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Study of the effect of pvp k30 in the enhancement of solubility of telmisartan by polymer assisted crystal agglomeration using polymer enriched bridging liquid technique

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ABSTRACT

Polymer Enriched Bridging liquid is a novel approach for enhancing the flow characteristics, micromeritic properties, solubility and dissolution of poorly water-soluble drugs. Telmisartan is an orally effective Angiotension II receptor antagonist used extensively for the effective management of hypertension. Telmisartan is a poorly water-soluble drug and an ideal candidate for this approach. PVPK30 is used as the hydrophilic polymer. Various formulations were prepared with the addition of PVPK30 in the bridging liquid by Polymer Enriched Bridging Liquid Technique (PEBL). The preparations were subjected to particle size analysis, micromeritic characteristics, FTIR, differential scanning calorimetry (DSC) and Scanning Electron microscopic analysis. The crystal agglomerates were found to be spherical in nature with excellent flow characteristics. The crystallinity of the pure drug was found to be decreased without any drug-polymer interaction. The saturation solubility studies showed that the optimized formulation STP04 showed 30.695 folds increase in solubility in water and 29.462 folds enhancement in pH 7.5 phosphate buffer. The *in vitro* drug release studies also confirmed the enhancement in dissolution rate. The stability of the prepared aggregates was determined by accelerated stability studies. The addition of polymer in the bridging liquid during crystallization stage improved the effective incorporation of the hydrophilic polymer in the aggregates. Polymer Enriched Bridging Liquid technique can be considered as an ideal technique for solubility and dissolution enhancement.

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INTRODUCTION

The oral route is considered as the most important route of drug administration owing to the ease of administration, dosage accuracy, negligible sterility considerations and lower cost. Among the oral dosage forms, tablets are the foremost choice of drug administration (Wening and Breitkreutz, 2011). But the core setback in the formulation of oral solid dosage forms is the solubility of the drug, which ultimately leads to poor bioavailability. The drugs possessing poor water solubility is required to be administered in very high doses to attain therapeutic plasma concentration (Kerns and Di, 2008).

The primary challenge is to improve the solubility of poorly water-soluble drugs belonging mainly to BCS class II for the enhancement of bioavailability, as the solubility being the rate-limiting step (Savjani *et al.*, 2012).

Spherical aggregation is a technique developed for the formulation of directly compressed drugs. The drug was converted to a spherical form which enhances the flow characteristics, compressibility, solubility and dissolution. It involves the concurrent crystallization along with agglomeration resulting in the transformation of crystals into a spherical stature (Kawashima *et al.*, 2003).

Various methods for attaining spherical agglomeration are quasi-emulsion solvent diffusion method, wet spherical agglomeration, neutralisation technique and ammonia diffusion method (Kovačič *et al.*, 2012). The concept of Spherical agglomeration requires three solvent systems, the good solvent, bridging liquid and the poor solvent for the drug. (Pitt *et al.*, 2018). The bridging liquid is the one which acts as a binder between the particles and helps in the formation of crystal agglomerates. It should not have an affinity with the poor solvent but capable of wetting the crystals precipitated. It acts by the formation of liquid bridges which links the crystals. Interfacial tension and negative capillary pressure are the key forces resulting in the liquid bridge formation (Chow and Leung, 1996; Thati and Rasmuson, 2011).

Polymer enriched bridging liquid technique (PEBL) is a novel technique for enhancing the solubility of poorly water-soluble drugs. The technique involves the incorporation of hydrophilic polymer into the bridging liquid. The addition of bridging liquid incorporated with a hydrophilic polymer during crystal formation will bring the crystals together and assist in the integration of polymer within the crystal aggregates as well as outside the aggregates. Telmisartan is an orally effective angiotensin II receptor antagonist blocking selectively the receptors of angiotensin II. It is used widely for the effective management of hypertension (Sharpe *et al.*, 2001). It is poorly soluble in water (Park *et al.*, 2019; Patel *et al.*, 2012).

The aim of the study was to analyse the feasibility of new technique "Polymer Enriched Bridging liquid" in enhancing the solubility of poorly water-soluble drug Telmisartan using PVP K30 as the hydrophilic polymer. The prepared crystals aggregates were characterised and evaluated for the enhancement in the solubility, dissolution and improvement in the micromeritic properties.

MATERIALS AND METHODS

Telmisartan was gifted for research from M/S Cipla Ltd, PEG 4000, Polyvinylpyrrolidone K30 from Sigma Aldrich Germany, Chloroform, and Dichloromethane from Merck. All chemicals used for the study were of analytical grade. Ultrapure water was obtained from a Milli-Q water purification system (Millipore, Germany).

