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(RESEARCH ARTICLE)

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# Improvement in solubility of BCS class II drug: Telmisartan

Geeta Bhagwat [1], Rubana Adul Hameed Arkate [2], Samreen Idrees Pasha Shaikh [2] and Sudha Ramnihor Vishwakarma [2]

[1] *Associate professor; Department of Pharmaceutics, DY Patil university school of pharmacy, Mumbai, India.*
[2] *Students; Department of Pharmaceutics, HK College of Pharmacy, Mumbai, India.*

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## Abstract

Telmisartan is used in the treatment of Hypertension (high blood pressure), prevention of heart attacks, strokes and heart failure. It is an angiotensin II type -1 receptor antagonist. Telmisartan belongs to class II under biopharmaceutical classification system. Hence, the solubility is the main issue. To increase the oral absorption, telmisartan requires enhancement in solubility and dissolution. The present study was aimed to increase the solubility of telmisartan by various techniques such as complexation and Solid dispersion. The tablet formulation was prepared to enhance the solubility and dissolution and compared with the drug release profile of the marketed preparation.

**Keywords:** Hypertension; Anti-hypertensive agent; Telmisartan; BCS class II drug; Solubility enhancement; Complexation; Solid dispersion

## 1. Introduction

The solubility and permeability of the drug is the main characteristics to classify the drug into different Biopharmaceutics Classification System classes (BCS) [1]. The aqueous solubility of the drug plays an important role in drug absorption after oral administration. The bioavailability of the drug affects due to poor solubility and low dissolution in the gastrointestinal fluids [2]. Telmisartan (TLM) is chemically referred to as 2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl]phenyl]benzoic acid, a nonpeptide angiotensin II type-1 receptor antagonist, is widely used for the treatment of arterial hypertension. TLM can be found as two polymorphs and one pseudo-polymorph in its three crystalline forms. The aqueous solubility of TLM is highly pH-dependent. TLM is the BCS class II drug which exhibits low solubility in the pH range of 3-7 which is the physiological pH. Hence, the solubility is the main challenge [3]. Apart from the solubility problem, TLM is rapidly absorbed from the gastrointestinal tract (GIT) and the maximum absorption was found to be the small intestine where the intraluminal pH was found to be 5-7 to achieve the maximum absorption. The present work illustrates the attempt to improve the solubility of the drug by using different methods of complexation and solid dispersion.

* Corresponding author: Sudha Vishwakarma

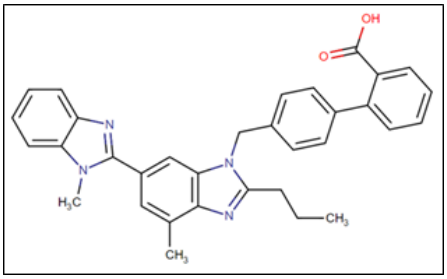


**Figure 1** Telmisartan (TLM)

## 2. Hypertension

Hypertension is the condition where the systolic and diastolic blood pressure is too high (140-160 or above) over the normal blood pressure (≥160). It is very common in young and old age group people (age 45-65) [4]. Although in recent years hypertension has been de-fined as a BP of 140/90 mmHg or more. Hypertension is a major risk factor for ischemic and haemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline, and premature death [5]. Intrauterine malnutrition, family history of hypertension, obesity, particularly excess abdominal fat, insulin resistance, high dietary sodium intakes, low dietary intakes of calcium, potassium and magnesium, physical inactivity, high alcohol intakes, tobacco use, drug use (e.g., cocaine, ecstasy, anabolic steroids), emotional stress, diet pill use, oral contraceptives are the factors associated with development of hypertension [6].

### 2.1. Antihypertensive Drugs

Antihypertensive drugs that are used to control the high blood pressure and brings the blood pressure down to the normal in various way. There are different types of antihypertensive agents, and they work in different ways to controls blood pressure. Some agents remove extra fluid and salt from the body. Other agents relax and widen the blood vessels or slow the heartbeat [7].

