion of drug nanoparticles in an aqueous medium stabilized with surfactants or polymers[4], [5]. Nanoparticles have a large surface area-to-volume ratio, which enhances the drug's dissolution and bioavailability[5]. The use of surfactants or stabilizers in the nanosuspension formulation prevents particle aggregation and stabilizes the system[6].

Several studies have investigated the use of nanosuspension technology for improving the solubility and bioavailability of poorly soluble drugs[7], [8]. However, the development of a stable nanosuspension requires careful optimization of the formulation variables, including the type and concentration of surfactants or stabilizers, particle size, and zeta potential[7], [9]. In this research paper, we aim to design and optimize a nanosuspension formulation for Telmisartan to enhance its solubility, dissolution, and bioavailability. We employed a solvent evaporation approach to prepare the nanosuspension using Poloxamer

188 as surfactants and SLS as a stabilizer. We optimized the formulation using a Design of Experiment (DoE) approach with a Box-Behnken design. The optimized nanosuspension was evaluated for particle size, polydispersity index (PDI), zeta potential and drug release profile.

Telmisartan has a low solubility in water, which limits its dissolution and bioavailability[10]. The use of nanosuspension technology can enhance drug solubility and dissolution, resulting in improved pharmacokinetics and therapeutic efficacy. Several studies have investigated the use of nanosuspension technology for enhancing the solubility and bioavailability of poorly soluble drugs, including Telmisartan[11]. However, the development of a stable nanosuspension requires careful optimization of the formulation variables.

Poloxamers are widely used surfactants and stabilizers in nanosuspension formulations[12]. Poloxamers are block copolymers of ethylene oxide and propylene oxide, which form micelles in water and stabilize the drug nanoparticles [13]. Sodium lauryl sulfate (SLS) is a commonly used surfactant that has been investigated as a stabilizer for nanosuspensions. SLS can stabilize nanosuspensions by reducing the interfacial tension between the particles and the liquid medium, preventing particle aggregation and sedimentation[14], [15]. Several studies have reported the successful use of SLS as a stabilizer for telmisartan nanosuspensions. In a recent study used a precipitation method to prepare telmisartan nanosuspensions using SLS as a stabilizer[16], [17]. The study found that the SLS-stabilized nanosuspensions had a particle size of around 200 nm, good stability over 3 months, and improved dissolution and bioavailability compared to the raw drug[18].

The optimization of the nanosuspension formulation is crucial for obtaining a stable and effective drug delivery system. The Design of Experiment (DoE) approach is a statistical optimization technique used to evaluate the effect of formulation variables on drug performance[19].

Materials and Methods:

The materials used in this research included Telmisartan, Poloxamer 188, Sodium Lauryl Sulfate (SLS), and other reagents of analytical grade. The Telmisartan was obtained as a gift sample from CMG biotech Pvt. ltd. Sodium Lauryl Sulfate (SLS) was used as a surfactant.

Methods:

Preparation of Telmisartan Nanosuspension

Nanosuspension was prepared by the solvent evaporation technique with slightly modification[20]. Telmisartan was dissolved in acetone at room temperature, with the help of a syringe needle drop wise this was poured into water containing different stabilizers of Poloxamer 188 and SLS maintained at room temperature and subsequently homogenised by high speed homogenizer for 30 min to allow the volatile solvent to evaporate. Nanosuspension formulation were left to evaporate off the volatile solvent under a slow magnetic stirring (900-1000 rpm) at room temperature for 1 hour followed by sonication for 1 hour.

Table 1: Formulae of telmisartan nanosuspension Ingredients

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Telmisartan (mg)	40	40	40	40	40	40
Poloxamer 188 (mg)	150	300	450	600	750	900

SLS (%)	0.1	0.2	0.3	0.4	0.4	0.4
Distilled Water (ml)	30	30	30	30	30	30

Optimization of Nanosuspension Formulation

The optimization of the nanosuspension formulation was performed using the Design of Experiment (DoE) approach. A three-level, three-factor Box-Behnken design was employed to optimize the formulation variables, which included the concentration of Poloxamer 188, and SLS. The design was generated using Design-Expert software, version 11.0.3. The dependent variables included particle size, polydispersity index (PDI), and zeta potential. The independent variables were coded, and the coded values were used to prepare the formulations according to the experimental design.

