

FORMULATION AND EVALUATION OF TELMISARTAN TERNARY SOLID DISPERSION FOR ENHANCED SOLUBILITY AND DISSOLUTION

**Priyadharshini M.¹, Umamaheswari D.^{1*}, Gayathri K.², Keerthana M.³, Ruba Sree N.⁴,
Gowtham A⁵, Senthil Prabhu R⁶**

^{1,2,3,4,5}PG. Scholar, ^{1*,6}Assistant Professor,

Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-625020.

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***Corresponding Author**

Umamaheswari D.

Assistant Professor, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-625020.



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ABSTRACT

The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges. Solubility and dissolution are the crucial parameters in order to get the required drug concentration in the systemic circulation for pharmacological response. A significant obstacle to the development of many pharmaceutical products, especially those in Classes II and IV of the Biopharmaceutics Classification System (BCS), is due to their poor aqueous solubility. As a result, it is becoming increasingly crucial to identify new ways to overcome solubility and dissolution limits so that the potential therapeutic benefits of these active compounds can be achieved. Several strategies are being used by pharmaceutical companies to enhance the oral bioavailability of poorly water-soluble drugs. But among of these approaches solid dispersion is easy and give the high accuracy result of enhancement of solubility. Improving oral

absorption and oral bioavailability of poorly water-soluble medications is the main objective of solid dispersion development. Although it is widely used approach it has some disadvantages. To overcome these limitations the Ternary Solid Dispersion (TSD) is one of the recent best approaches to enhance the solubility and dissolution rate thereby improve its drug-release characteristics. It is a novel and popular technique for boosting solubility and

dissolving rate, especially for BCS class II medications. A key factor in TSD success is the careful selection of excipients. The present study is based on the preparation of Ternary Solid Dispersion of Telmisartan using HPMC E5 and Poloxamer 407 as carriers for enhanced solubility and dissolution of Telmisartan by Solvent Evaporation method.

KEYWORDS: Telmisartan, Ternary Solid Dispersion, HPMC E5, Poloxamer 407, Solubility enhancement, Dissolution enhancement. Solvent Evaporation.

INTRODUCTION

Poor aqueous solubility and dissolution is a major formulation challenge for orally administered drugs because dissolution in gastrointestinal fluids precedes absorption. Solid dispersion is a commonly used approach in which a poorly soluble drug is dispersed in a suitable carrier to improve wettability, surface area, particle-size characteristics where achieved which reduces crystallinity. Ternary solid dispersions extend the binary system by adding a third functional component such as a polymer, surfactant, solubilizer or pH modifier allowing complementary formulation functions.

Telmisartan is an angiotensin II receptor blocker used in the management of hypertension. It is a BCS Class II drug with high permeability but very poor aqueous solubility (~ 0.09 $\mu\text{g/mL}$), so oral bioavailability is dissolution-rate limited. The pH-dependent solubility of telmisartan is attributed to its three pKa values 3.5, 4.1 and 6.0 corresponding to its carboxylic (acidic) and two benzimidazole (basic) functional groups, respectively. Its amphoteric nature, gives a U-shaped pH-solubility profile with a solubility minimum across pH 3–7. At acidic pH, the N of benzimidazole of TLM gets ionized, forming a cationic center, and at basic pH, the carboxylic group of TLM is ionized, forming an anionic center, which is responsible for its maximum solubility at extremely high and low pH. Even though TLM exhibits a good solubility profile at extremely high and low pH, it exhibits low solubility in the pH range of 3–7, i.e. in the physiological pH range.^[4] These properties support investigation of a formulation strategy directed primarily toward solubility and dissolution enhancement. HPMC E5 was selected as the primary hydrophilic carrier because of its water-soluble, low-viscosity cellulose-ether characteristics and it contributes to wetting and recrystallization inhibition. Poloxamer 407 was selected as the third component, a ternary agent because its amphiphilic PEO–PPO–PEO structure can improve wetting, solubilization and stabilization of a hydrophobic drug. The present work therefore aimed to formulate

Telmisartan TSDs with varying HPMC E5, Poloxamer 407 ratios and to identify a formulation with improved solubility and dissolution.

Solid dispersions are described as molecular mixtures of **poorly water-soluble drugs that are dispersed in a hydrophilic or inert carrier (such as a polymer or sugar)** to increase surface area and improve solubility.^[5] The use of recent methods has become increasingly popular in recent decades as a potential solution to the limitations of the solid dispersion approach.

Recent Methods

Co-amorphous system (CAMS)

CAMS are defined as incorporating drugs **with small molecules instead of using macromolecules such as polymers**. CAMS are, therefore a single-phase amorphous solid system made up of two or three components. Mostly, the term CAMS refers to binary CAMS. In such systems, molecular interactions between the involved components play a crucial role. Considering the choice of co-formers, **binary CAMS** may also be described as drug-excipient and drug-drug CAMS.

However, in some circumstances, the efficacy of binary CAMS **solubilization and stabilization is poor, resulting in limited bioavailability improvement** and therefore has necessitated using another ingredient. To improve the drug dissolution profile, numerous researchers have included a third ingredient in drug formulations to improve physical stability and drug solubility. To optimize the binary CAMS, the third ingredient often used may be a surfactant, polymer, or another small molecule. This may be incorporated into the binary CAMS after the binary CAMS is formed (external third ingredient), or may be included in the CAMS alongside the other ingredients (internal third ingredient) to prepare **Ternary CAMS**.^[9]

Binary solid dispersion

A Binary solid dispersion is a solid system composed of two components (**Drug + one single carrier**) **generally a poorly water-soluble drug and typically a hydrophilic polymer**. The drug may be dispersed in the carrier as molecularly dispersed material, an amorphous phase, fine crystalline particles or a combination of these forms. Modern pharmaceutical solid dispersions commonly use hydrophilic polymers as carriers.^[1] The main objective of binary

solid dispersion is to increase the dissolution rate and consequently, improve the oral bioavailability of poorly water-soluble drugs.

