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Development, characterization and solubility enhancement of poorly water soluble drug telmisartan by polymer enriched bridging liquid technique using peg 4000 as hydrophilic polymer

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ABSTRACT

The solubility and bioavailability enhancement of poorly water soluble drugs has been a foremost challenge in formulation development. Telmisartan belonging to Angiotension II receptor antagonist, extensively used candidate for the treatment of hypertension possess poor water solubility and bioavailability. Polymer Enriched Bridging Liquid (PEBL) method was adopted here for enhancing the flow properties and solubility of Telmisartan. The techniques involve the incorporation of a hydrophilic polymer, PEG4000 into the bridging liquid during the crystallisation process. The drug content determination suggested the better incorporation of polymer into the crystal aggregates. The FTIR analysis showed the absence of any chemical interaction. The DSC analysis showed a significant reduction in the enthalpy and melting point. The crystallinity of Telmisartan was reduced from 50.789 to 34.655% indicated by the reduction in peak intensity analysis and peak area calculation by X-Ray diffraction. The SEM analysis revealed the spherical nature of crystals resulting in the improvement of flow properties. The saturation solubility analysis revealed that the formulation STPG03 has shown 25.86 fold increase in the solubility in water and 24.217 folds in pH7.5 Phosphate buffer. The *in vitro* dissolution data also supported the results of solubility analysis. Hence, PEBL technique provided a better alternative to enhance the flow characteristics, solubility, dissolution and bioavailability of Telmisartan.

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INTRODUCTION

The high-throughput screening techniques developed have generated immense of molecules having specific activity towards the receptor of choice (Malamatari *et al.*, 2018). The developed moieties were highly lipophilic in nature with higher molecular weight (Ding *et al.*, 2019). These physicochemical characteristics usually will lead to poor solubility in water and result in dissolution failure. The recent studies have described that around 40 % of moieties developed were being suffered from poor and erratic bioavailability. This usually will lead to the difficulty for the optimisation of lead compounds (Merisko-Liversidge and

Liversidge, 2008). This was evident in the case of class II of the Biopharmaceutical Classification System (BCS). The step which limits the rate of drug absorption in this category is the dissolution, which leads to poor bioavailability. Even though the drug has adequate permeability, the solubility constrains resulted in the limitation of drug transport and absorption (Junyaprasert and Morakul, 2015).

Telmisartan is an angiotension II receptor antagonist commonly used in the management of hypertension (Choe *et al.*, 2019). Telmisartan is practically insoluble in the pH range of 3 to 7. The poor solubility became a major barrier in the bioavailability of Telmisartan, which was reported to be 42-58%. To overcome the pH-dependent solubility, the formulation industries use very strong alkalinizers like potassium hydroxide, meglumide, sodium hydroxide or their combinations as pH modifying agents (Kundu *et al.*, 2018).

Spherical crystallisation is a technique for enhancing the flow characteristics and solubility of drugs having poor micromeritic characteristics and water solubility (Peña *et al.*, 2017). The spherical crystallization technique utilises a three solvent approach. The good solvent is the one which dissolves the drug, whereas the drug should be insoluble the bad solvent. The third solvent used in the process is bridging liquid, which connects the wetted particles by the formation of liquid bridges. The various mechanisms of adhesion involved between the wet particles are Vander Waals forces, electrostatic forces, and the liquid bridge forces. The liquid bridges generate static bridge force resulting from the curvature of the bridge and the force due to interfacial tension (Mu and Su, 2007; Simons, 1996). This resulted in the formation of spherical crystal agglomerates. (Pitt *et al.*, 2018) This increased the particle size and contributes for direct tabletting due to enhancement incompressibility and micromeritic characteristics (Subero-Couroyer *et al.*, 2006).

Polymer assisted crystal agglomeration technique via Polymer Enriched Bridging Liquid Technique (PEBL) utilises the wetting and solubilising property of hydrophilic polymer in enhancing the solubility of poorly water soluble drugs. This was achieved by the incorporation of the hydrophilic polymer in the bridging liquid during the crystal agglomeration process. The addition of polymer in the bridging liquid enabled the better incorporation of polymer in the crystal agglomerates which aided in wetting and dissolution of the drug. The bridging liquid has more affinity towards the good solvent, which helps in the better incorporation of polymer in the crystal aggregates during its formation.