**Table 1** Classification of Antihypertensive Drugs

| Class | Sub- Class | Drugs |
|---|---|---|
| Diuretics | Thiazides | Chlorthiazide, Hydrochlorothiazide, Indapamide |
| | High ceiling | Furosemide |
| | Potassium Sparingly Soluble | Spironolactone, Eplerenone, Amiloride |
| Renin angiotensin system inhibitors | ACE inhibitors | Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril, Quinapril, Trandolapril |
| | Angiotensin receptor blockers | Losartan, Candesartan, Valsartan, Telmisartan, Irbesartan, Olmesartan |
| | Direct renin inhibitor | Aliskiren |
| Sympathetic inhibitor | Beta adrenergic blockers | Propranolol, Metoprolol, Atenolol |
| | Alpha+Beta adrenergic blockers | Labetalol, Carvedilol |
| | Alpha adrenergic blockers | Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine |
| | Central sympatholytics | Clonidine, Methyldopa |
| Calcium channel blockers | phenylalkylamine | Verapamil |
| | benzodiazepine | Diltiazem |

| | | |
|---|---|---|
| | Dihydropyridines | Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, Lercanidipine, Benidipine |
| Vasodilators | Arteriolar dilator | Hydralazine, Minoxidil, Diazoxide |
| | Arteriolar + Vasodilators | Nitroprusside |

**Table 2** Anti-Hypertensive Drugs belonging to BCS Class II

| **Class** | **Drugs** |
|---|---|
| Sympathetic inhibitors | Carvedilol, Prazosin, Doxazosin |
| Calcium channel blockers | Nifedipine, Felodipine, Lercanidipine, Verapamil. |
| Renin - angiotensin system inhibitor | Trandolapril, Candesartan, Valsartan, Telmisartan, Irbesartan, Olmesartan |
| Diuretics | Hydrochlorothiazide, Spironolactone |

## 3. Material and method

### 3.1. Material

Telmisartan was procured from Glenmark Pharmaceuticals Ltd as a gift sample, Solapur (India); Beta Cyclodextrin, PEG 4000, PEG 6000, DMSO procured from Vishal Chem Mumbai. Hydroxypropyl beta cyclodextrin procured from Medley Pharmaceuticals Ltd. Methanol procured from Dolphin Chem. Sodium Benzoate procured from Loba Chemie Pvt. Ltd. Mumbai. Urea procured from Research-Lab Fine Chem Industries Mumbai.

### 3.2. Identification Test for Telmisartan

*3.2.1. U.V Spectral Analysis:*

The 10ppm solution (10µg/ml) of telmisartan was prepared in 0.1 N NaOH by using Shimadzo UV visible instrument and spectrum of drug was taken in the range 200-400 nm wavelength. The λ max of the solution was discovered at 295 nm, which is as per USP.

*3.2.2. Calibration curve of telmisartan (Validation Intraday)*

Initially, 1000 ppm (1000µg/ml) of standard solution of TLM was made, from this solution 100ppm (100µg/ml) solution was prepared and appropriate dilutions were made to prepare 4,8,12,16,20 µg/ml were prepared and absorbance was measured at wavelength 295nm. The calibration curve was plotted at over the range of 4-20µg/ml with correlation coefficient of 0.9996 for the proposed method. Linearity range shown in *Fig 02.*

*3.2.3. Calibration curve of Telmisartan in 1% SLS*

For the calibration curve of Telmisartan in 1% SLS, initially 1000 ppm (µg/mL) of standard solution was prepared, from the standard solution 100 ppm (µg/mL) of stock solution was prepared in 100 mL volumetric flask. From the stock solution series of dilution was prepared such as 4, 8, 12, 16, 20 µg/mL and analyzed the absorbance of different concentration at 295 nm (λ max) against blank using UV- Visible spectroscopy. The calibration curve of telmisartan in 1 % SLS in which the curve was plotted absorbance against concentration (ppm) over the range of 4-20 µg/ml with correlation coefficient of 0.9979 for the proposed method.

### 3.3. Methods used to enhance solubility

There are different methods to enhance the solubility-

*3.3.1. Solid Dispersions*

Poorly soluble drugs can be offered solid dispersion to increase their oral absorption, solubility, and dissolution rates [8]. The drug can be distributed molecularly, in crystalline or amorphous particles. The dispersion of one or more active substances in an inert matrix at a solid state created by the melting, solvent, and melting solvent technique is known as solid dispersion [9]. The soli dispersion describes a class of solid substances that typically have two separate

ingredients: a hydrophilic matrix and a hydrophobic medicament. The matrix may be crystalline or amorphous. Solid dispersion was mainly used to create a eutectic combination of pharmaceuticals with water soluble carriers in counteract the limited bioavailability of lipophilic drugs [10]. Eutectic or solid solution products can be produced using solid dispersion processes. A chemical combination known as a eutectic system solidifies at a lower temperature than any of the constituent substances [11]. The eutectic melting point has a clearly defined range of temperatures where it happens. Because of its enormous surface area, a eutectic system will facilitate disintegration [12]. Improved bioavailability is the outcome of dissolving weakly water- soluble drugs in solid solutions in a carrier with comparatively excellent aqueous solubility [13]. By adjusting the characteristics of the carrier and solid dispersion particles, the suitable drug release profile is achieved using solid dispersions [14]. Telmisartan solid dispersions were prepared by using different carriers such as PEG 4000 and PEG 6000 in 1:3 molar ratio (drug: carrier). The drug and carrier were mixed in the petri dish in the water bath and the mixture was heated to and then dried for 24 hours. The resultant solid dispersion was collected [15].