Formulation of Crystal agglomerates by Polymer Enriched Bridging liquid

The required quantity of Telmisartan as per Table 1 was accurately weighed and dissolved in chloroform. The above solution was added to 50 ml of ultrapure water (Millipore) in a 100 ml beaker. The dispersion was stirred continuously using magnetic stirrer at 900 ±20 RPM. A solution of PVP K30 in dichloromethane (bridging liquid) was prepared and added to the above dispersion. The stirring was carried out for 4 hours crystallization and stabilization. The aggregates obtained were separated by vacuum filtration using a 0.45 membrane filter. The crystal aggregates were dried in vacuum desiccator charged with calcium chloride. The amount of bridging liquid and stirring speed was previously optimized to alter the characteristics of the crystal aggregates.

In vitro Characterization of Crystal aggregates

Particle size and shape

The particle size and the shape were preliminary screened using digital optical microscope (DMWB1series, Motic, China) with a built-in digital camera having a resolution of 720x576 pixels. About 500 particles were randomly selected and analysed for particle size using Motic Images Plus 2.0 software. It was further characterized using Scanning Electron Microscopy.

Micromeritic characteristics

Bulk density and tapped density

The bulk density and tapped density were determined with tap densitometer (EI instruments). 3g of the crystals were weighed and added to a 25 ml measuring cylinder, the volume was noted as the bulk volume. The bulk density was obtained by dividing mass by bulk volume. The measuring cylinder was then tapped in the apparatus for 100 times. The tapped density was determined from the tapped volume similar to the determination of bulk density. The experiments were repeated in triplicate, and the average was noted (Krishna *et al.*, 2013).

Carr's Compressibility Index and Hausner's ratio

Table 1: Composition of Crystal agglomerates

Ingredients	ST01	STP01	STP02	STP03	STP04	STP05
Telmisartan (mg)	200	200	200	200	200	200
Chloroform (ml)	6	6	6	6	6	6
PVPK30 (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

Carr's compressibility index and Hausner's ratio was determined using tapped density and bulk density. Carr's index is represented by the equation (Kaialy *et al.*, 2014; Kedia and Wairkar, 2019).

$$Carrs\ compressibility\ index = \frac{Tapped\ density - bulk\ density}{Tapped\ density} * 100$$

Hausner's ratio was determined by dividing tapped density with a bulk density

$$Hausner's\ ratio\ = \frac{Tapped\ density}{bulk\ density}$$

The angle of repose

Fixed funnel method was used for the determination of the angle of repose. The funnel was adjusted to a fixed height of about 4cm (h) from the tip of the funnel to the horizontal surface. The powder about 3g was added through the funnel, and the radius(r) of the heap of granules formed was measured. The following formula was used to determine the angle of repose. The experiments were carried out in triplicate (Shah *et al.*, 2008).

$$The\ angle\ of\ repose = \tan^{-1}(h/r)$$

Percentage Yield and percentage drug content

The crystal aggregates after drying was weighed, and the practical yield was determined. The percentage yield was calculated using the formula (Deshkar *et al.*, 2017)

$$Percentage\ yield = \frac{Total\ weight\ of\ crystal\ aggregates}{Total\ weight\ of\ drug\ and\ excipients} \times 100$$

For drug content determination, the formulations were weighed (10 mg), dissolved in 0.5ml of 0.1M NaOH and made up to 10ml with 7.5 Phosphate buffer followed by vortexing for 15 min. It was then filtered using 0.45μm nylon filter (Merck millipore) and analyzed by UV spectrophotometric analysis at 296nm after suitable dilutions with pH 7.5 Phosphate buffer.

Determination of Saturation Solubility

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

Fourier transform infrared (FTIR) spectrophotometric analysis

The FTIR spectral analysis of pure drug and crystal aggregates were carried out using Agilent Cary 630 FTIR. About 1-2 mg of sample was taken and triturated with potassium bromide (KBr). The mixture was then compressed into a disc using a hydraulic press. The disc was then kept in the light path, and the spectrum was recorded between the wavelength of 4000-400cm^{-1}. (Ren *et al.*, 2017).

Differential scanning calorimetry

The Differential scanning calorimetric analysis was carried out using DSC-8000 (Perkin Elmer, Japan). The samples were placed in aluminium pans. Lids were placed and crimped using crimper. The crimped aluminium cups containing samples were kept in the sample chamber, and empty crimped aluminium pan was taken as the reference. The heating rate was done at 10^{0}C /min from 25 to 250 ^{o} C (Gupta *et al.*, 2007)

X-ray Diffraction Studies

X-ray diffraction studies were carried out to analyze the percentage crystallinity and its effect on solubility. It was carried out using Rigaku Miniflex 600 X-ray diffractometer (Japan), in the range of 2θ from 50° - 130° at ambient temperature using nickel filter. The X-ray generated up to 40 kV and a current of 15 mA.