For example: **Poorly soluble drug + hydrophilic polymer = Binary solid dispersion**

Binary solid dispersion is also known as Amorphous solid dispersion (ASD) containing APIs dissolved within amorphous hydrophilic polymer carriers. The idea is that crystalline drugs are transformed into their amorphous state by combining them with amorphous polymers. Although this approach offers obvious benefits, it is also often accompanied by challenges, such as difficulties with the manufacturing and processing of solid dispersions, the hygroscopicity of many polymers and often the limited miscibility of the APIs with the polymers.^[7]

Drawbacks of binary solid dispersion

Binary solid dispersions (BSDs), may have certain limitations including inadequate physical stability, recrystallization of the amorphous drug, poor wettability, precipitation during dissolution and difficulty in maintaining supersaturation. A single polymer may not be able to simultaneously provide sufficient drug solubilization, inhibition of recrystallization and stabilization of the supersaturated state. In contrast, ternary solid dispersions (TSDs) incorporate an additional component, such as a second polymer, surfactant, pH modifier or adsorbent, which can provide complementary or synergistic effects. The third component can enhance drug–excipient interactions, reduce molecular mobility, improve wettability, dissolution, inhibit precipitation and recrystallization thereby enhance the physical stability and overall performance of the formulation. To overcome these limitations the **TSD is one of the recent best approaches to enhance the solubility and dissolution rate and thereby improve its drug-release characteristics**. Also, TSDs can overcome several limitations associated with conventional binary solid dispersions and may provide greater improvements in stability and bioavailability of poorly water-soluble drugs.^[8]

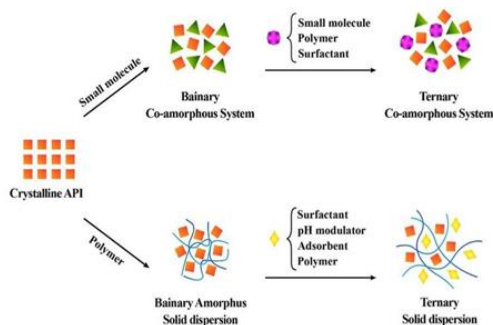


Fig. 1: A Schematic illustration of a Ternary co-amorphous system and Ternary solid dispersion.

Binary CAMS < Ternary CAMS < Binary ASD < Ternary Solid Dispersion (TSD)

TERNARY SOLID DISPERSION (TSD)

The solid dispersion of the active ingredient in two separate components of a drug delivery system consisting of three main components, namely **drug, primary polymeric carrier and a Polymer /a Surfactant/ a pH modulator, or a solubilizer** in a solid state is referred to as a Ternary solid dispersion (TSD).

It is a **novel approach which has been emerged to address the solubility and bioavailability challenges associated with amorphous drugs.**

It is the solid dispersion system of APIs dispersed into two different excipients at a solid state. The incorporation of a third component, such as a polymer, a surfactant or other compatible excipient in the drug formulation serves to enhance solubility and promotes increased stability. This is achieved through intermolecular interactions between the drug and solubilizer, as well as between the drug, a primary polymer and a third component, resulting in improved solubility and reduced recrystallization.^[7]

Basic composition: Drug + Polymer + Third component → Ternary solid dispersion

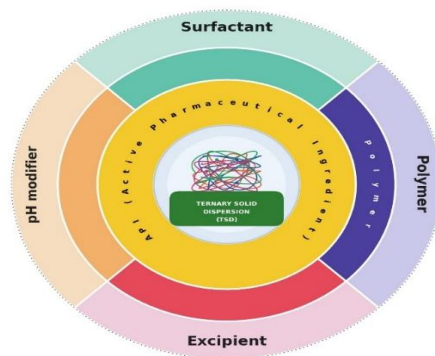


Fig. 2: Components of Ternary Solid Dispersion.

The third component can complement the function of the primary polymer. For example, the polymer can help maintain the drug in an amorphous state, while a surfactant can improve wettability and inhibit aggregation or precipitation after the dispersion contact's water. The classification of the TSD system based on the composition can be seen in **Fig.2**. This is supported by recent reviews, which identify **physical instability, precipitation during dissolution, wettability and processing limitations** among the major challenges of binary systems that TSDs are designed to address. In the ASD+ polymer system, the addition of a third polymer can form hydrogen bonds with both the drug and the polymer. The binary system sometimes is because of the lack of non-covalent bonding between the drug and polymer. Thus, adding the third polymer can form a hydrogen bond with the drug and polymer, leading to a more thermodynamically stable system. This system also resulted in a synergistic enhancement of amorphous stabilization and dissolution and precipitation inhibition and supersaturation.

Table 1: Comparison of Binary Solid Dispersion and Ternary solid dispersion.

Binary Solid Dispersion	Ternary solid dispersion
Drug + Polymer → not sufficient to satisfy all the criteria such as improved solubility, dissolution, recrystallization inhibition + supersaturation + stabilization.	Drug + Primary Polymer + a Polymer /a Surfactant/ a pH modulator, or a solubilizer → provides multiple functions. ✓ Greater stability ✓ Better drug-exipient interaction ✓ Improved wettability ✓ Enhances solubility and processibility ✓ Higher dissolution ✓ Superior inhibition of recrystallization ✓ Inhibition of precipitation ✓ Prolonged supersaturation maintenance

Criteria for the selection of carriers used in the preparation of Ternary solid dispersions: The carrier used for the preparation of solid dispersion should possess the following properties:

- It should be pharmacologically inert and non-toxic.
- It should be water-soluble and should enhance the dissolution of the drug.
- It should have good solubility in a large number of solvents.

- It should be compatible with the drug.
- It should increase the aqueous solubility of the drug.
- It should have a low melting point and should be thermally stable for the preparation method.
- It should form only weakly bound complexes with the drug.
- It should have a good flow index and compressibility index.
- If polymer is the carrier the nature of hydrophilicity and lipophilicity is important.
- It should have a high glass transition temperature (T_g) at least 50°C higher than the storage temperature, mostly >150°C to improve the stability of the solid dispersion.
- If the carrier is surfactant, it should have appropriate HLB value (>15) and appropriate CMC.
- It should be capable of forming a solid solution in the presence of the drug.
- It should have the ability to protect the drug from moisture.

Criteria for the selection of solvents used for the preparation of Ternary solid dispersion: The solvent used for the formulation of solid dispersion should satisfy the following criteria:

- Both the drug and carrier should be soluble in the selected solvent.
- Toxic solvents should be avoided because of the risk of residual solvent after preparation, e.g., chloroform and dichloromethane.
- Ethanol can be used as an alternative solvent because it is less toxic.
- Water-based systems are preferred whenever possible.
- Surfactants may be used to prepare drug-carrier solutions. However, surfactants can reduce the glass transition temperature (T_g), so they should be used carefully.