*3.3.2. Cyclodextrin Complexation*

A potential method for improving the solubility and bioavailability of pharmaceuticals that are weakly water soluble is known as cyclodextrin inclusion complexation, which involves the development of host-guest inclusion complexes via weak intermolecular contact [16]. The solubility of several drugs, including celecoxib, clofibrate, cyclosporine A, melarsoprol, paclitaxel, and rofecoxib, has been found to be improved using this technique [17]. The process of cyclodextrin (CD) complexation also aids in increasing solubility, drug release and bioavailability of BCS Class II drugs [18]. Through a variety of interactions, cyclodextrin absorbs lipophilic medicines into its cavity, increasing the solubility and stability of the medication. The resultant complex is a water-soluble CD-drug complex that nevertheless has hydrophilic hydroxyl groups exposed to the aqueous environment. Complex of telmisartan with Beta Cyclodexhydroxypropyl beta-cyclodextrin prepared by physical method [19]. Telmisartan was mixed with hydroxypropyl beta-cyclodextrin were mixed in 1:1 molar ratio in mortar pestle for about 30 minutes with constant trituration.

*3.3.3. Polymeric encapsulation*

The pharmaceutical industry has a significant problem in the development of methods to increase the bioavailability of drugs with low water solubility. Particle size reduction and encapsulation with hydrophilic polymers can both enhance the immersion [20]. Utilizing various polymers, such as PEG4000 and PEG6000, in varying ratios might increase the permeability and stability of the active ingredient and, consequently, its bioavailability when it is enclosed in biodegradable polymers [21].

*3.3.4. In silico method (HSPIP SOFTWARE)*

The Hildebrand solubility parameter (HSPIP Software), which is a numerical evaluation of the amount of interaction between materials, is a trustworthy indication of solubility. The Hansen solubility parameters were developed by Charles Hansen to test if one chemical will dissolve in another and form a solution [22]. It is required to make emulsions and determine their miscibility (Hansen, 1967, 2007). They are an extension of Hildebrand's solubility parameters. The solubility parameter of a liquid combination is proportional to the quantity of each liquid, assuming that the two liquids are completely miscible [23]. The solubility parameters, like the Hildebrand parameters, can be derived by measuring the solubility. A drug's solubility is evaluated using a range of solvents and an unnamed Hansen. Solubility tests are performed, in silico. This will reduce the time as well as efforts of the scientist [24].

### 3.4. Formulation of Telmisartan Tablets

The Drug combined with Complexes to enhance the solubility and other ingredients was weighed accurately. It was mixed with the help of mortar pestle and transferred to the sieve with the mash size 20#. The mixer was granulated with the binding agent [25]. The granulating mixer was allowed to dry at room temperature and the dried granules was passed through a sieve with a mesh size of 20# and the mixer was collected on the sieve 40#. Lubricant was evenly and the tablet was compressed with a single punch compression machine [26].

**Table 3** Formulation table of Telmisartan Tablet

| Ingredient | Formula 1 (For 1 tablet) | Formula 2 | Role of ingredient |
|---|---|---|---|
| Telmisartan and HPβ- CD Complex | 130 mg | - | Anti-Hypertensive |
| Telmisartan and PEG-Complex | - | 160 mg | |

| | | | |
|---|---|---|---|
| Microcrystalline cellulose | 90 mg | 60 mg | Diluent |
| Magnesium oxide | 20 mg | 20 mg | Diluent |
| Croscarmellose sodium | 4.8 mg | 4.8 mg | Disintegrant |
| Polyvinylpyrrolidone (PVP) | q.s | q.s | Binder |
| Extra granulating material | | | |
| Talc | 0.5% of tablet weight | | Glidant |
| Magnesium stearate | | | Lubricant |

### 3.5. *In vitro* Dissolution Studies:

The dissolving investigations were conducted out utilizing paddle type equipment at 75 rpm and 37±0.5°C. Each jar was filled with tablets [27]. 0.1% sodium Lauryl Sulphate was used as the dissolving media. SLS works as a surfactant in the dissolving of medications that are poorly soluble. At defined time intervals, 5 ml samples were taken and replaced promptly with an equivalent volume of fresh medium. At 295 nm, the samples were examined [28].