***In vitro* dissolution studies**

The *in-vitro* dissolution rate was determined using USP type II apparatus using a paddle (Swiss make).

The dissolution studies were carried out for Telmisartan and crystal aggregates equivalent to 20mg of pure drug. The dissolution studies were performed in 900 ml of pH 7.5 phosphate buffer (Indian pharmacopoeia, 2014) and also in water. The medium was maintained at a temperature of 37 ± 0.5^0C. A samples volume of 5ml was withdrawn at time intervals of 15, 30, 45 and 60 minutes followed by replacement with fresh buffer solution. The samples were filtered using 0.45μm syringe filter and analysed by UV spectrophotometer at 296nm. The results were plotted as percentage cumulative drug release (CDR) against time in minutes.

Scanning Electron Microscopy

Scanning electron microscopy was carried out to study the shape and surface characteristics of the Telmisartan pure drug crystals as well as the crystal aggregates. It also might provide the possible mechanism of drug-polymer association as well as crystal agglomeration. The SEM was performed on Hitachi SU6600 at various magnifications. The pure drug as well as the crystal aggregates was sputter-coated with gold under argon atmosphere using Hitachi E-1010 coater (Bhattacharjya and Wurster, 2008).

Stability studies

The optimized formulation of Telmisartan crystal aggregates (STP04) was kept for accelerated stability study 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 samples were kept in USP type I glass tubes, amber, flat bottom, with polypropylene screw cap and PTFE Liner (Borosil). The samples were withdrawn at 3 sample points (e.g. 0, 90 and 180 days), and tested for different parameters such as physical characteristics, drug content and *in-vitro* dissolution in water and pH 7.5 phosphate buffer to verify the stability during stressed conditions (Isaac *et al.*, 2016).

RESULTS AND DISCUSSION

The crystal aggregates were prepared by polymer enriched bridging liquid (PEBL) technique. The concept of spherical agglomeration via Quasi Emulsion Solvent Diffusion requires three solvent systems. It includes the good solvent for the drug, the poor solvent system for the drug and a bridging liquid. The bridging liquid is added during the crystallisation stage to bring the crystals together for agglomeration. It mainly acts as a binder between the particles and gets squeezed out after aggregation. It should be wet the crystals formed but should not have any affinity towards the bad solvent. It acts by the formation of liquid bridges which helps in the linkage of crystals with the aid of interfacial tension and negative capillary pressure.

Polymer enriched bridging liquid technique (PEBL) is a novel technique for enhancing the solubility of poorly water-soluble drugs. The technique composed of a formulation of crystal aggregates incorporated with a hydrophilic polymer, which can improve the solubility, *in vitro* dissolution and other micromeritic characteristics. The addition of bridging liquid incorporated with a hydrophilic polymer during crystal formation will bring the crystals together and assist in the integration of polymer within the crystal aggregates as well as outside the aggregates.

Telmisartan was dissolved in chloroform (good solvent) and added to purified water (millipore), the poor solvent for the drug. The dispersion was then stirred continuously using magnetic stirrer at 1000 RPM. The hydrophilic polymer PVP K30 was added for enhancing the wettability of crystals. PVP K30 was dissolved in bridging liquid (Dichloromethane) and added to the above dispersion. The addition of drug in a good solvent to the poor solvent leads to the formation of a quasi emulsion. The diffusion and counter diffusion of solvents and also the evaporation of chloroform lead to the precipitation of crystals. The addition of bridging liquid incorporated with PVP K30 brings the precipitated crystal together, and the crystals start aggregating. The stirring rate was kept at 900$\pm$20 rpm as the deviation in speed leads to the formation of crystals with variable sizes. The stirring was carried out for 3 hours. The crystal aggregates obtained were separated by vacuum filtration using a 0.45 membrane filter. The crystal aggregates were dried in vacuum desiccator charged with calcium chloride.

The formulation ST01 was initially prepared without the addition of PVP K30. The formulations STP01 to STP05 were prepared with an increasing amount of hydrophilic polymer (PVP K30). The amount of Telmisartan, DCM and Chloroform was kept constant for analysing the influence of the addition PVP K30 on the solubility of poorly water-soluble Telmisartan.