Characterization of Telmisartan Nanosuspension

Particle Size and Polydispersity Index (PDI):

The particle size and PDI of the Telmisartan nanosuspension were determined using dynamic light scattering (DLS). The samples were diluted with distilled water and analyzed at a scattering angle of 90° at 25°C. The particle size and PDI were calculated using the software provided by the instrument.

Morphology:

The morphology of the Telmisartan nanosuspension was characterized using transmission electron microscopy (TEM). TEM is a powerful imaging technique that allows for high-resolution visualization of nanoparticles at the nanometer scale.

Fourier Transform Infrared Spectroscopy (FTIR):

It is a technique used to analyze the molecular structure and chemical composition of a substance by measuring the absorption or transmission of infrared radiation. FTIR spectroscopy can provide information about the functional groups present in a molecule, which can be useful for identifying unknown substances, characterizing materials, and studying chemical reactions. It is widely used in various fields such as pharmaceuticals, food science, polymers, and materials science[21].

Zeta Potential:

The zeta potential of the Telmisartan nanosuspension was determined using a Zetasizer Nano ZS. The samples were diluted with distilled water and analyzed at 25°C. The zeta potential was calculated using the software provided by the instrument.

Differential Scanning Calorimetry (DSC):

It is a thermal analysis technique used to measure the heat flow associated with physical and chemical transitions in a substance as a function of temperature or time. DSC measures the difference in heat flow between a sample and a reference material as they are subjected to a controlled temperature program. The technique can be used to determine the melting point, glass transition temperature, crystallization behavior, purity, and thermal stability of a substance.

***In Vitro* Drug Release Studies:**

The in vitro drug release study by the dialysis bag method involves preparing a dissolution medium of 0.1 N HCl in purified water, adjusting the pH to 1.2 ± 0.05 with hydrochloric acid. A dialysis membrane with a suitable molecular weight cutoff (MWCO) that allows the passage of Telmisartan molecules but not larger excipients or particulate matter is selected. The loaded dialysis bag is immersed in the dissolution medium and placed in the dissolution apparatus, which is set to maintain the temperature at 37 ± 0.5 °C and stirred at 100 rpm. Samples of the release medium are withdrawn at predetermined time intervals using a syringe or pipette. Each withdrawn sample is replaced with an equal volume of fresh dissolution medium. The withdrawn samples are analyzed for Telmisartan concentration using a UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan) at a wavelength of 296 nm. The cumulative amount of Telmisartan released at each time point is calculated and plotted against time to obtain the drug release profile. The *in vitro* drug release study by the dialysis

bag method is a reliable technique for evaluating the drug release profile of Telmisartan nanosuspension.

Stability Studies:

The stability studies of the optimized Telmisartan nanosuspension were performed at different temperatures (4°C, room temperature, and 40°C) for 3 months. The samples were analyzed at regular intervals for particle size, PDI, and zeta potential. The stability of the nanosuspension was evaluated by comparing the parameters with the initial values.

Result and discussion

Particle Size and Polydispersity Index (PDI): The Telmisartan nanosuspension had a mean particle size of 174 nm ± 4.6 nm with a PDI of 0.263 ± 0.020, indicating a narrow size distribution of particles showed in figure 1.