SELECTION OF CARRIERS

Among HPMC grades (E5, E15, K4M), E5 was identified as optimal because of its lower viscosity/molecular weight allows better molecular-level drug entrapment and more efficient inhibition of drug recrystallization during solvent evaporation, compared to higher-viscosity grades (E15, K4M) which can hinder solvent removal and uniform dispersion formation. HPMC also has established hydrogen-bonding interaction potential with telmisartan (via its carboxylic/benzimidazole groups), supporting amorphous stabilization and helps in better processability and faster drug release.^[10]

Poloxamer 407 was favored over Poloxamer 188 (and other surfactants like SLS, TPGS explored in your series) because its higher molecular weight/greater hydrophobic PPO block content gives stronger micellar solubilization capacity and better interaction with the poorly wettable telmisartan surface, translating to superior dissolution enhancement in your comparative screening, the basis for selecting it as the lead surfactant. Poloxamer 407 plays a dual function in the TSD responsible for amorphous stabilization and maintenance of supersaturation. Also, it has excellent compatibility with the HPMC.^[15]

MATERIALS AND METHODS

Telmisartan was kindly provided as a gift sample by Kawman Pharma (A Division of K.P. Manish Global Ingredients Pvt. Ltd.). The polymer HPMC E5 and surfactant Poloxamer 407, were obtained from Apex Laboratories Pvt. Ltd. and Madras Pharmaceuticals. All the analytical reagents and solvents, including methanol, were used as received. Distilled water was used throughout the study.

Table 2: Formulation of Telmisartan Ternary solid dispersion at different ratios.

Formulation	Telmisartan	HPMC E5	Poloxamer 407
TTSD1	1	0.5	0.5
TTSD2	1	1	1
TTSD3	1	1.5	1.5
TTSD4	1	2	2
TTSD5	1	2.5	2.5
TTSD6	1	3	3
TTSD7	1	3.5	3.5
TTSD8	1	4	4
TTSD9	1	4.5	4.5

Method of Preparation of Ternary Solid Dispersions (TSDs)

Solvent Evaporation method

The components were accurately weighed according to the selected ratios. Telmisartan was dissolved in the selected solvent, while HPMC E5 was separately dissolved/hydrated and Poloxamer 407 was incorporated with continuous stirring. The Telmisartan solution was added gradually to the HPMC E5–Poloxamer 407 system and stirred to obtain a homogeneous mixture. The solvent was removed by rotary evaporation under reduced pressure; where a rotary evaporator was unavailable, the thesis describes spreading the solution in multiple Petri dishes and controlled drying. The resulting solid was dried to constant weight, pulverized and passed through sieve No. 60 before storage in a dry airtight container.

Characterization of Telmisartan Ternary Solid Dispersions (TTSDs)

Preformulation Studies of Telmisartan

Pre-formulation studies represent a crucial step in the rational design of pharmaceutical dosage forms. These investigations provide essential information about the physical and chemical properties of the drug substance and its compatibility with various excipients, which aids in developing a stable, effective and safe formulation. In the present study, a series of pre-formulation tests were performed to evaluate the properties of Telmisartan, which is the drug of choice for the preparation of Ternary Solid Dispersion.

Organoleptic properties: A small amount of Telmisartan was visually examined under natural daylight and evaluated for its organoleptic features.

Melting point: A capillary melting point apparatus was employed. The drug sample was filled in a capillary tube, and the temperature at which melting occurred was recorded to confirm the purity and thermal characteristics of Telmisartan.

Solubility studies: In this method, an excess amount of Telmisartan were taken in 25 ml conical flasks containing 10 ml of solvent/buffer (e.g., distilled water, ethanol, and buffer solutions at various pH levels). The flasks were shaken for 24 to 48 hours at 100 rpm and temperature of $37\pm0.5^{\circ}\text{C}$ in orbital-incubator shaker. The solutions were filtered using $0.45\mu\text{m}$ membrane filter. The filtrate obtained was suitably diluted with respective solvent/buffer and the amount of drug was estimated by UV Spectrophotometrically at their relevant λ max.

Saturation solubility

Saturation Solubility study is to evaluate the increase in solubility of Telmisartan in different media. In this method, an excess amount of pure Telmisartan and Telmisartan Ternary Solid Dispersions (containing an equivalent amount of Telmisartan, 40 mg) were taken in 10 ml volumetric flasks containing 10 ml of various solvents/buffers. The flasks were shaken for 24 to 48 hours at 100 rpm and temperature of $37\pm0.5^{\circ}\text{C}$ in orbital-incubator shaker. The solutions were filtered using $0.45\mu\text{m}$ membrane filter. The filtrate obtained was suitably diluted with respective solvent/buffer and the amount of drug was estimated UV Spectrophotometrically at their relevant λ max. From the absorbance-concentration data, saturation solubility values were calculated.

Percent practical yield

Percent practical yield was calculated to find out the efficiency of the method. The Ternary solid dispersions were collected and simply weighed to determine practical yield (PY) from the equation (Eq. 1.0). The study was performed in triplicate.

Percent drug content

Drug content can be evaluated to measure the amount of drug present in the prepared ternary solid dispersion and to ensure the uniform distribution of the drug in the polymer matrix. In this method an accurately weighed Telmisartan ternary solid dispersion (containing an equivalent amount of Telmisartan, 40 mg). Then it was transfer into a 10 mL volumetric flask containing methanol. Sonicate the solution for 10–15 minutes to dissolve the drug completely. Filter the solution using Whatman filter paper. Dilute suitably and measure absorbance using a UV spectrophotometer at 296 nm. The actual drug content (DC) was calculated using the equation (eq.2.0). The study was performed in triplicate.

In-vitro dissolution

In-vitro dissolution study was performed to determine the rate and extent of drug release from the formulation. This can be performed by using USP Dissolution Apparatus II (Paddle type). An accurately weighed quantity of pure Telmisartan, marketed tablet formulation (Telma 40) and selected Ternary solid dispersion formulation (containing an equivalent amount of Telmisartan, 40mg) was added in dissolution flask containing 900 mL of phosphate buffer pH 6.8 as dissolution medium. Maintain temperature at $37 \pm 0.5^{\circ}\text{C}$ and paddle speed at 100 rpm. Withdraw 5 mL samples at predetermined time intervals (5,10,15,20, 30, 45, 60 minutes) and replace withdrawn volume with fresh dissolution medium to maintain sink condition throughout the process. Filter samples and dilute appropriately and then the absorbance at 296 nm using UV spectrophotometer. Calculate percentage drug release.

Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) is used for the identification of functional groups and detection of drug-polymer interactions. The dried samples of the prepared optimized Ternary solid dispersion were separately mixed with potassium bromide (KBr). Then compress into a KBr pellet using a pellet press. Place the pellet in FTIR spectrophotometer. Scan in the range of $4000\text{--}400\text{ cm}^{-1}$. Compare spectra of pure drug, excipients and selected optimized ternary solid dispersion to detect interactions.

SEM Analysis (Scanning Electron Microscopy)

Scanning Electron Microscope (SEM) is used to analyze surface morphology and particle structure of the dispersion of pure drug and the optimized formulation. For this add the samples in a small amount of sample on aluminium stub using double-sided adhesive tape. Coat the sample with a thin layer of gold or platinum using sputter coating attached to the instrument. Observe under SEM instrument at suitable magnification. Study the surface morphology and particle shape of the optimized Ternary solid dispersion compare with the pure Telmisartan. However, the SEM micrograph is not very conclusive in this case.