***In vitro* Characterization of Crystal aggregates**

Particle size and shape

The particle size was initially screened using a digital optical microscope and further confirmed with Scanning Electron Microscopy. The pure drug Telmisartan has a particle size of 0.521$\pm$0.101μm and was found to be needle-like crystals. The particle size of formulations ST01 was found to be 52.13$\pm$2.34 μm. The particle size of other formu-

lations prepared by PEBL technique varied from 75.43±3.21 to 141.08±10.13. The highest particle size was found to be for the formulation STP05 (141.08±10.13). The particle size increased with an increase in polymer concentration. All the formulations were observed to be nearly spherical in shape.

Micromeritic characteristics

The micromeritic characteristics of pure drug and various formulations were shown in Table 2. The pure drug exhibited poor flow and compressibility characteristics. The formulation ST 01 prepared without the addition of polymers has shown betterment in the Carr's index, Hausner's ratio and angle of repose. The results also clearly indicated that the flow characteristics improved with an increase in the concentration of polymer PVP K30. The formulations STP02 to STP05 has shown excellent flow property. This was due to the aggregation of particles to form a spherical nature. The sphericity contributed for improvement in the flow property.

Percentage Yield and Percentage drug content

The percentage yield of various formulations was given in Table 3. The formulation ST01 prepared without PVP K30 has shown a yield of 82.50%. The percentage yield of other formulations lies within 75.88% to 83.09%. The percentage yield was found to be decreasing with an increase in polymer concentration. The decrease in yield with an increase in the amount of polymer incorporation was due to the solubilisation of PVPK30 in water (the bad solvent used in crystallization) due to its high solubility. The drug content analysis has proved that the drug content decreased with an increase in polymer concentration. The results suggested the incorporation of polymer in the crystal agglomerates, and the proportion of polymer incorporated in the agglomerates increased with increase in polymer concentration. The formulations STP04 to STP05 have more than 15 percent polymer incorporated in the aggregates.

Determination of Saturation Solubility

The saturation solubility analysis of pure Telmisartan and various formulations were determined in ultrapure water (Millipore) and pH 7.5 phosphate buffer (Figure 1). The Telmisartan was almost insoluble in water (1.270±0.021μg/ml) and pH 7.5 Phosphate buffer (2.078±0.034 μg/ml). The formulation ST01 showed 6.44 folds increase in the solubility in water. The solubility in water was augmented with the incorporation of PVP K30. The formulation STP04 prepared with 75 mg of PVP K30 has shown the highest solubility in water (38.980±0.987 μg/ml) and pH 7.5 phosphate buffer (61.235±0.998 μg/ml). The addition of PVP K30 in the bridging liquid has shown about 30 folds solubility enhancement in water and pH 7.5 phosphate buffer. Further increase in the amount of PVP K30 (STP05) in the bridging liquid has not shown any significant enhancement of solubility in either of the media. The addition of hydrophilic polymer PVP K30 caused wetting of the hydrophobic Telmisartan. The addition of polymer in the bridging liquid enables the better incorporation of polymer within the aggregates as well as on the surface of the aggregates, as the bridging liquid has more affinity towards the drug in a good solvent.

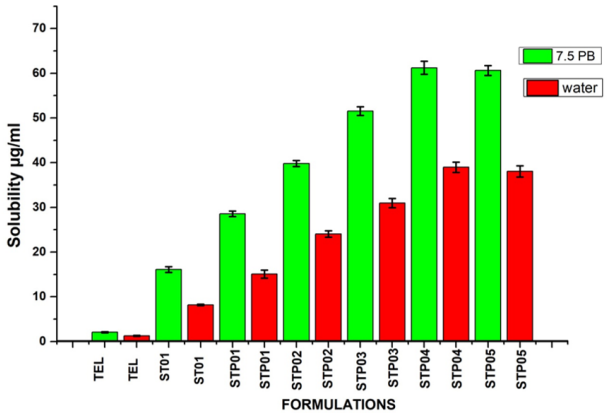

Figure 1: Solubility analysis data of Telmisartan (Tel), and crystal aggregates in water and pH 7.5 Phosphate buffer (mean ± SD, n=3)

Fourier transform infrared (FTIR) spectrophotometric analysis

Telmisartan exhibited characteristic peaks at 3479(-OH stretch), 2952 (C-H stretch), 1693 (C=O stretch), 1125 (C-O stretch), which confirms the identity of the drug **(**Figure 2). All the characteristic peaks of Telmisartan was observed in drug excipient mixture (TPVP), indicating the absence of incompatibility between drug and PVP K30. All the formulations prepared (ST01, STP01-STP05) also showed the characteristics peaks of Telmisartan, indicating the absence of chemical modifications which might have taken place during the crystallization process (Figure 3).