The poorly water-soluble drugs pose great difficulty in the design of dosage form. It affects the bioavailability of the drug. The drugs belonging to BCS class II, having poor water solubility and high permeability can be considered for this approach of solubility enhancement (Charalabidis *et al.*, 2019).

This study was focussed on the development of novel technique "Polymer Enriched Bridging liquid" for the improvement of micromeritic properties, solubility and dissolution of Telmisartan, poorly water soluble drug using PEG4000 as hydrophilic polymer.

MATERIALS AND METHODS

Telmisartan was obtained as a gift sample from Cipla Ltd, Polyethylene glycol (PEG) 4000 from Sigma Aldrich, Germany, Dichloromethane and chloroform from Merck Ltd. The other chemicals used in the study were analytical grade. The purified water used was ultra-pure grade from Milli-Q water purification (Millipore, Germany).

Preparation of Crystal agglomerates by Polymer Enriched Bridging liquid

The crystal aggregates of Telmisartan were formulated using Polymer Enriched bridging liquid technique (PEBL). The Telmisartan was weighed as per the formula is given in Table 1. Chloroform was used as a good solvent, Dichloromethane (DCM) was used as bridging liquid, and ultrapure water (milli-Q) was used as a bad solvent. The solution of Telmisartan was made in chloroform and added to 50ml of water. It was stirred at 900RPM using magnetic stirrer (REMI). A solution of Polyethylene glycol (PEG 4000) was made in DCM, and it was added to the above dispersion. The stirring was continued for 4 hours for the formation and stabilisation of crystal agglomerates. The crystal agglomerates were then separated using vacuum filtration by passing through 0.45μm membrane filter. It was followed by drying under vacuum desiccator. Formulation ST01 was also prepared using the above procedure without the incorporation of PEG 4000.

Percentage yield and drug content

The percentage yield was determined after drying the crystal agglomerates. It was calculated using the formula (Ganesan *et al.*, 2015).

Percentage yield=

$$\frac{Actual\ yield}{theoretical\ yield\ (drug + polymer)} x100$$

The percentage drug content (Zhong *et al.*, 2013) was determined by weighing about 10 mg of the

Table 1: Composition of crystal agglomerates prepared using PEBL technique

Ingredients	ST01	STPG01	STPG02	STPG03	STPG04	STPG05
Telmisartan (mg)	200	200	200	200	200	200
Chloroform (ml)	6	6	6	6	6	6
PEG4000 (mg)	-	10	25	50	75	100
DCM (ml)	2.5	2.5	2.5	2.5	2.5	2.5
Water (ml)	50	50	50	50	50	50

crystal agglomerates, crushed and dissolved in 0.5ml of 0.1M NaOH and made up to 10ml with 7.5 Phosphate Buffer, vortexed for 15 min. It was filtered using 0.45μm syringe filter (Merck Millipore) and analyzed UV spectrophotometrically at 296nm after suitable dilutions.

Micromeritic Properties

The micromeritic properties were determined by initially calculating the bulk density and tapped density. It was used for the determination of Carr's Compressibility index and Hausner's ratio. The angle of repose was calculated using the fixed funnel method (Shah *et al.*, 2008; Al-Hashemi and Al-Amoudi, 2018).

Saturation Solubility analysis

The saturation solubility analysis was determined for Telmisartan and crystal agglomerates. It was carried out in ultrapure water and pH of 7.5 Phosphate Buffer (Indian pharmacopoeia, 2014). An excess amount (about 100 mg) of Telmisartan was added to 25ml of water/pH 7.5 phosphate buffer and shaken at 100 agitations per min in a shaker water bath at room temperature. It was centrifuged, and the supernatant was separated and filtered through 0.45μm syringe filter and analysed using UV spectrophotometer at 296 nm (Park *et al.*, 2013).

Fourier Transform- Infrared analysis

The FTIR analysis of Telmisartan, PEG 4000 and the crystal aggregates were carried out using Agilent Cary 630 FTIR. About 3mg of the samples were gently grounded and mixed with Potassium bromide (IR grade) and then compressed at 10tonnes using the hydraulic press for 5 min to form discs. The discs were analysed by recording the spectra between the wavelength of 4000-400cm^{-1}. (Marques *et al.*, 2018; Patel *et al.*, 2015).