RESULTS AND DISCUSSION

Pre formulation studies

Organoleptic properties: The drug was evaluated for its organoleptic properties, its appearance is white to off-white solid crystalline powder, has no odour and bitter in taste.

Melting point: The drug sample melting point was determined by capillary tube method and the result is 261.3°C.

Solubility studies: Telmisartan has been studied for its solubility in various solvents like Distilled water, Methanol, 0.1 N HCl pH1.2, Acetate buffer pH 4.5, Phosphate buffer (pH 6.8 and 7.4) solution. Telmisartan was found to have highest solubility in Methanol.

Table 3: Solubility of Telmisartan in available solvents/Buffers.

Medium/Solvent	Observation
Methanol	Very soluble
0.1 N HCl pH1.2	Freely Soluble
Phosphate buffer pH 7.4	Moderately Soluble
Phosphate buffer pH 6.8	Slightly Soluble
Acetate buffer pH4.5	Very Slightly Soluble
Distilled water	Practically Insoluble

Fourier Transform Infrared Spectroscopy (FTIR) Studies

FT-IR spectroscopy gives the possible information about the interaction between the drug and excipients. The characteristic peaks confirm the identity of the pure drug, HPMC E5, Poloxamer 407 and in the physical mixture the lack of any additional peaks in the spectra confirms the absence of any chemical interactions between drug and carriers.

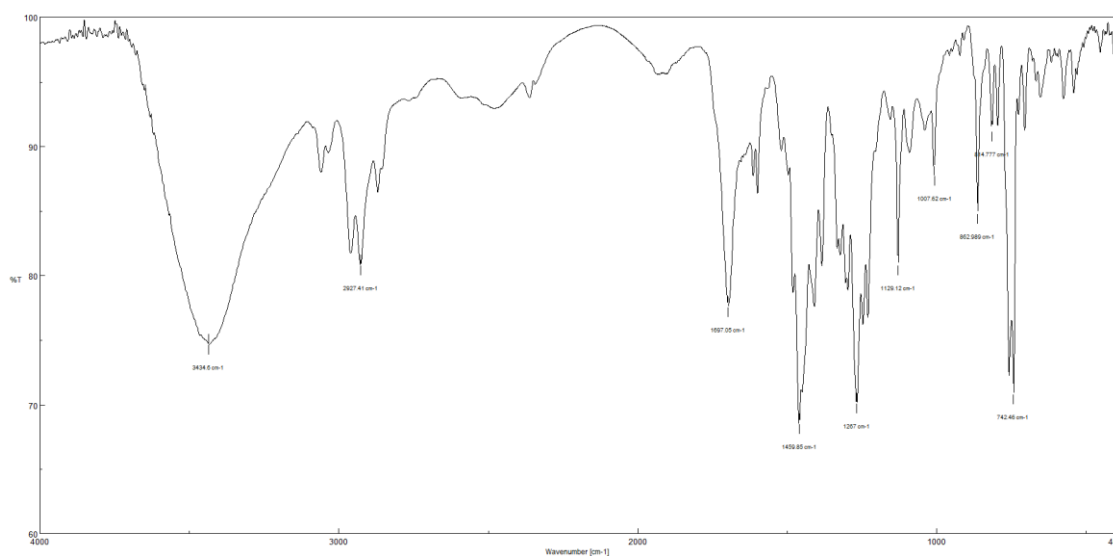


Fig. 3: IR Spectrum of pure drug Telmisartan.

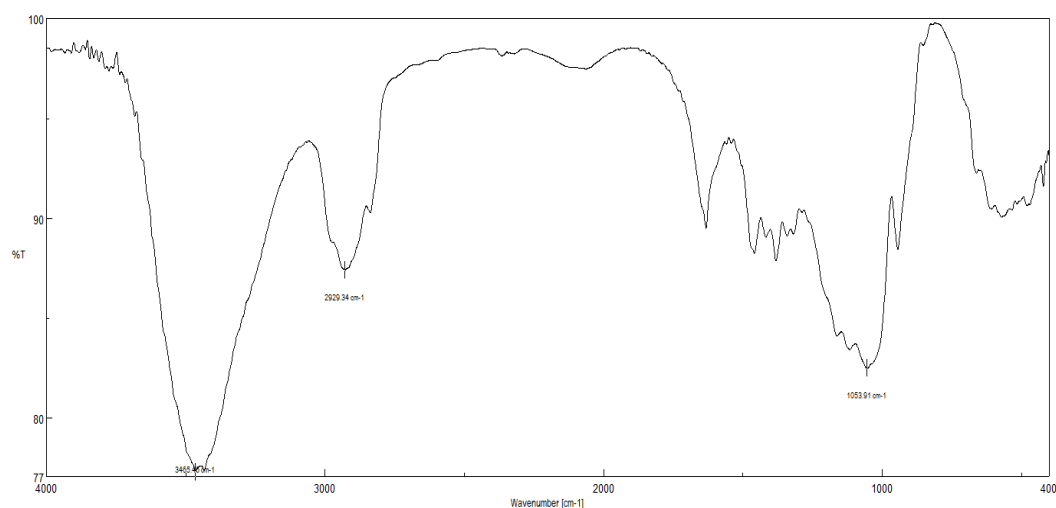


Fig. 4: IR Spectrum of HPMC E5.

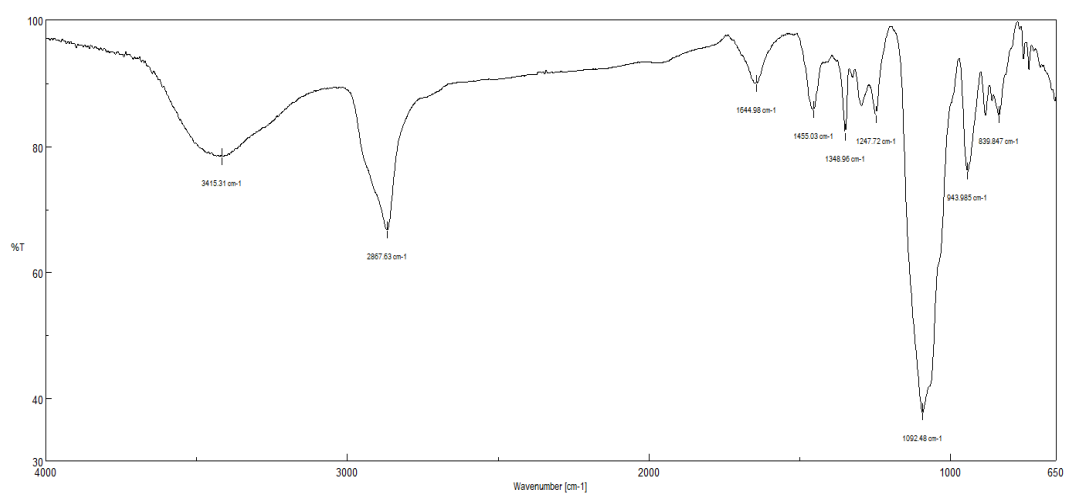


Fig. 5: IR Spectrum of Poloxamer 407.