Differential scanning calorimetry

The DSC analysis of Telmisartan (Figure 4) showed a sharp endothermic peak at 271.80^{0}C. This suggested that the drug exists in pure crystalline form having an enthalpy of -117.18J/g. The drug excipient physical mixture has also showed a sharp peak at 271.55^{0}C without considerable change enthalpy indicating the absence of any chemical incompatibility between the drug and excipient. The formulation prepared without the addition of PVPK30 has

Table 2: Micromeritic characteristics

Formulations	Bulk Density* (g/ml)	Tapped density* (g/ml)	Carr's Index*(%)	Hausner's* Ratio	Angle of Repose (0) *
TEL	0.280±0.009	0.556±0.007	49.524±0.825	1.981±0.032	47.505±1.196
ST01	0.263±0.007	0.395±0.019	33.325±0.889	1.500±0.020	30.716±0.435
STP01	0.226±0.012	0.283±0.015	20.303±0.262	1.255±0.004	27.767±0.622
STP02	0.216±0.021	0.256±0.008	15.819±1.041	1.188±0.015	23.200±0.258
STP03	0.219±0.011	0.256±0.030	14.589±1.088	1.171±0.015	20.096±0.196
STP04	0.219±0.034	0.254±0.004	13.865±1.180	1.161±0.002	19.554±0.486
STP05	0.221±0.055	0.254±0.005	13.237±0.167	1.153±0.002	19.441±0.184

(*Mean±SD, n=3)

Table 3: Percentage Yield and Percentage drug content formulations (ST01, STP01-05)

Formulation	% Yield*	%Drug Content*
ST01	82.50±2.12	99.98±0.12
STP01	83.09±1.98	95.58±1.25
STP02	82.46±2.88	91.94±1.89
STP03	80.57±2.23	85.64±1.23
STP04	78.72±2.76	84.80±1.53
STP05	75.88±1.96	83.49±1.11

(*Mean±SD, n=3)

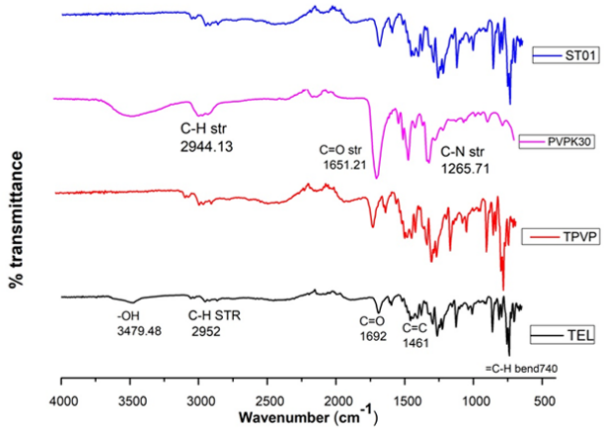

Figure 2: FTIR spectrum of Telmisartan (Tel), Telmisartan PVP K30 physical mixture (TPVP), PVPK30 and formulation ST01

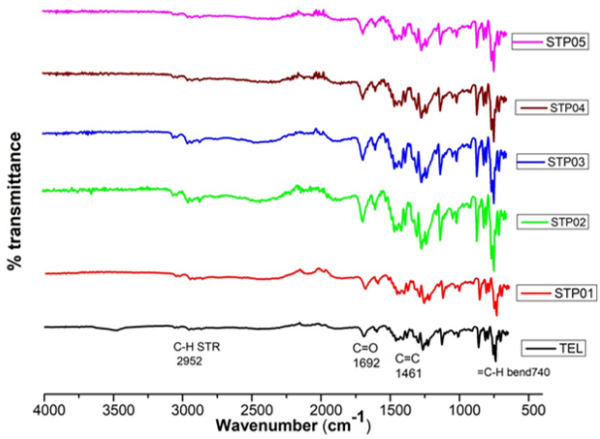

Figure 3: FTIR spectrum of Telmisartan (Tel) and formulation STP01-STP05

Table 4: Percentage Yield and Percentage drug content formulations (ST01, STP01-05)

Formulation	% Crystallinity
Telmisartan (Pure Drug)	50.789
ST01	49.631
TPVP	49.334
STP01	39.664
STP02	36.883
STP03	35.856
STP04	34.655
STP05	34.386

also shown a sharp peak at 271.25^{0}C. The formulations prepared by Polymer enriched bridging liquid have shown a decrease in the melting point. The melting point has reduced to 262.49^{0}C (STP05). The broadening of the peaks was observed for formulations STP02 to STP05 (Figure 5). The enhancement of polymer concentration reduced the melting point of drug up to 10^{o}C along with lowering of enthalpy from -117.8J/g to -68.97J/g. The above observations indicated the incorporation of polymer into the crystal aggregates and resulted in the amorphization of