### 3.6. Dissolution Study Protocol (USP)

- Apparatus: USP Type II
- Speed: 75 rpm
- Time of sample withdrawal: 10, 20, 30, 45, and 60 minutes
- Temperature: 37°C ± 0.5°C
- λ max: 295 nm.

## 4. Results and discussion

### 4.1. U.V Spectral Analysis

The spectral analysis was done to identify the drug by using UV spectrophotometry.

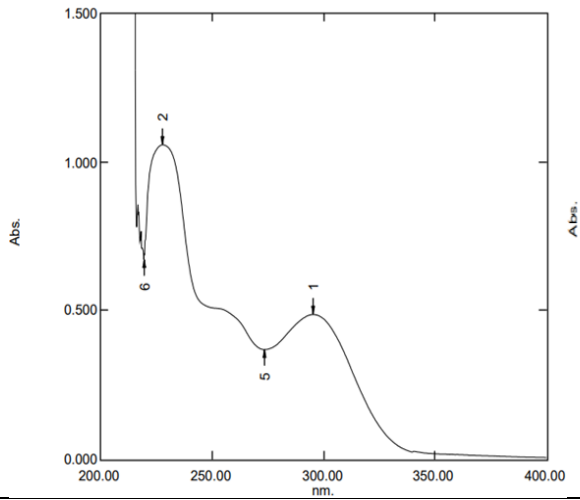


**Figure 2** Spectrum of telmisartan in 0.1N NaOH

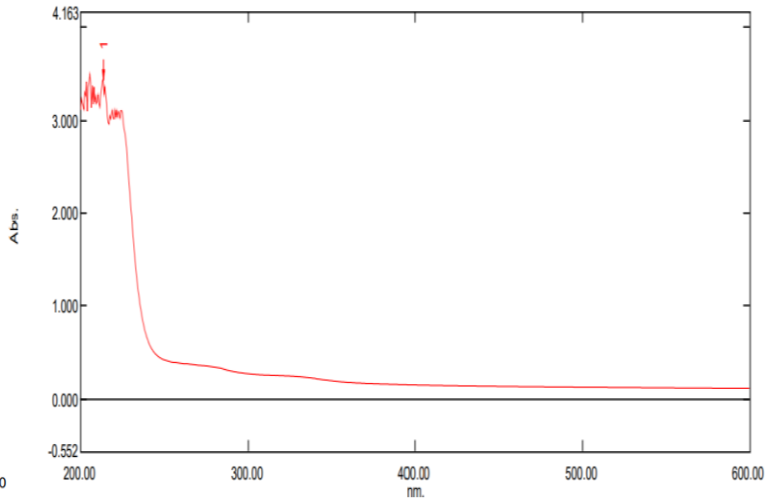


**Figure 3** Spectrum of telmisartan in distilled water

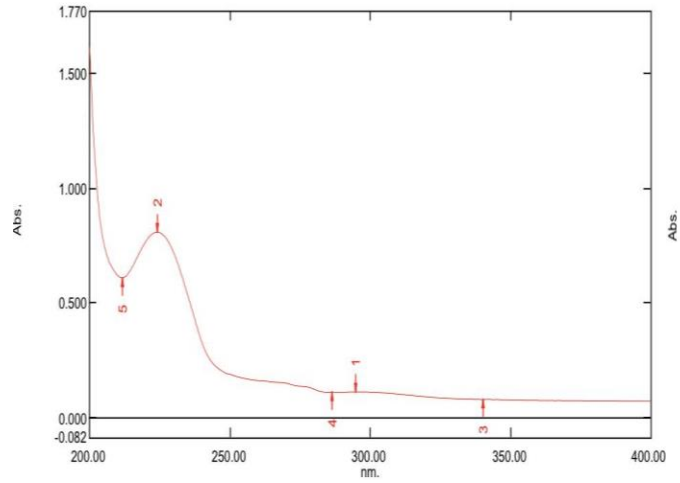


**Figure 4** Spectrum of telmisartan and PEG 4000 complex

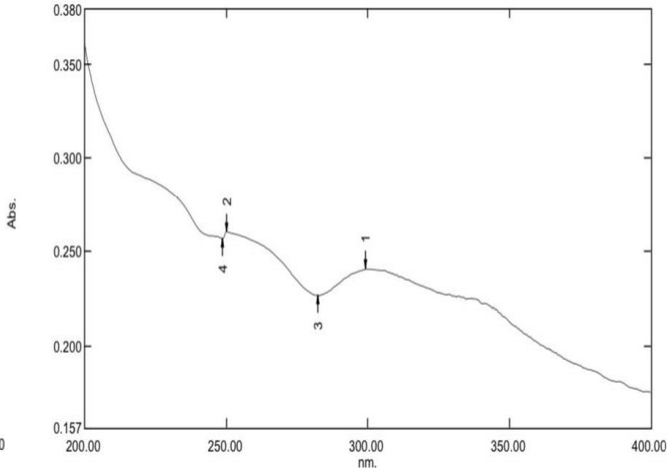


**Figure 5** Spectrum of telmisartan and PEG 6000 complex

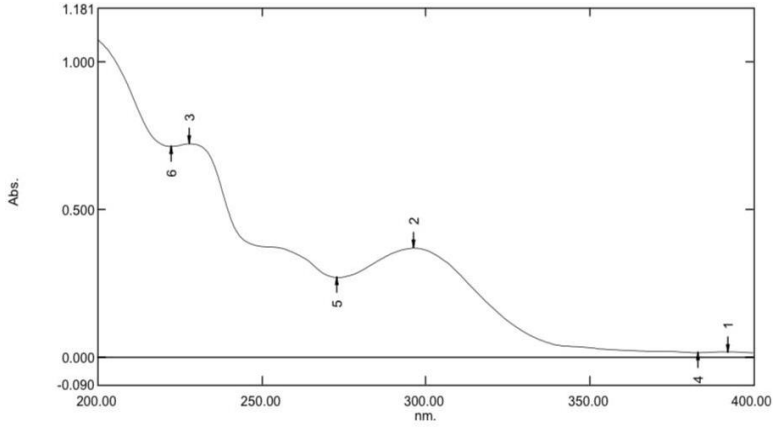


**Figure 6** Spectrum of telmisartan and HPβ-CD complex

*Figure- 2* shows the spectrum of TLM in 0.1 N NaOH and the peak 1 showed the good absorbance at wavelength 