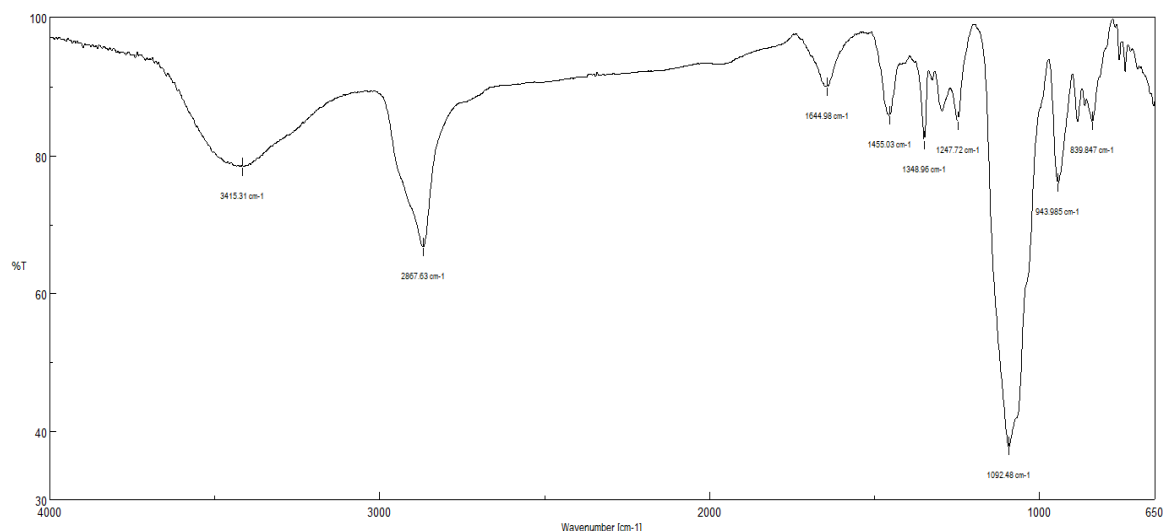


Fig. 6: IR Spectrum of Physical Mixture.

UV spectral analysis

Determination of λ max of Telmisartan

UV analysis of the pure drug was conducted for λ max determination. 10 μ g /ml solution of Telmisartan in Methanol was scanned between 200 nm to 400 nm and λ max was found to be 296 nm are shown in Fig.7

Determination of Calibration Curve of Telmisartan

The calibration curve of Telmisartan in methanol exhibited good linearity within the concentration range of 2-10 μ g/ml, with a correlation coefficient (R^2) of 0.9997.

Table 4: Concentration and Absorbance Data of Telmisartan at 296 nm.

Conc. (μ g/ml)	Mean Absorbance at 296 nm; ($\pm$ SD) n=3
2	0.0918 $\pm$ 0.007
4	0.1736 $\pm$ 0.008
6	0.1786 $\pm$ 0.010
8	0.2654 $\pm$ 0.012
10	0.439 $\pm$ 0.011

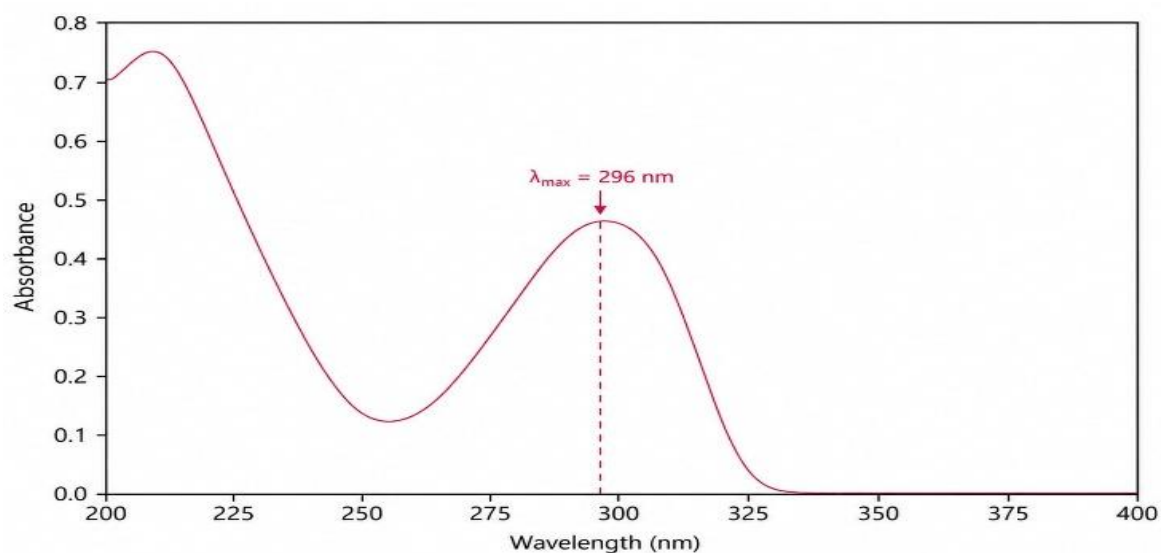


Fig. 7: Determination of λ max of Telmisartan.