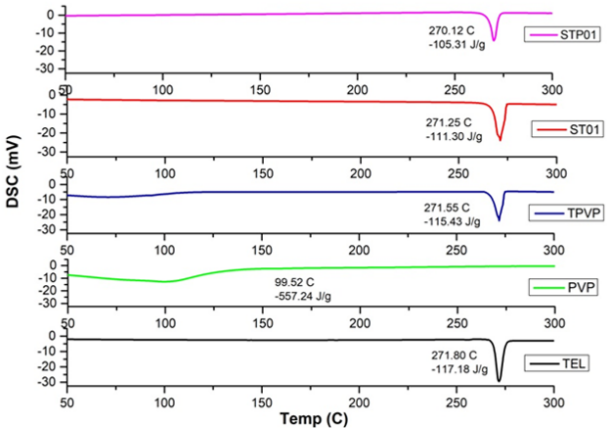

Figure 4: DSC thermograms of Telmisartan (Tel), PVP K30 (PVP), Telmisartan -PVP K30 physical mixture (TPVP), formulations ST01 and STP01

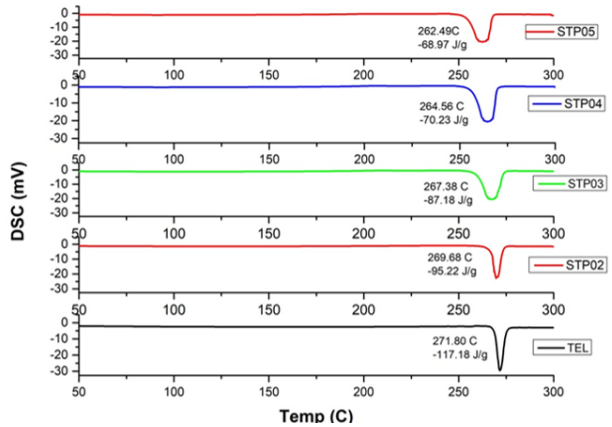

Figure 5: DSC thermograms of Telmisartan (Tel) and formulations STP01 to STP05

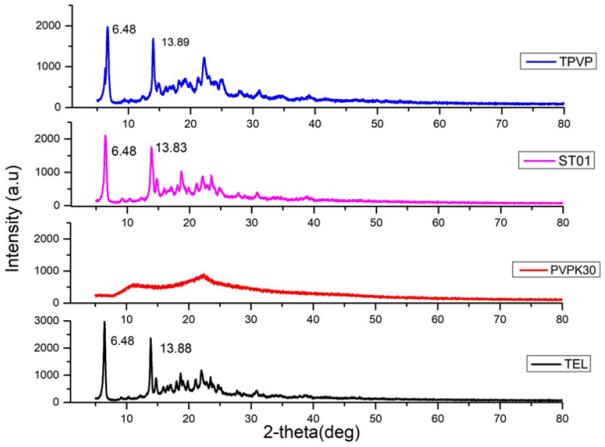

Figure 6: Continuous XRD patterns of Telmisartan (Tel), PVP K30, Telmisartan-PVPK30 physical mixture and formulation ST01

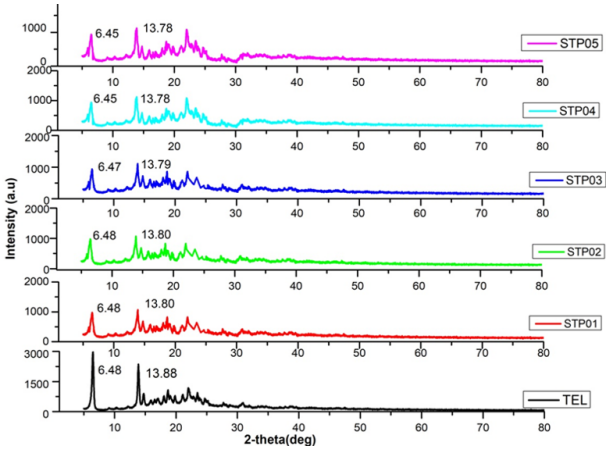

Figure 7: Continuous XRD patterns of Telmisartan, formulation STP01-STP05

drug and reduction in Crystallinity. This was evident from the reduction in enthalpy and broadening of peaks.

X-ray Diffraction Studies

The X-ray diffraction studies were performed for the pure Telmisartan, PVP K30, Telmisartan-PVPK30 physical mixture and the formulations. The pure drug exhibited prominent characteristic peaks at diffraction angles of 6.48 and 13.88(2θ) (Figure 6). The peaks were sharp, and the same pattern was observed for the drug excipient physical mixture and also the formulation ST01. The incorporation of PVP K30 via polymer enriched bridging liquid has resulted in the reduction in the intensity of characteristic peaks. This was evident from the halo peaks and lowering of intensities of Braggs peaks of binaries prepared out by Polymer enriched bridging liquid technique (STP01-STP05) (Figure 7).