295 nm and the spectra was compared to the spectrum given of TLM in IP which is confirmed that the drug is TLM. Fig: 3 express the intense peak of TLM in distilled water. Fig: 4 shows the spectrum of TLM with PEG 4000 complex in which peak 1 appear at λmax 295nm. The spectrum of TLM with PEG 6000 complex in which the intense peak 1 express at 295nm in Fig 5 and the spectral analysis of TLM with HPβ-CD complex shows the peak 2 at 295nm which is confirms that the drug is stable and showing the good solubility with these complexes.

### 4.2. Calibration curve

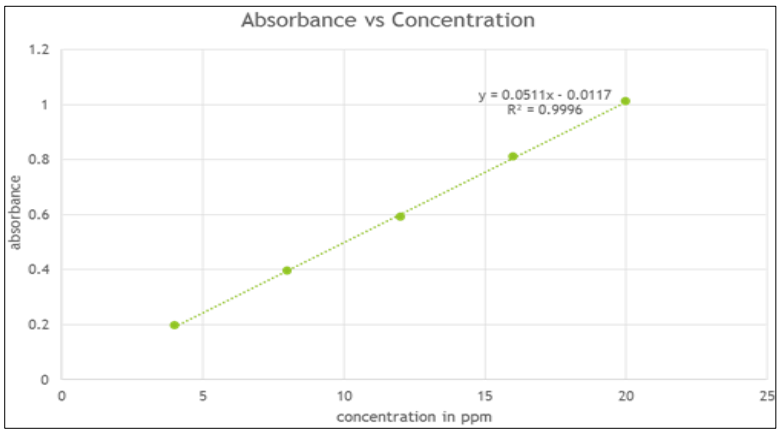


**Figure 7** Calibration Curve of TLM in 0.1N NaOH

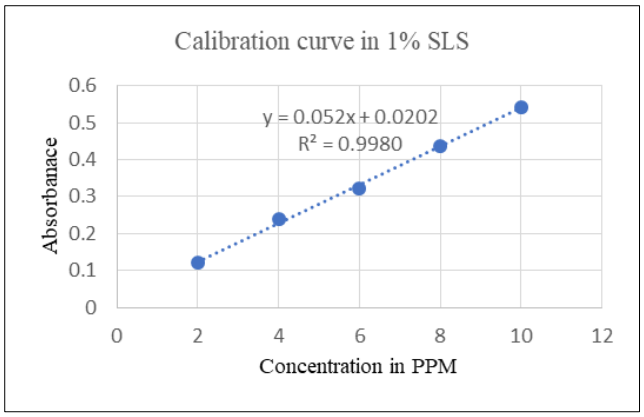


**Figure 8** calibration curve of TLM in 1% SLS

The calibration curve was taken to determine the linearity of the drug. It shows the linear response with the coefficient correlation between 0.998 to 0.9996 in 1% SLS and 0.1N NaOH.