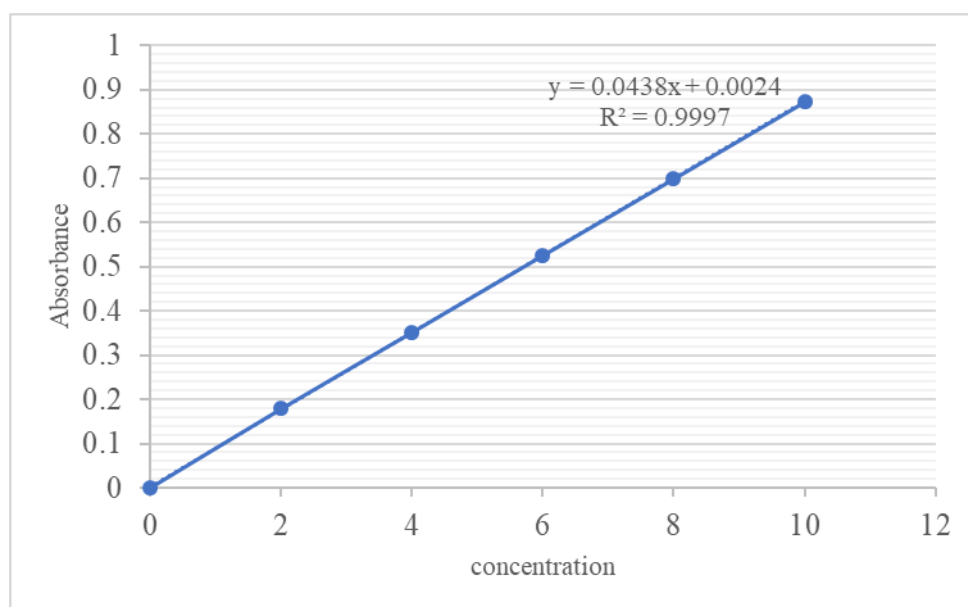


Fig. 8: Standard Calibration Curve of Telmisartan.

Formulation of Telmisartan Ternary Solid Dispersion

Nine formulations of Ternary solid dispersion were prepared using Telmisartan, HPMC E5 and Poloxamer 407 at different ratios.



Fig. 9: Preparation of Telmisartan Ternary Solid Dispersion.

Saturation solubility studies

The saturation solubility studies of Pure Telmisartan and the prepared Telmisartan Ternary Solid Dispersions, containing an equivalent amount of Telmisartan, 40mg (TTSD1, TTSD2, TTSD3, TTSD4, TTSD5, TTSD6, TTSD7, TTSD8, TTSD9) were conducted in various solvents/buffers like Distilled water, Methanol, 0.1 N HCl pH1.2, Acetate buffer pH4.5, Phosphate buffer (pH 6.8 and 7.4). From the results it was clear that Ternary Solid Dispersion formulation TTSD showed highest solubility in Methanol, then 0.1N HCl (pH 1.2) buffer which is in acidic condition and further decreased its solubility in phosphate buffer pH7.2, phosphate buffer pH 6.8 conditions, thereby showing its pH dependency. It shows a U-shaped pH-solubility profile - most soluble in strongly acidic media (protonation) and least soluble across the pH 3–9 range, where it's largely unionized. Out of the (TTSD1 to TTSD9) formulations, **the Ternary Solid Dispersion (TTSD7) showed better solubility enhancement of Telmisartan which has appropriate concentration of HPMC E5 and Poloxamer 407.** And, among these ternary solid dispersions were found to have higher solubility increasing potential in comparison to the pure Telmisartan.

Table 5: Saturation Solubility Profile of pure Telmisartan in Solvents/Buffers.

Solubility (mg/ml) $\pm$ SD; n=3						
Sample	Methanol	0.1N HCl pH 1.2	Phosphate Buffer pH 7.4	Phosphate Buffer pH 6.8	Acetate Buffer pH 4.5	Distilled water
Pure Telmisartan	0.0836 $\pm$ 0.008	0.0750 $\pm$ 0.002	0.0742 $\pm$ 0.007	0.0731 $\pm$ 0.006	0.0668 $\pm$ 0.003	0.0554 $\pm$ 0.01

Table 6: Saturation Solubility Profile of Telmisartan Ternary Solid Dispersions in various Solvents/Buffers.

Solubility (mg/ml) $\pm$ SD; n=3						
Formulation Codes	Methanol	0.1N HCl pH 1.2	Phosphate Buffer pH 7.4	Phosphate Buffer pH 6.8	Acetate Buffer pH 4.5	Distilled water
TTSD1	1.1150 $\pm$ 0.001	0.9632 $\pm$ 0.009	0.8605 $\pm$ 0.007	0.4729 $\pm$ 0.005	0.3783 $\pm$ 0.003	0.3011 $\pm$ 0.004
TTSD2	1.1162 $\pm$ 0.007	0.9684 $\pm$ 0.005	0.8692 $\pm$ 0.008	0.4768 $\pm$ 0.004	0.3826 $\pm$ 0.004	0.3014 $\pm$ 0.009
TTSD3	1.1185 $\pm$ 0.003	0.9706 $\pm$ 0.006	0.8754 $\pm$ 0.009	0.4799 $\pm$ 0.006	0.3845 $\pm$ 0.004	0.3013 $\pm$ 0.001
TTSD4	1.2508 $\pm$ 0.002	0.9719 $\pm$ 0.008	0.8863 $\pm$ 0.011	0.4865 $\pm$ 0.008	0.3862 $\pm$ 0.003	0.3016 $\pm$ 0.002
TTSD5	1.2861 $\pm$ 0.005	0.9843 $\pm$ 0.004	0.9028 $\pm$ 0.009	0.4993 $\pm$ 0.006	0.4029 $\pm$ 0.002	0.3028 $\pm$ 0.003
TTSD6	1.3254 $\pm$ 0.004	0.9910 $\pm$ 0.008	0.9095 $\pm$ 0.008	0.5119 $\pm$ 0.009	0.4087 $\pm$ 0.006	0.3042 $\pm$ 0.008
TTSD7	1.3324 $\pm$ 0.002	0.9916 $\pm$ 0.002	0.9125 $\pm$ 0.004	0.5210 $\pm$ 0.003	0.4089 $\pm$ 0.002	0.3046 $\pm$ 0.005
TTSD8	1.3162 $\pm$ 0.009	0.9896 $\pm$ 0.003	0.9039 $\pm$ 0.006	0.5006 $\pm$ 0.007	0.4053 $\pm$ 0.008	0.3039 $\pm$ 0.007
TTSD9	1.2850 $\pm$ 0.007	0.9835 $\pm$ 0.004	0.8989 $\pm$ 0.005	0.4887 $\pm$ 0.009	0.3899 $\pm$ 0.007	0.3018 $\pm$ 0.006