The percentage degree of crystallinity (Xc) was calculated from the ratios of the area of the crystalline peaks and amorphous (halo) areas. Ac represents the total crystalline areas, and Aa represents the total amorphous area (Rani *et al.*, 2015).

$$Xc = \frac{Ac}{Ac + Aa} \times 100$$

The results were given in Table 4. The results indicated that the pure drug was highly crystalline, having a crystallinity of 50.789%. The simple physical mixture of drug with polymer (TPVP) has not shown any significant decrease in crystallinity. Similarly, the formulation ST01 also has not contributed for crystallinity reduction. The formulations prepared out of Polymer enriched bridging liquid technique using PVP K30 as the hydrophilic polymer reduced the crystallinity. The same is evident the reduction in the intensity and peak area of crystalline peaks. The crystallinity reduced with increase in polymer

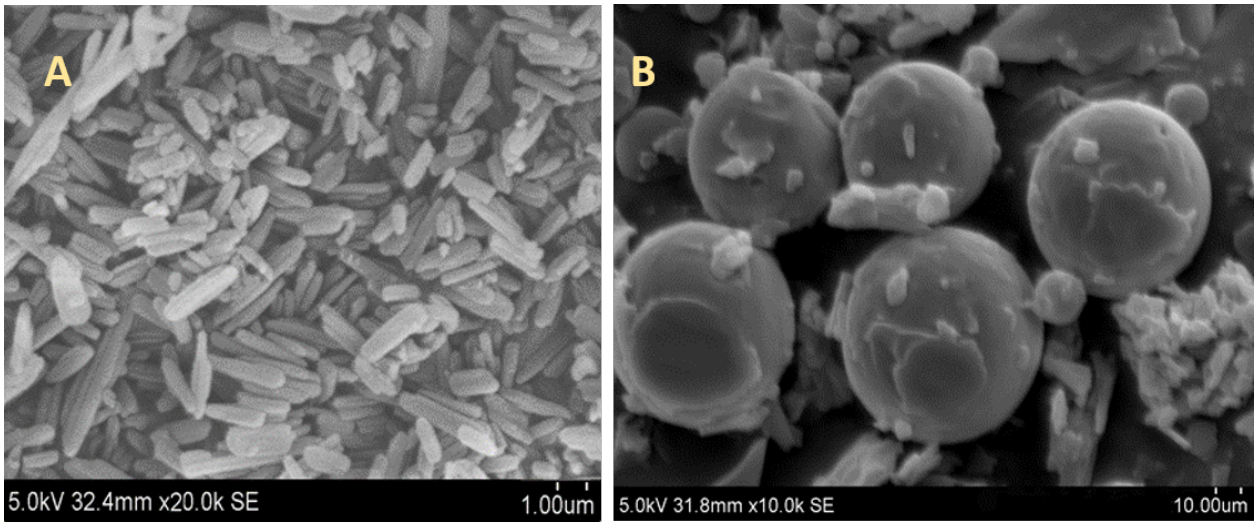

Figure 8: SEM images of a) Telmisartan and b) formulation STP04

concentration. The results suggest the amorphization of Telmisartan due to the incorporation of the hydrophilic polymer during the crystallization process.

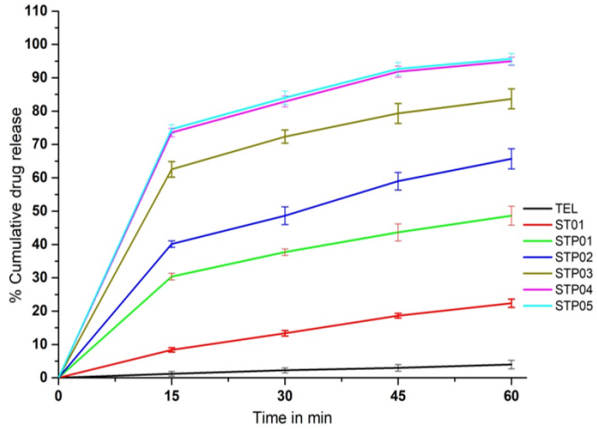

Figure 9: In-vitro drug release profile of Pure Telmisartan and formulations (ST01, STP01-STP05) in water (mean ± SD, n=3)

Scanning Electron Microscopy

The SEM images revealed the crystalline nature of pure Telmisartan (Figure 8 a). The crystals were sharp rod-like having a particle size of 0.521±0.101μm. The formulation of STP04 was subjected to SEM analysis. It was found to spherical in nature, having a smooth surface (Figure 8 b). This resulted in the improvement of flow characteristics of the formulations. The change in the surface characteristics due to the incorporation of PVPK30 during the crystallization stage might have resulted in the enhancement of solubility.