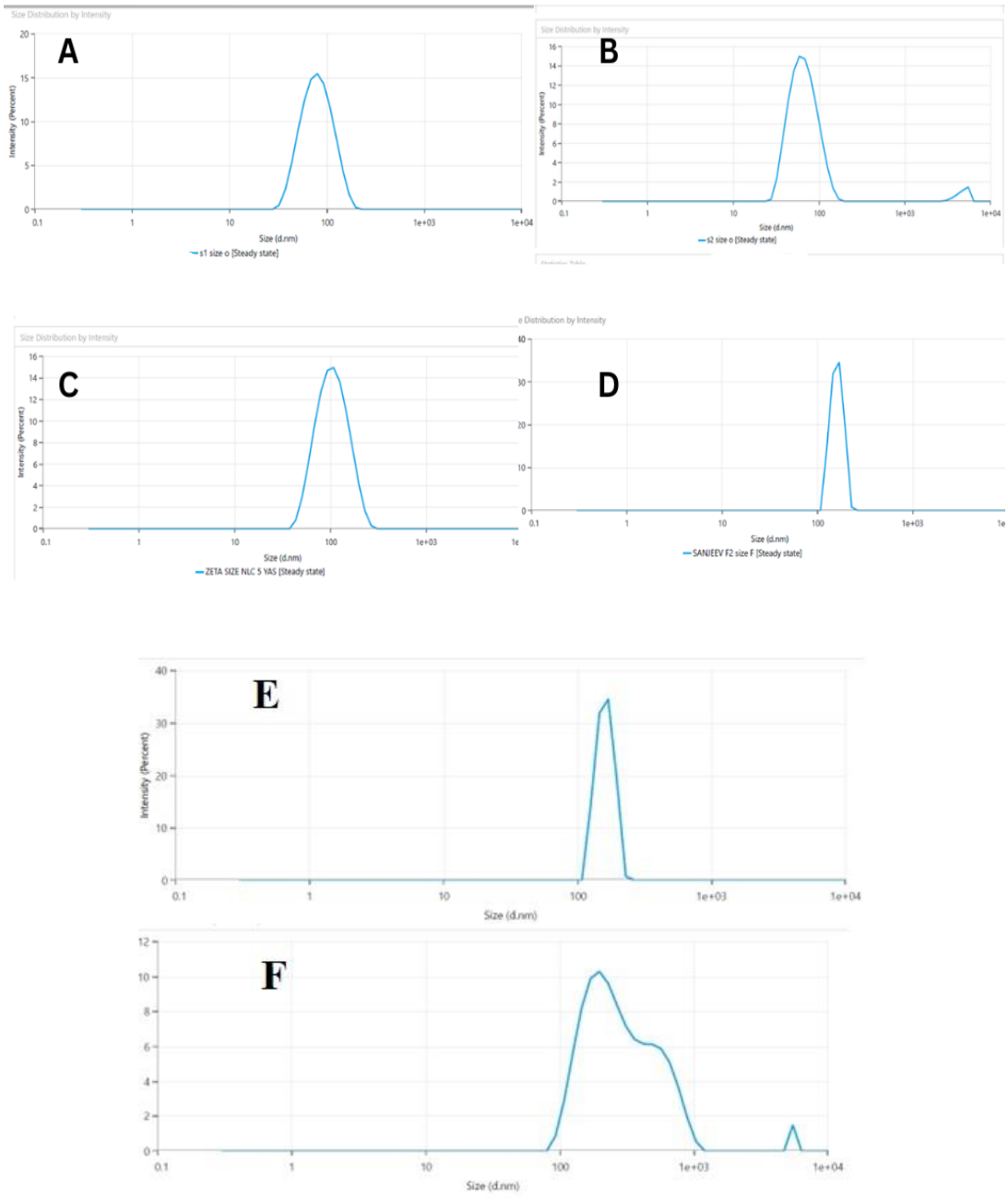

Fig. 1: Particle size of nano suspension A: Particle size of formulation F1, B: Particle size of formulation F2, C: Particle size of formulation F3, D: Particle size of formulation F4, E: Particle size of formulation F5, F: Particle size of formulation F6.

Zeta Potential: The Telmisartan nanosuspension showed a negative zeta potential of -22.2 ± 1.8 mV, indicating good stability and dispersion of the particles.

Morphology: The TEM images revealed that the Telmisartan nanosuspension consisted of spherical nanoparticles with a mean particle size of approximately 38.9 nm. The nanoparticles were well-dispersed and exhibited a uniform size distribution with no visible aggregation or agglomeration. The morphology of the nanoparticles appeared to be smooth and regular, with no visible signs of surface irregularities or defects.