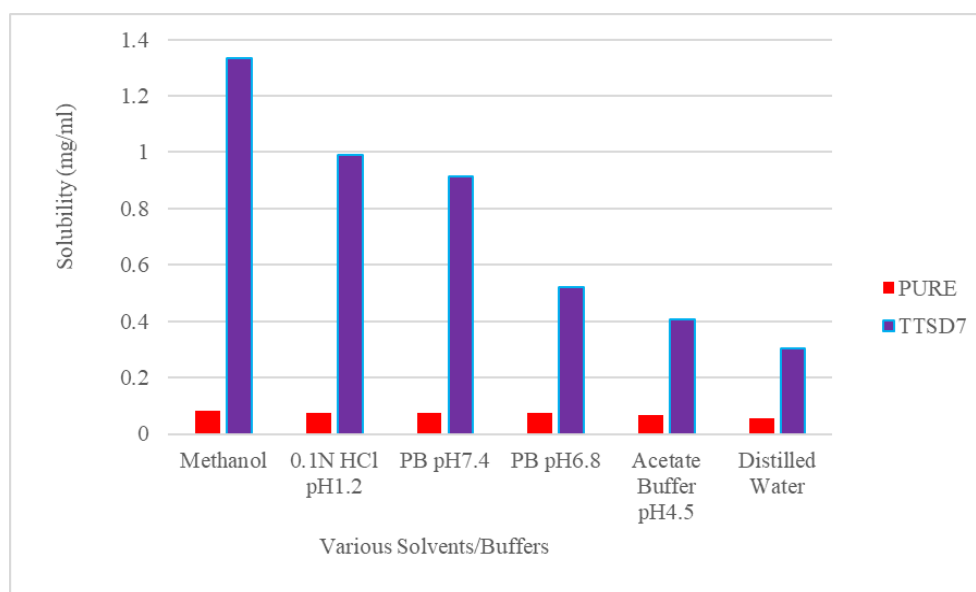


Fig. 10: Comparison of Saturation solubility Profile of TTSD7 and Pure Telmisartan in various solvents and buffers.

Percent practical yield

The percent practical yield of ternary solid dispersions prepared by solvent evaporation method was found to be in the range of **97.79 to 98.89%**. This **better yield found with the solvent evaporation method indicates that the method is efficient**. Out of the (TTSD1 to TTSD9) formulations, the **Telmisartan Ternary Solid Dispersion (TTSD7)** showed better result.

Drug content

The drug content studies of the TTSDs (containing an equivalent amount of Telmisartan, 40mg), it was found that the drug content ranged from **98.18 -99.93 %** in TTSDs. Out of the (TTSD1 to TTSD9) formulations, the **Telmisartan Ternary Solid Dispersion (TTSD7)** showed better result. This drug content indicates that the Polymer HPMC E5 and Surfactant Poloxamer 407 have the **highest drug loading capacity**.

Comparative in-vitro dissolution study

The in-Vitro dissolution studies of an accurately weighed quantity of pure Telmisartan, marketed tablet formulation (Telma 40) and Ternary solid dispersion formulation (containing an equivalent amount of Telmisartan, 40mg) 'TTSD7' were performed. From the results, it was found the selected **Ternary Solid Dispersion 'TTSD7' formulation (containing an equivalent amount of Telmisartan, 40mg) has the cumulative % drug release of 85.63 % which is much higher than the pure Telmisartan (35.57%) and the Marketed**

formulation (56.86%) in 60 minutes. As the TTSD7 formulation contains both HPMC E5 and Poloxamer 407, which are the hydrophilic polymer and surfactant carriers with additional activity and is prepared by solvent evaporation method. So, there will be a better wettability, reduced particle size, reduced crystallinity, higher surface area and the Telmisartan existed in the amorphous form, so no energy is required to break up the crystal lattice during the dissolution process.

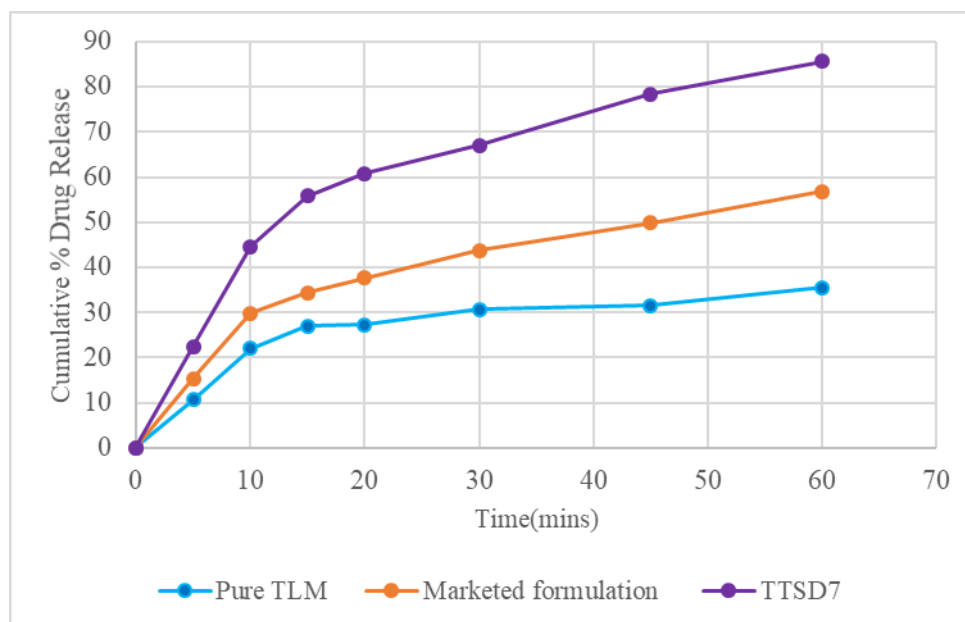


Fig. 11: Comparative In-Vitro dissolution profile of Pure Telmisartan, marketed formulation (Telma 40) and Selected Ternary Solid Dispersion Formulation ‘TTSD7’
FT-IR study for best formulation of Telmisartan Ternary Solid Dispersion (TTSD7).

The sample of selected Ternary Solid Dispersion formulation ‘TTSD7’ were characterized for identification of functional groups and detection of drug-polymer interactions of the optimized formulation using Fourier Transform Infrared Spectroscopy (FTIR). From the report of IR spectrum, there was no new peaks appeared and no characteristic API peaks disappeared in any of the spectra thus, ruling out major chemical degradation or incompatibility. The physical mixture shows simple additive/unshifted peaks, confirming the components are just co-existing. In contrast, the TTSD7 formulation shows peak broadening and a shift/splitting of the carbonyl band (1697.05 cm^{-1}), consistent with hydrogen-bonding interactions between the Telmisartan, HPMC E5 and Poloxamer 407 during the ternary solid dispersion process indicating with the amorphizing effect of Poloxamer 407 disrupting the drug's crystal lattice and the retained functional groups but with characteristic H-bond-induced shift/broadening of the C=O and O–H region plus reduced peak intensity which

indicates that the Telmisartan Ternary Solid Dispersion achieves better molecular interaction/amorphization within the HPMC E5–Poloxamer 407 matrix, which supports for improving the drug's aqueous solubility and dissolution rate, supporting molecular-level dispersion/amorphization and stabilization of the API within the carrier matrix while maintaining chemical compatibility. **Further the lack of any additional peaks in the spectra of TTSD7 formulation confirms the absence of any chemical interactions between drug and carriers in the Ternary Solid Dispersion formulation.** Since FTIR shifts alone are supportive but not fully conclusive of amorphous conversion. Further studies are required.