### 4.3. Dissolution studies

As a solid dosage form in the form of a tablet, telmisartan was investigated for in-vitro drug release studies. In this research, a commercial formulation of telmisartan (Mankind) tablets was contrasted with tablets containing telmisartan-PEG 6000 complex and hydroxypropyl beta cyclodextrin (HPβCD). The marketed formulation showed an initial larger release of almost 77% and gradually increased up to 90%. In contrast, the tablet containing PEG 6000 tablets of the indicated complexes initially had a delayed release until 60% CDR and increases upto 73%. Hence, PEG 6000 is considered to enhance the solubility of poorly soluble drug and can be used to study further to achieve the better dissolution of drug in tablet dosage form. The study found that Telmisartan's solubility has greatly increased consequently.

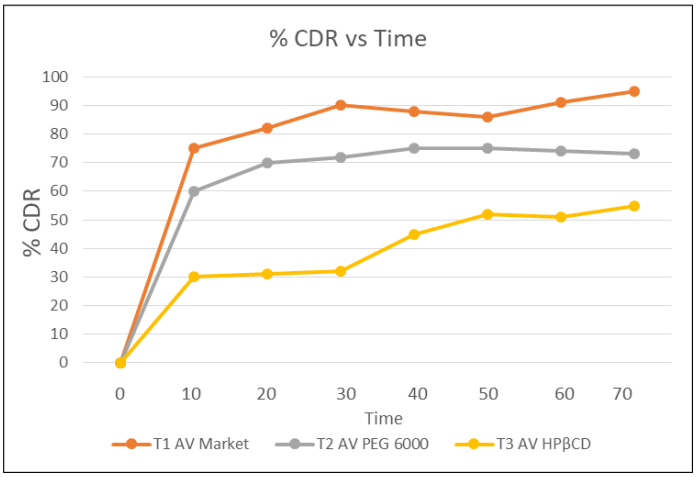


**Figure 9** Dissolution Profile of the Telmisartan Tablet

## 5. Conclusion

Telmisartan is a BCS Class II medication with strong permeability and low solubility. Telmisartan solubility in aqueous solution is substantially pH dependent, with maximal solubility reported at high and low pH. It is thus necessary to improve Telmisartan solubility at neutral pH. Telmisartan's minimal aqueous solubility or hydrophobicity is attributed to the presence of non-polar functional groups in its structure, so in this study some polar excipients such as hydroxypropyl beta cyclodextrin, PEG4000, PEG6000 were used to significantly enhance the drug's solubility, and it was discovered that hydroxypropyl beta cyclodextrin, PEG4000, PEG6000 could contribute. In the experiment, the concentration of the Hydroxypropyl beta cyclodextrin drug combination was maximum when a spectroscopic assessment was done at max 295 nanometers. However, because the complex has a strong peak at 296.40 and two weak peaks at 228.0 and 392.20, it may be deduced that the complex contains more medication in soluble form than the other

complexes with PEG4000 and PEG 6000, which were also utilized in the experiment to increase drug solubility. Telmisartan was examined for in-vitro drug release studies as a solid dosage form - tablet. The study compared a commercial Telmisartan (Mankind) tablet formulation against tablets containing Telmisartan Hydroxypropyl beta cyclodextrin and Telmisartan – PEG 6000 complex. Both tablets of the stated complexes initially exhibited a slower release until 60% CDR; nevertheless, a continuous release, whereas the marketed formulation showed an initial greater release of roughly 80% but no further release was detected. Thus, Telmisartan PEG 6000 can be released over a longer length of time.

As a result, the study indicated that Telmisartan's solubility had significantly improved. The disintegration of tablets formed from the complexes has yielded promising results.

## Compliance with ethical standards

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All authors have participated in conception and design, or analysis and interpretation of the data; drafting the article or revising it critically for important intellectual content; and approval of the final version. This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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