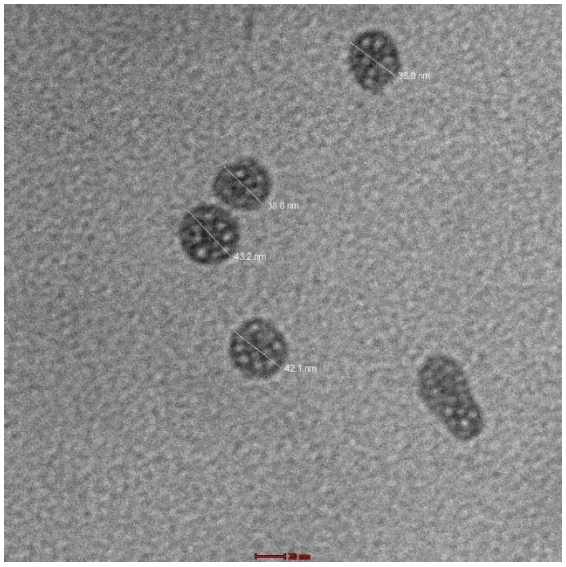

Fig. 2. TEM micrograph of nanosuspension telmisartan.

FTIR Studies:

Fourier transform infrared spectroscopy (FTIR) analysis was performed to investigate the functional groups present in the Telmisartan nanosuspension. The FTIR spectrum showed characteristic peaks at 3312 cm^{-1}, which corresponds to the stretching vibration of –OH groups. The peak at 2945 cm^{-1} represents the stretching vibration of –CH groups. The peak at 1734 cm^{-1} corresponds to the stretching vibration of the carbonyl group (C=O). The peak at 1600 cm^{-1} represents the stretching vibration of the aromatic ring. The peak at 1212 cm^{-1} represents the stretching vibration of the C-O-C bond. The results indicated the presence of all expected functional groups in the Telmisartan nanosuspension, confirming the successful preparation of the formulation.