Differential scanning calorimetry (DSC) analysis

The Differential scanning calorimetric (DSC) analysis were carried out using Perkin Elmer, DSC-8000 (Japan) (Oh *et al.*, 2019). The samples were placed in aluminium pans. Lids were placed and crimped using crimper. The crimped aluminium cups were kept in the sample chamber of the equipment, and empty crimped aluminium pan was taken as the reference. The heating rate was carried out at 10^{0}C /min from 25 to 250 ^{o}C.

X-ray diffraction analysis

X-ray diffraction studies were carried out to analyze the percentage crystallinity and its effect on solubility. It was carried out in the range of 2θ from 50° - 130° using (Rigaku Miniflex 600, japan) X-ray diffractrometer at ambient temperature using nickel filter. The X-ray generated up to 40 kV and a current of 15 mA. The diffraction angle (2Θ) was plotted against intensity (Tran *et al.*, 2008).

In vitro dissolution analysis

The *in-vitro* dissolution rate was analysed using USP type II apparatus (Patel *et al.*, 2012). The dissolution studies were carried out for Telmisartan and various formulations. 20 mg of pure drug and its equivalent for the formulations were subjected to dissolution analysis. It was performed in 900 ml of pH, 7.5 phosphate buffer (Indian pharmacopoeia, 2014). The temperature of the medium was maintained at 37$\pm$0.5^{0}C. A volume of 5ml of the samples were withdrawn at various time intervals of 15, 30, 45 and 60 minutes. It was replaced with fresh buffer solution maintained at the same temperature. The samples were filtered using 0.45μm syringe filter and analysed using UV spectrophotometer at 296nm.

Scanning Electron Microscopic analysis

The SEM analysis was performed on Hitachi SU6600. The pure Telmisartan, as well as the formulations, were sputter-coated with gold using Hitachi E-1010 coater under argon atmosphere (Gaur *et al.*, 2014).

Stability analysis

The optimized formulation of Telmisartan was kept for accelerated stability study as per ICH guidelines at a temperature of 40^{0}C $\pm$ 2^{0}C and relative humidity of 75$\pm$ 5% for a period of 180 days. The samples were withdrawn at 3 sample points (e.g. 0, 90 and 180 days), and tested for drug content and *in-vitro* dissolution to verify the stability of formulation during stressed conditions.

RESULTS AND DISCUSSION

The conventional spherical crystallisation approach mainly utilises a three solvent approach. The good solvent is the one which dissolves the drug, the bad solvent being water in which as the drug should be insoluble. The third solvent used in the process is bridging liquid, which connects the wetted particles by the formation of liquid bridges resulting in the formation of spherical crystal agglomerates (Pitt *et al.*, 2018). This increases the particle size and contributes for direct tabletting due to enhancement incompressibility and micromeritic characteristics (Subero-Couroyer *et al.*, 2006).

The polymer enriched bridging liquid (PEBL) technique is a novel technique for the solubility enhancement of drugs having poor water solubility and dissolution rate. The hydrophilic polymer (PEG 4000) used in the study was dissolved in the bridging liquid. The bridging liquid should be able to wet the crystals and possess poor affinity towards the bad solvent. The addition of polymer in the bridging liquid helps in the incorporation of polymer between the crystals during the agglomeration process. Chloroform was taken as the good solvent and dichloromethane (DCM) as bridging liquid. The poor solvent selected was water. The addition of a solution of Telmisartan in chloroform to water results in the formation of emulsion like dispersion. The stirring speed was initially optimized to obtain the crystals of the required size range. The addition of PEG 4000 dissolved in DCM (Bridging Liquid) to the above dispersion resulted in the formation of crystal aggregates, due to the diffusion of solvents followed by the counter diffusion and vaporisation of chloroform and dichloromethane.