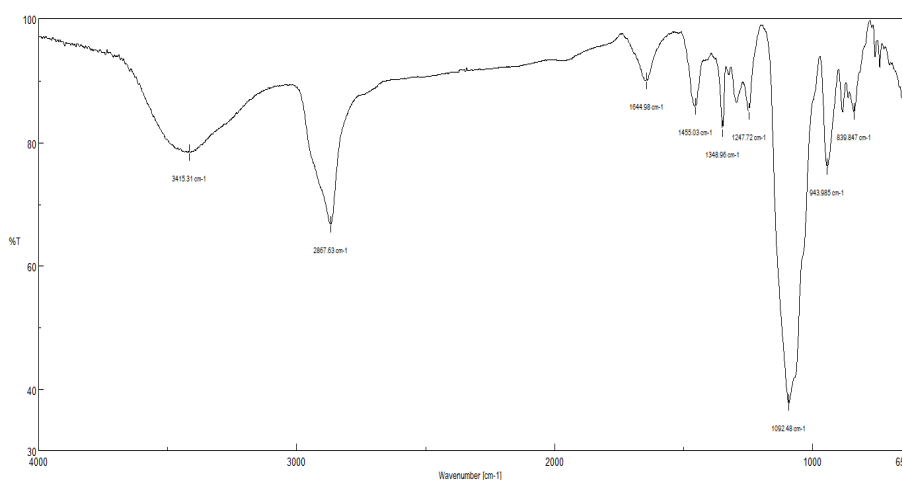


Fig. 12: IR spectrum of TTSD7.

Morphological studies by Scanning Electron Microscopy (SEM)

The samples of pure Telmisartan and selected Ternary Solid Dispersion formulation ‘TTSD7’ were characterized for morphological studies by Scanning Electron Microscopy.



Fig. 13: SEM Image of pure Telmisartan.

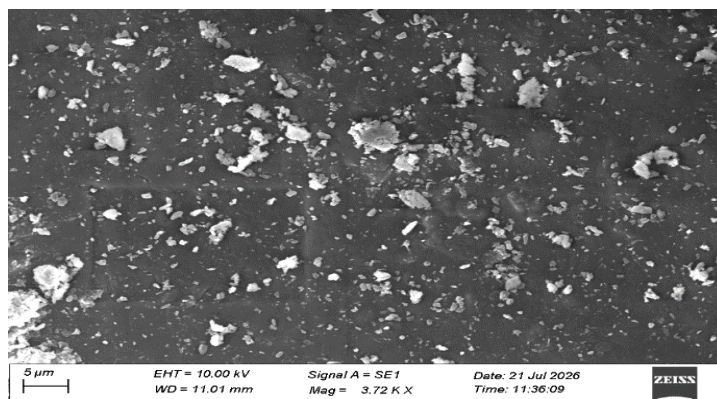


Fig. 14: SEM Image of TTSD7.

The micrograph of Pure Telmisartan showed the presence of definite structural shape of the telmisartan crystal but the Telmisartan Ternary Solid Dispersion ‘TTSD7’ formulation showed wrinkled and irregular surfaced pattern having and the absence of visible Telmisartan crystals, demonstrating the presence of either dissolved Telmisartan in the carrier or partial conversion of crystalline Telmisartan into an amorphous form. The **change in surface morphology of Telmisartan**, HPMC E5 and Poloxamer-407 could be due to process of solubilization and solvent evaporation which can be taken as an **indicator of successful formation of Ternary Solid Dispersions**. Thus, the absence of the telmisartan crystal image indicates the structural change of the drug crystal that might be attributed to the conversion of the crystalline drug to the amorphous state by Solvent Evaporation procedure and the appearance of irregular surface pattern of TSD supports for the enhancement of solubility due to increased surface area. However, the SEM micrograph is not very conclusive in this case. Therefore, the change in crystallinity is further assessed by thermal analysis and PXRD study.

CONCLUSION

The present study was successfully carried out to formulate and evaluate a Ternary solid dispersion (TSD) of Telmisartan using suitable hydrophilic carriers like HPMC E5 polymer and Poloxamer 407 surfactant by solvent evaporation method. The **prepared TSD showed a significant improvement in the solubility and dissolution of Telmisartan**. Compared with the pure drug, the optimized TSD exhibited approximately a **13-fold, 12-fold, 6.5-fold, 6-fold and 5-fold increase in solubility** in 0.1 N HCl pH 1.2, Phosphate buffer pH7.4, Phosphate buffer pH6.8, Acetate buffer pH 4.5 and Distilled water. In the in-vitro dissolution study **% cumulative drug release has also been increased for the TSD formulation than the pure Telmisartan**. This enhanced solubility and dissolution may be attributed to

improved wettability, reduced crystallinity and improved stabilization with uniform dispersion of telmisartan in the hydrophilic carrier matrix. Thus, the **Ternary solid dispersion approach proved to be an effective strategy for enhancing the solubility and dissolution enhancement of poorly water-soluble drug Telmisartan**. However, the SEM micrograph is not very conclusive in this case. Therefore, the change in crystallinity is further assessed by thermal analysis and PXRD study.

The whole sequence is shown below:

Methanol > 0.1N HCl > Phosphate Buffer pH 7.4> Phosphate Buffer pH 6.8>Acetate Buffer pH 4.5 > Distilled water

TTSD7 >TTSD6 >TTSD8 >TTSD5 >TTSD9 >TTSD4 >TTSD3 >TTSD2 >TTSD1

Telmisartan Ternary Solid Dispersion > Plain Telmisartan

FUTURE PERSPECTIVE

Since, the Telmisartan (TLM), a nonpeptide angiotensin II antagonist, is widely prescribed for treating arterial hypertension. Hypertension being a high-burden, lifelong, adherence-sensitive disease where even a pharmacologically well-suited drug like telmisartan underdelivers clinically due to solubility-driven bioavailability limitations, making solubility enhancement (via ternary solid dispersion) combined with a patient-friendly delivery format is essential. Hypertensive patients are often elderly, with higher rates of dysphagia or difficulty swallowing conventional tablets. So, ODFs (Orally Disintegrating Formulations) disintegrate rapidly in the oral cavity without water, improving compliance in a chronic, lifelong therapy where adherence is a major real-world determinant of blood pressure control. Thus, combining a solubility-enhanced TSD within a fast-disintegrating film format is a rational pairing, the film delivers the pre-amorphized, wetting-optimized drug directly for rapid dissolution and potential pre-gastric absorption onset, rather than relying on a conventional tablet to first disintegrate and then dissolve.

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