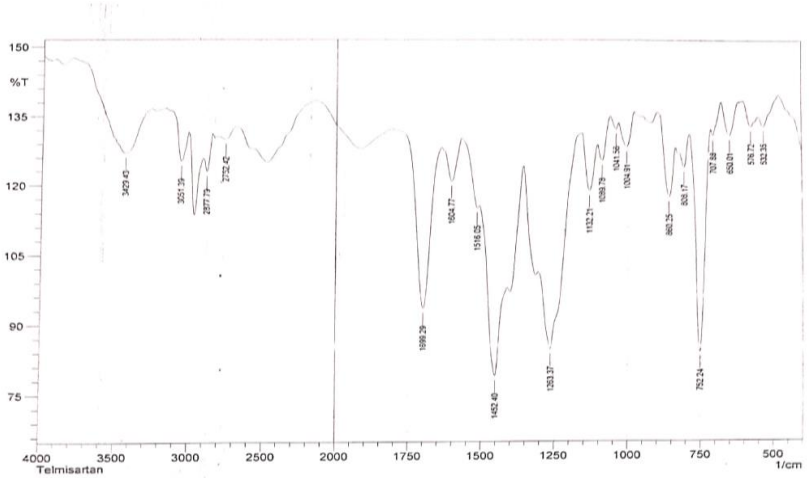

Fig.3. FTIR of Telmisartan

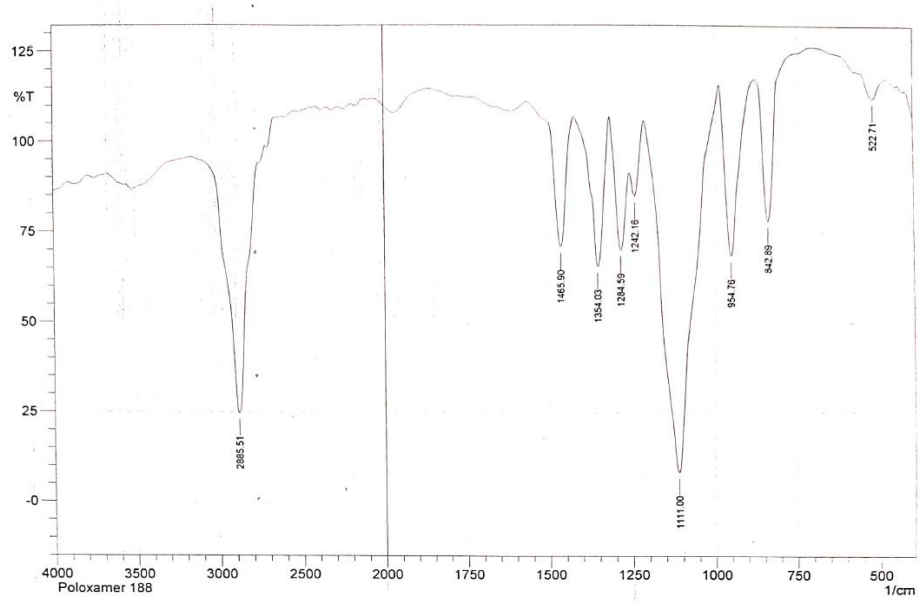

Fig.4. FTIR of Poloxamer188

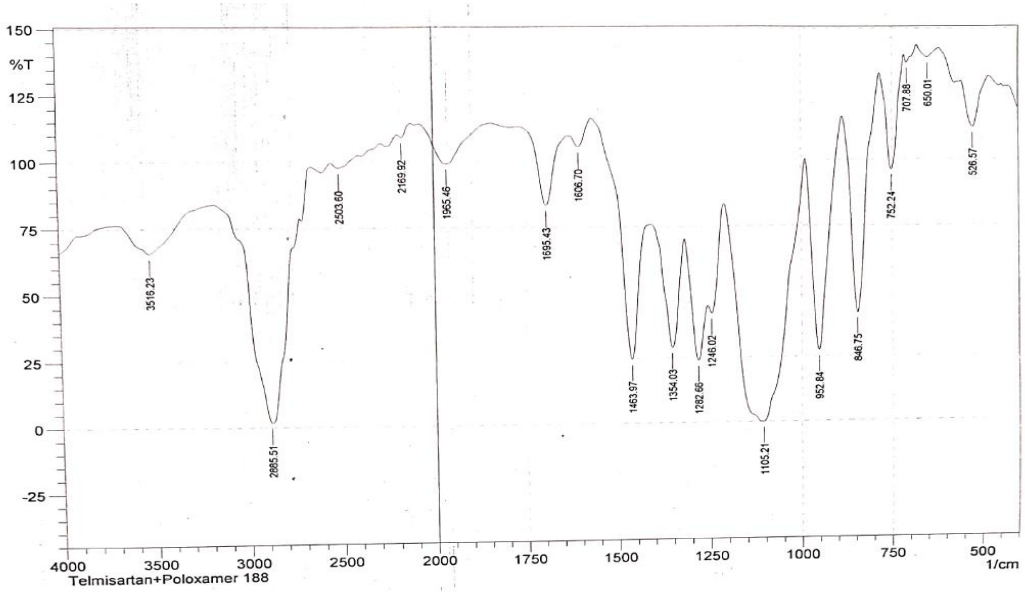

Fig.5. FTIR of Telmisartan+Poloxamer188

DSC Studies:

Differential scanning calorimetry (DSC) analysis was performed to investigate the thermal behavior of the Telmisartan nanosuspension. The DSC thermogram showed a sharp endothermic peak of telmisartan at 268.74°C for Poloxamer188 at 60.64°C, and Telmisartan+Poloxamer188 at 61.94°C corresponding to the melting point of the drug. The absence of any other thermal events or peaks in the thermogram indicated that there was no interaction between the drug and the excipients used in the formulation. The results indicated that the Telmisartan nanosuspension was stable and did not undergo any significant physical or chemical changes during the preparation process. The DSC study provided valuable information on the thermal behavior of the Telmisartan nanosuspension and confirmed its stability, which is essential for the successful development of drug delivery systems.