Micromeritic Properties

The micromeritic characteristics of Telmisartan (pure drug) and various formulations developed were shown in Table 2. Telmisartan exhibited extremely poor Carr's compressibility characteristics and flow property. The spherical crystals ST01 formulated without the addition of PEG 4000 has shown improvement in the flow characteristics. The formulations STPG02 to STPG05 have shown excellent flow properties. By analyzing the pattern of the results, it can be suggested that the increase in the amount of polymer in the bridging liquid increases the flow characteristics.

Percentage yield and drug content

The percentage yield of the formulations was carried out. It was found to be between 82.50±2.12 to 77.38±0.80. The percentage yield of formulation ST01 was found to be 82.50±2.12. The percentage yield increased with increase in polymer concentration up to formulation STPG02. The highest percentage yield was found to be for the formulation STPG02 (86.65±0.65). Further increase in polymer concentration has shown a decrease in the yield. This might be due to the solubilisation of PEG4000 in water. The drug content of formulation ST01 prepared without the addition of PEG4000 was found to be 99.98±0.05%. The percentage drug content of crystal aggregates prepared by PEBL technique has ranged from 95.01±0.14 to 80.25±0.21%. A decrease in percentage drug content was observed with increase in polymer concentration. This suggests that, the incorporation of polymer in the crystal aggregates increased with increase in polymer concentration in the bridging liquid.

Saturation Solubility analysis

The saturation solubility analysis was carried out in water and pH of 7.5 Phosphate buffer. The drug Telmisartan was almost insoluble in water and pH7.5 Phosphate buffer, having a solubility of 1.270±0.021 μg/ml and 2.078±0.034 μg/ml, respectively (Figure 1). The formulation ST01 devoid of the polymer has shown a 6.5 fold increase insolubility in water and 7.75 folds in the buffer. The highest solubility was observed for formulation STPG03 (32.843±0.428 μg/ml) with a 25.86 fold increase insolubility in water and 24.217 folds in pH7.5 Phosphate buffer (50.333±1.854 μg/ml). The solubility increased with increase in the concentration of PEG4000, up to an optimum concentration. Further increase in the concentration of PEG4000 has not shown any significant improvement insolubility.

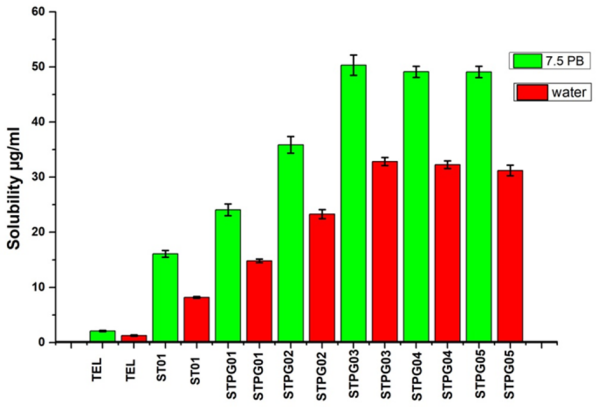

Figure 1: Saturation solubility analysis data of Telmisartan and formulations in water and pH 7.5 Phosphate buffer (7.5PB) (all values expressed in mean±SD, n=3)

Fourier Transform- Infrared analysis

The FTIR analysis was carried out for Telmisar-

Table 2: Micromeritic characteristics of Telmisartan and formulations (all values expressed in mean±SD, n=3)

Formulations	Carr's Index (%)	Hausner's Ratio	Angle of Repose (0)
Telmisartan	49.524±0.825	1.981±0.032	47.505±1.196
ST01	33.325±0.889	1.500±0.020	30.716±0.435
STPG01	22.134±0.317	1.284±0.005	28.834±0.382
STPG02	20.635±1.375	1.260±0.022	24.777±0.289
STPG03	15.774±2.074	1.188±0.029	21.935±0.232
STPG04	14.364±1.281	1.168±0.015	20.210±0.196
STPG05	14.276±1.108	1.166±0.015	19.450±0.125

tan, PEG 4000, formulation ST01 and formulations STPG03 and STPG04 prepared using PEG4000 as hydrophilic polymer. Telmisartan exhibited characteristic peaks at 3479 cm^{-1}(-OH stretch), 2952 cm^{-1} (C-H stretch), 1693 cm^{-1} (C=O stretch), 1125 cm^{-1} (C-O stretch), and CH bending at740 cm^{-1} (Figure 2) which confirmed the identity of the drug. The formulation ST01 and other formulations prepared using PEBL technique using PEG4000 (STPG03 and STPG04) has shown all the characteristics peaks of Telmisartan without any major shift in wavenumber. It indicated the absence of chemical modifications which might have taken place during the process. It also eliminated the possibility of covalent bonding between the drug and PEG4000.

