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FABRICATION AND ASSESSMENT OF TELMISARTAN SOLD DISPERSION FOR SOLUBILITY ENCHANCEMENT BY THE INFLUENCE OF VARIABLE POLYMERS

Nazemoon Reddy[1*], Swarnalatha Dugasani[2], Devanna Nayakanti[3]

[1*]Research scholar, Jawaharlal Nehru Technological University Anantapur, Anantapuramu, Andhra Pradesh, India.
[2]Department of Pharmacognosy, Annamacharya College of Pharmacy, Rajampet, Kadapa, Andhra Pradesh. India.
[3]Director, Oil Technological and Pharmaceutical Research Institute, Jawaharlal Nehru Technological University Anantapur, Anantapuramu, Andhra Pradesh, India.

***Corresponding author: E-mail:** nazemoonr@gmail.com

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ABSTRACT

The authors aimed to design solid dispersion with Telmisartan (TSN) with PVP K-30, Poloxamer-188, and HPMC K4M as carriers. Various mixtures of TSN and polymers (PVP K-30 Polaxamer-188 and HPMC K4M) were made in 1:1,1:3, 1:5 and 1:7 ratios, and the solid dispersion was prepared by solvent evaporation method tactic, later compressed into tablets. Drug excipients compatability studies for examined by DSC and FTIR studies. TSN was found to compatable with carriers used. The TSN solid dispersion was measured for physicochemical quality both in solid dispersion SD, and tablet states. The TSN solid dispersion found to have excellent flow possession and compression assets. The yield of prepared solid dispersion was absorbed to be more than 90% and the formulation TPOX-7 has showed a good yield of 95.8 ±2.36 %, the tablets which were compressed for solid dispersion were found to have a uniform in size, shape, color, and consistency. The tablets were observed to have a uniform thickness, and weight and ranged 300.2± 1.36 to 303.0 ± 1.28 mg the loss on friability was less than 1% and the hardness was more than 4kg/cm² indicates significant mechanical strength and the TSN content was also found to be uniform (96.8± 1.35 to 99.9± 2.34). The solubility of TSN was found to be good in 0.1N HCL and diminished with an increase in PH of buffer. TSN released from the tablet were firstly by eruption followed by zero-order. The dissolution was found to be good in solid dispersion with TSN: Poloxamer-188 at the ratio of 1:5.The results obtained satisfactory. The study concludes that TSN solid dispersion (TPOX-7) with 1:5 ratios of TSN and Polaxamer-188 was found to be a better carrier than PVP K-30 and HPMC K4M in increasing the solubility of TSN from the solid dispersions.

INTRODUCTION

Hypertension is well endorsed as major risk factor for cardio vascular diseases even though there are evidence to assist the beneficial effects of antihypertensive therapy on mobility and mortality. A appropriate B.P management still remains suboptimal [1]. Temisartan (TSN) is prescribed for its calcium channels blocking activity and prescribed for hypertension. It is a BCS class-2 drug with t ½ of 8H and bioavailability of 10% [2]. TSN have no issue with membranes permeation but actual problem with its low aqueous solubility.[3] The researches do various trails in elevating the solubility of such drugs. Several methodologies adopted to uplift the drug

solubility [4,5] Amongst solid dispersion (SD) methodology situated on the top priority, for its ease, modest and resourceful scheme in amassing the solubility[6] Literature review revealed many attempts have been tried for making solid dispersion using the carriers used in the study, but no attempts have been made in combination of these carriers (PVP K30 polaxamer-188 and HPM K4M). So the scholars made an effort in apprising the TSN solubility by SD made by solvent evaporation method by using Polyvinyl pyrrolidone (PVP) K 30 , Poloxamer – 188 and Hydroxy propyl methyl cellulose(HPMC) K4M

MATERIALS AND MATERIALS

Methods

Telmisartan was gift sample from Cipla Ltd, Bengaluru. PVP K-30, Poloxamer 188, HPMCK4M were purchased from Amrutha organics, Hyderabad. Double distilled water was used when needed

TSN and the polymer mix were taken as per table 1, dissolved in dichloromethane (DCM) and stirred until the DCM evaporated totally. The obtained mass was shifted to Cal. Chloride containing desiccators till it dries.[7,8] The resulting solid dispersions was then crumpled in a mortar and allowed through # 60 sieve and stored in a dessicator tills.

2.3. Preparation of solid dispersion tablets

The SD corresponding to 20 mg of TSN were prepared after combination[9] with components compressed in the 8 station tablet compression machine (karnavati, India.)

2.4 Evaluations

2.4.1. Melting point

The crystalline chemicals and drugs are available as pure from and sharp melting points [10] .The preliminary evaluation is the determination of the TSN melting point using the melting point apparatus (MT-934, Mumbai).The melting temperature of the TSN was recorded three times.

2.4.2. Solubility studies

TSN pure drug was examined for solubility in 0.1N Hcl, Acetate buffer pH 4.5, Phosphate buffers pH 6.8 and pH 7.5 [11].