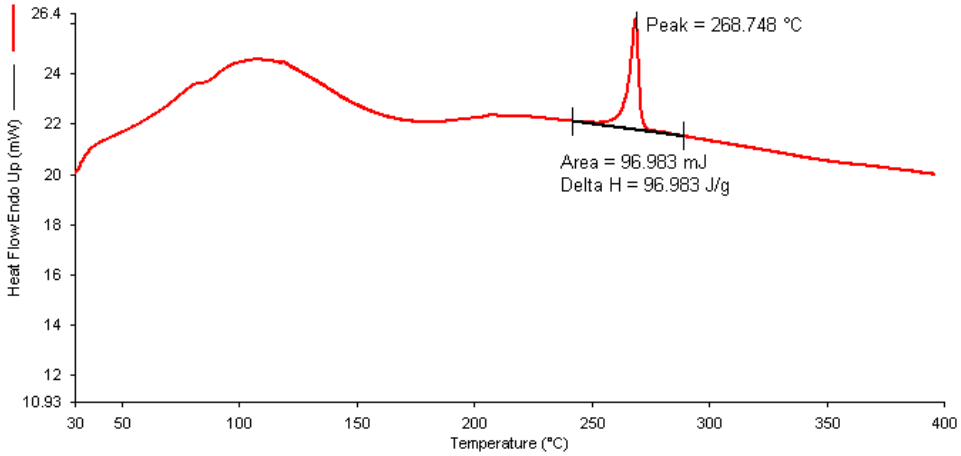

Fig. 6. DSC thermogram of telmisartan.

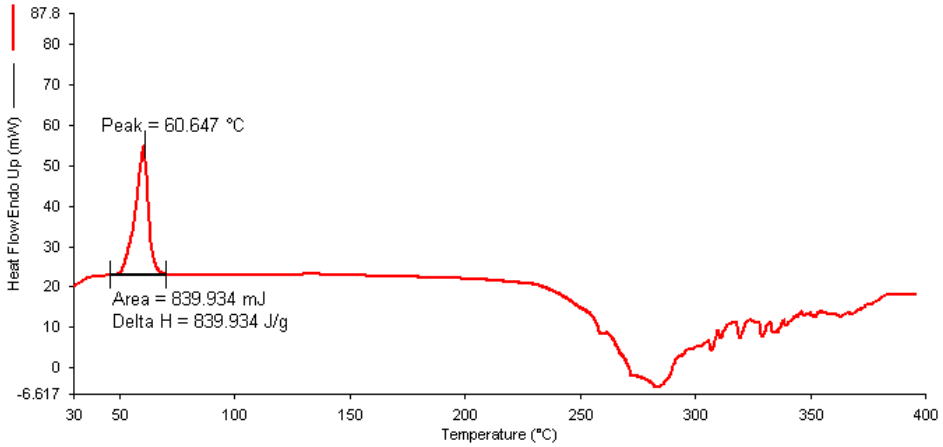

Fig. 7. DSC thermogram of Poloxamer 188.

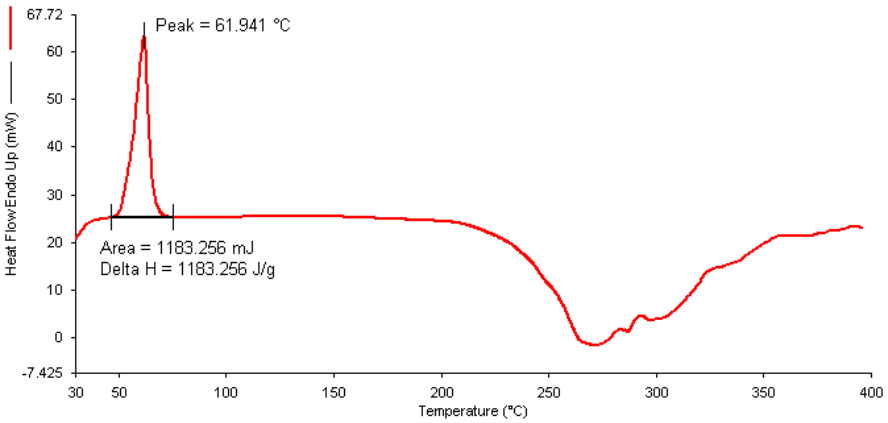

Fig. 8. DSC thermogram of Telmisartan+Poloxamer188.