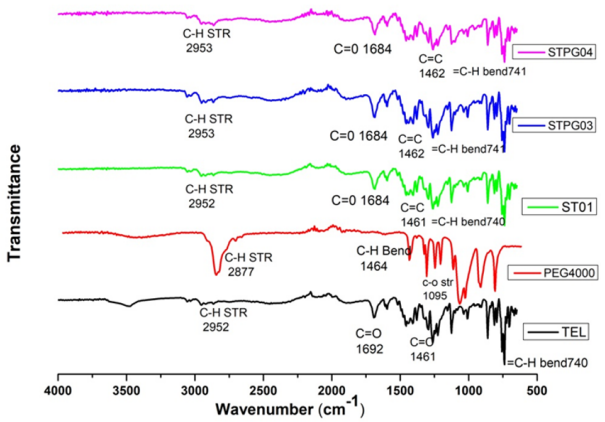

Figure 2: FTIR analysis data of Telmisartan (Tel), PEG4000, ST01 and formulations prepared using PEBL technique (STPG03 and STPG04)

Differential scanning calorimetry (DSC) analysis

The Differential Scanning Calorimetric analysis of Telmisartan (Figure 3) showed a sharp peak at 271.80^{0}C. This indicated that Telmisartan existed in pure crystalline form and has an enthalpy of -117.18J/g. The PEG 4000 has shown a peak at 59.92^{0}C with an enthalpy of -72.26J/g. The formulation ST01 prepared without the addition of PEG has shown an endothermic peak at 271.31^{0}C and enthalpy of -110.29J/g. The formulations STPG03 and STPG 04 showed broadening of peaks and a decrease in melting point and enthalpy. The melting endotherm was found to be 266.64^{0}C and 264.97^{0}C respectively for STPG 03 and STPG04 respectively. The enthalpy was also found to be reduced in both the formulations. This suggested that the formulations prepared using the PEBL technique has resulted in the reduction in crystallinity and resulted in amorphization of Telmisartan.

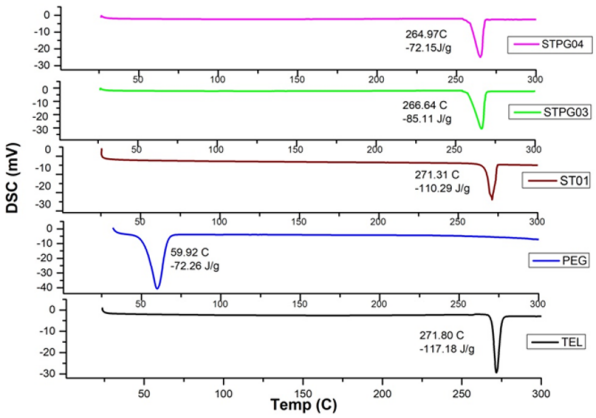

Figure 3: DSC analysis data of Telmisartan (TEL), PEG4000 (PEG), ST01 and formulations prepared using PEBL technique (STPG03 and STPG04)

X-ray diffraction analysis

The X-ray diffraction studies were performed for Telmisartan, PEG4000, ST01, STPG03 and STPG04 (Figure 4). Telmisartan exhibited characteristic peaks at the diffraction angles of 6.48 and 13.88(2θ). The similar peaks with a slight reduction in intensity were observed for formulation ST01. The addition of PEG4000 using PEBL technique resulted in the reduction in the intensity of peaks. This was evident from the halo regions in the XRD data of formulations STPG03 and STPG04. The percentage of crystallinity was determined by peak area calcula-

tion method. The percentage crystallinity of Telmisartan was 50.789. The formulation of ST01 has not shown any significant reduction in crystallinity (49.334%). The formulations prepared by PEBL technique showed a significant reduction in crystallinity. The % crystallinity of formulations STPG03 and STPG04 was found to be 35.856 and 34.655% respectively.