The surface hydrophilicity contributed by the polymer PVP K30 also resulted in wetting and solubility

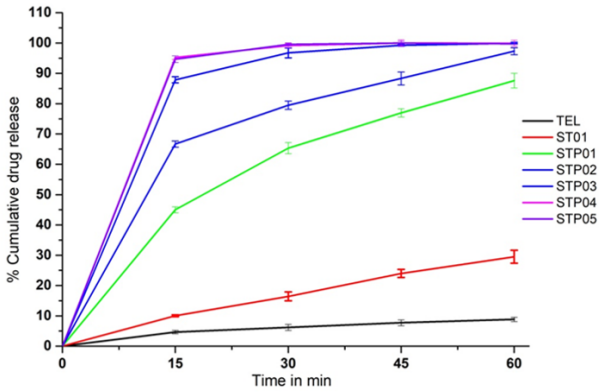

Figure 10: In vitro drug release profile of Pure Telmisartan and formulations (ST01, STP01-STP05) in pH 7.5 Phosphate buffer (mean ± SD, n=3)

enhancement. The size of the aggregates is found to be 115.64μm±8.05μm suggesting the aggregation of small crystals into uniform sized spherical crystal agglomerates.

In vitro dissolution studies

The *in vitro* dissolution studies were carried out in pH 7.5 Phosphate buffer as the Indian Pharmacopoeia, suggested it as the medium of dissolution for Telmisartan tablets. The pure drug exhibited 8.856±0.714 % at the end of 60 minutes (Figure 9). The formulation ST01 showed a slight improvement in the dissolution characteristics. But the formulations prepared using PVP K30 showed excellent improvement in drug release. The initial release in the first 30 minutes and also the total amount of drug released also increased with increase in PVP K30 concentration. The formulation STP04 showed 95.205±0.588% cumulative drug release in 15 min

and 99.175±0.658% CDR in 30 minutes, which was much higher than the official limits. It suggests that the drug is completely soluble in pH 7.5 phosphate buffer in 30 minutes. The formulation STP05 prepared by increasing the PVP K30 concentration (100mg) also showed a similar drug release, and there was no further improvement. Hence formulation STP04 having drug: polymer ratio of 1:0.375 can be considered as an optimized formulation.

The release studies were repeated in ultrapure water to ensure solubility enhancement. The pure drug has shown the highest %CDR of 3.96±1.25% in 60 min (Figure 10). The formulation ST01 prepared devoid of PVP K30 has shown a release of 22.36±1.23% in 60 min. The formulations prepared out of increasing concentrations of PVP K30 confirmed the augment in the release as that of pH 7.5 phosphate buffer. Formulation STP04 made a release of 73.56±1.25% in 15 min, 82.92±1.65% in 30min and 95.01±1.25% in 60 minutes. The *in vitro* dissolution studies confirmed that the formulation developed was capable of dissolving the drug in water as well as pH 7.5 Phosphate buffer.

Stability studies

The optimized formulation of Telmisartan crystal aggregates (STP04) was kept for accelerated stability study as per ICH guidelines at a temperature of 40^0C ± 2^0C and relative humidity of 75± 5% for a period of 180 days. The samples were analyzed at regular intervals. The physical characteristics were not altered during storage. The percentage of drug content was found to be 83.80±1.53. The *in-vitro* dissolution studies also showed a %CDR of 94.01±1.31 and 98.475±0.938 in water and pH 7.5 Phosphate buffer respectively at the end of 60 minutes. Hence, formulation STP04 was found to be retaining its properties and stability under accelerated conditions.

CONCLUSION

The crystal aggregates of Telmisartan prepared by polymer enriched bridging liquid using PVP K30 as hydrophilic polymer was capable of increasing the solubility and dissolution of poorly water-soluble Telmisartan. The system was capable of enhancing the solubility in water and pH 7.5 phosphate buffer. The micromeritic properties of the drug were highly improved and became ideal for the manufacture of formulations. The sphericity of the preparations contributed for enhancing the flow property. The decrease in crystallinity and the hydrophilicity of the polymer contributed for the enhancement of solubility. Hence formulation STP04 can be considered as the ideal candidate for formulation development. This technique (PEBL) is ideal for the incorporation of polymers into the matrix as well as on the surface.

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