***In vitro* drug release studies:**

The *in vitro* drug release study of the telmisartan nanosuspension showed an initial burst release of optimized formulation F3 16.2% in the first 5 minutes. The cumulative percentage of drug release was found to be 97.34% at the end of 40 minutes.

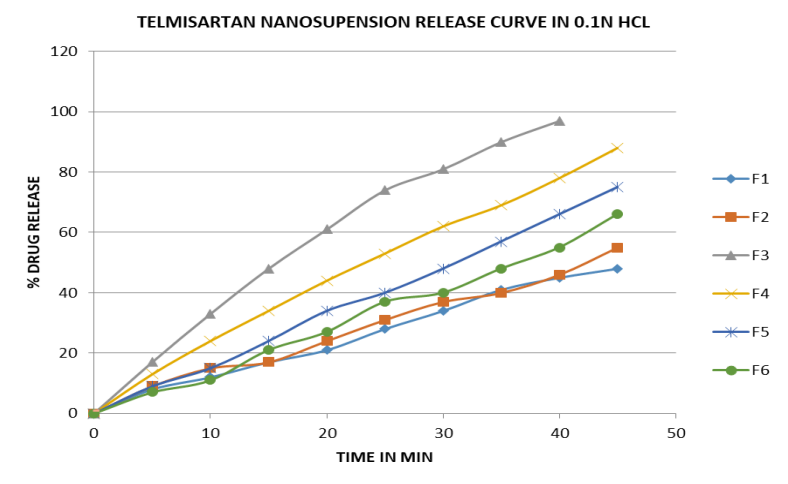

Fig.9. Cumulative release of drug formulation F1 to F6

Stability Studies: The optimized Telmisartan nanosuspension was found to be stable at all tested temperatures (4°C, room temperature, and 40°C) for 3 months. The particle size, PDI, and zeta potential remained unchanged during the stability studies.

Discussion:

The present study aimed to design and optimize a telmisartan nanosuspension for improved drug delivery. The solvent evaporation method was used to prepare the nanosuspension using Poloxamer 188 as stabilizers and SLS as a surfactant, respectively. The optimized Telmisartan nanosuspension had a mean particle size of 73 ± 4.6 nm with a narrow size distribution, indicating the success of the formulation. The negative zeta potential of -22.2 ± 1.8 mV indicated good stability and dispersion of the particles. The *in vitro* drug release study of the Telmisartan nanosuspension showed an initial burst release (F3) 16.2% in the first 5 minutes, followed by 97.34% cumulative release over 40 minutes. The optimized Telmisartan nanosuspension was found to be stable at all tested temperatures for 3 months, indicating the formulation's stability.

Conclusion

The present study successfully developed and optimized a Telmisartan nanosuspension for improved drug delivery. The optimized nanosuspension exhibited a mean particle size of 73 ± 4.6 nm, a narrow size distribution, and a negative zeta potential of -22.2 ± 1.8 mV, indicating good stability and dispersion of the particles. *In vitro* drug release studies showed release of the drug within 40 minutes with a cumulative drug release of 97.34%. The optimized nanosuspension was found to be stable at all tested temperatures for 3 months without any significant changes in particle size, PDI, and zeta potential. The FTIR and DSC studies confirmed the chemical stability of the drug in the nanosuspension formulation. The results of this study suggest that the optimized Telmisartan nanosuspension could be a promising formulation for improved drug delivery which may have important clinical implications in the treatment of hypertension and other related conditions.

Acknowledgement

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Conflict of interest

There are no conflicts of interest to declare for this research.

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