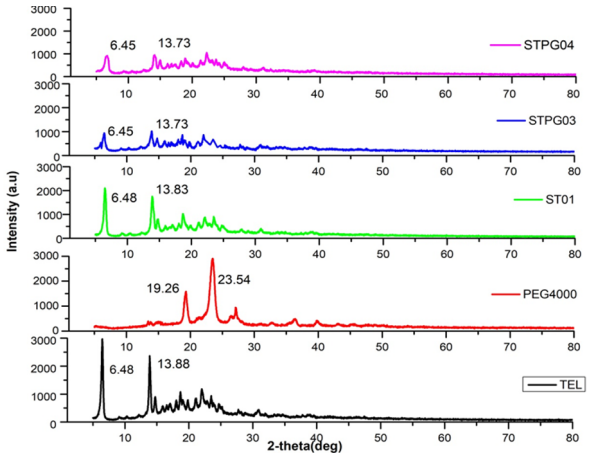

Figure 4: XRD analysis data of Telmisartan, PEG4000, ST01 and formulations prepared using PEBL technique (STPG03 and STPG04)

In vitro dissolution analysis

The *in vitro* dissolution of the pure drug and formulations were carried out in phosphate buffer pH 7.5. The medium for dissolution mention in Indian pharmacopoeia was pH 7.5 for Telmisartan formulations. The pure drug showed a release of less than 9 % at the end of 60 minutes (Figure 5). The formulation ST01 increased the drug dissolution to 29.507% $\pm$2.125% at the end of one hour. The formulations STPG01 to STPG05 showed significant improvement in drug dissolution. The formulations STPG03 showed a percentage cumulative drug release (%CDR) of 86.120$\pm$1.669, 95.231$\pm$1.765 and 99.185$\pm$0.216 at the end of 15, 30 and 45 minutes respectively. The formulations STPG04 and-STPG05 also has shown similar drug release profile. Hence formulation STPG03 prepared using 200mg of Telmisartan and 50mg of PEG4000 via Polymer enriched bridging liquid can be used as a novel technique for the enhancement of solubility and dissolution of poorly water soluble Telmisartan.

Scanning Electron Microscopic analysis

The Scanning microscopic images revealed the pure Telmisartan was crystalline in nature. The crystals were sharp rod-like having a particle size of 0.521$\pm$0.128μm (Figure 6 a). The formulation STPG03 which showed enhanced solubility and dissolution rate was subjected to SEM analysis. It was

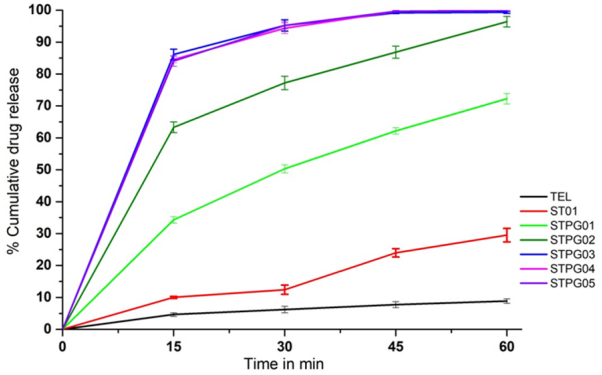

Figure 5: In vitro drug release profile of Telmisartan and formulations (ST01, STPG01 to STPG05) in phosphate buffer pH7.5

found to spherical in nature (Figure 6 b), which contributed for the improvement of flow characteristics of the formulations. The change in the surface characteristics might be due to the incorporation of PEG4000 during the crystallization stage, which has resulted in the enhancement of water solubility by increasing the wettability. The porous nature of the aggregates and surface hydrophilicity also resulted in enhanced wetting and solubility characteristics. The size of the aggregates was found to be 125.21$\pm$7.25 um suggesting the aggregation of small crystals into uniform sized spherical crystal agglomerates.

Stability studies

The optimized formulation of Telmisartan crystal aggregates (STPG03) was kept for accelerated stability studies as per ICH guidelines, at a temperature of 40^0C $\pm$ 2^0C and relative humidity of 75$\pm$ 5% for a period of 180 days. The analysis of the samples was carried out at regular intervals. The physical characteristics observed using a microscope under 40X magnification revealed that characteristics of crystal aggregates were not distorted during the storage. The percentage of drug content was found to be 80.20$\pm$0.37 at the end of 180 day. The percentage drug content of STPG03 was 82.20$\pm$0.23 before carrying out stability analysis. There was only a 0.975% decrease in drug content after carrying out the stability analysis. The *in-vitro* dissolution studies also showed a % CDR of 84.3698$\pm$0.968, 94.162$\pm$1.834, 98.658$\pm$0.381 in 15, 30 and 45 minutes respectively in pH 7.5 Phosphate at the end of 180 days. Hence, formulations STPG03 was found to be maintaining its properties and stability under accelerated conditions.

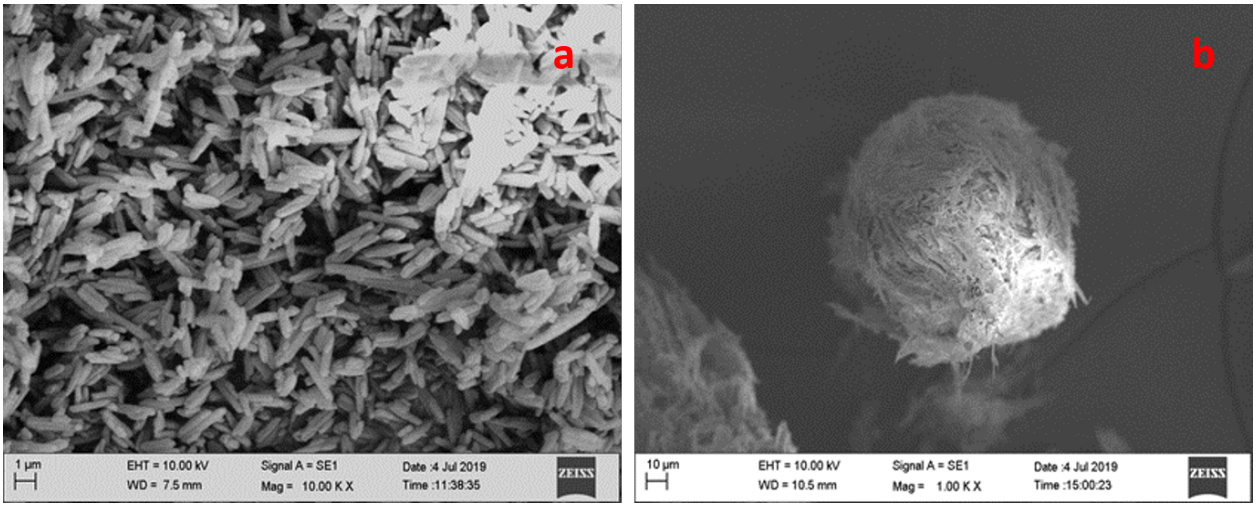

Figure 6: Continuous XRD patterns of a) Telmisartan and b) formulation STPG03

CONCLUSION

The Polymer enriched bridging liquid using PEG4000 as the hydrophilic polymer was used for the preparation of crystal agglomerates for the enhancement the flow characteristics, solubility and dissolution. The incorporation of polymer in the bridging liquid during crystallization process resulted in the incorporation of polymer into the crystal aggregates. This contributed to the enhancement in the wettability and solubility. The drug content studies indicated that the enhancement of polymer concentration in the bridging liquid improves the polymer inclusion into the aggregates. The micromeritic characteristics were improved with polymer addition. There was no chemical interaction between the Telmisartan and PEG4000. The crystallinity of Telmisartan was reduced by PEBL technique and the saturation solubility studies showed that formulation STPG03 formulated with Drug: polymer ratio of 4:1 have shown significant enhancement insolubility in water and pH 7.5 Phosphate buffer. The *in vitro* dissolution studies also confirmed the enhancement of dissolution of formulation STPG03 prepared by PEBL method. This technique provided a better alternative to enhance the solubility, dissolution and bioavailability of Telmisartan without the use of high alkalizers.

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