2.4.3. Drug- Excipient Compatibility Studies: The compatibility of TSN & the carriers used in making SD were tested by Differential Scanning Calorimetry (DSC) and Fourier Transform Infra-Red spectrophotometr

2.4.3.1. Differential Scanning Calorimetry (DSC): 1:1 ratio of pure TSN and the carriers were placed in DSC crucible and heated from till 500°C in DSC apparatus (Schimadzu DSC-50 Japan).

2.4.3.2. Fourier Transform Infra-Red (FTIR) spectroscopic study: The dealing among constituents of the SD were established using scanning in FTIR spectroscopy. The FTIR spectra of the TSN with combination were renowned by FTIR spectrometer (Bruker) by scanning at 400 to 4000 cm^{-1}.

2.5 Evaluations of TSN solid dispersions

2.5.1.Flow properties

The solid dispersion (SDs) were assessed for flow restraints viz., Angle of Repose, Densities, Compressibility Index, Hausner's ratio [12, 13]

2.5.2. Yield of prepared solid dispersions

The weight of dried SD to the total weight of ingredients used in making of SDs can be assessed by the formula given.[14]

$$\%Yield = \frac{\text{Actual weight of the product}}{\text{Total weight of drug and excipients}} X100$$

2.6. Depiction of tablets made with SD

The SD were compressed into tablets and were measured for the following propertiess

2.6.1. Uniformity in size and shape

The SD tablets were inspected under a dissection microscope (DM-100,Mumbai) for their size and shape[15].

2.6.2. Thickness: Tablets were evaluated for their thickness using digital vernier Calipers (Qumuos Enterprises , India) jaws and breadth was assessed 3 times.[16]

2.6.3. Uniformity of weight : 20 tablets from each batch were separately weighed with electronic digital balance (Citizen, CY-104) and the average was assessed and then checked for IP specifications[17]

2.6.4. Hardness

The tablets were pushed between the two extremes of Pfizer tablet hardness tester. The force of fracture was recorded and repeated thrice to get a mean.[18]

Scheming of solid dispersion: Telmisartan solid dispersions were exemplifies in table 1

Drug: Carrier	Drug: Carrier ratio	Formulation code
TSN: PVP K30	1:1	TPVP-5
	1:3	TPVP-6
	1:5	TPVP-7
	1:7	TPVP-8
TSN: Poloxamer 188	1:1	TPOX-5
	1:3	TPOX-6
	1:5	TPOX-7
	1:7	TPOX-8
TSN: HPMC K4M	1:1	THPM-5
	1:3	THPM-6
	1:5	THPM-7
	1:7	THPM-8

Table 2. Formulation of tablet containing solid dispersions (TSN)

Ingredients	Quantity per tablet (mg)
Solid dispersions equivalent to 40 mg of TSN	150
Lactose	75
Starch	15
MCC	50
Magnesium stearate	5
Talc	5
Weight of the tablets	300

2.6.5. Friability: Surface abrasion may emerge while tablets handling can be assessed by Roche Friabilator[19]. Initially weighed tablets (10) placed in the friabilator and allowed to fall from 6 inches at 100 rpm for 4 min, de-dusted and weighed. The % friability (F) was then assessed by formula given.[19]

$$F=\frac{W\text{initial}-W\text{final}}{W\text{initial}}X\ 100\ \ldots..(6)$$

% friability of tablets less than 1% is considered to be acceptable

2.6.6. Calibration Curve: Dissolve 100 mg of TSN in pH 1.2 of 0.1N HCl solution .Dilution (2, 4, 6, 8, 10, 12, 14 µg/mL) were prepared and scanned spectrophotometrically at λ_{max} 291 nm then the calibration curve was obtained form the data of concentration v/s absorbance.[20]

2.6.7. Uniformity of drug content was dissolved in methanol, diluted and the absorbance was measured at λmax 291 nm.[21]

2.6.8. *In-vitro* drug release studies: USP dissolution apparatus II containing 0.1M Hcl (900ml).stirred at 100rpm and retained at 37±0.5°C.The media was withdrawn at regular intervals for 1hr.filtered using Whatman filter paper and diluted to10ml with 0.1M HCl and analysed at 291nm by UV-Visible spectrophotometer was assessed by zero-order[22].first-order[23]. And Hixson crowell's models.[24]

2.7. Scanning Electron Microscopy: The surface topography of SD was confirmed by scanning the surface of SD by scanning electron microscopy [25] (Perkin Elmer, USA). An accelerating voltage of 20KV was used and the images obtained at the magnification of x500

3. RESULTS AND DISCUSSION

TSN melts at 262.2 ±0.5ºc designates the purity of the TSN (as it melts in between 261-263º c) the TSN presented good solubility in 0.IN HCL (0,313± 0.0.1 µg/mL) relatively in water, Acetate buffer (pH4.5), phosphate buffer (pH6.8) and phosphate buffer (pH 7.4) The solubility data for pure TSN was illustrated in figure 1.

Differential Scanning Calorimetry: The DSC thermograms of TSN with PVP K-30,

Poloxamer 188, HPMC K4M carriers were moved to the lesser temperature representing certain associating of TSN with carriers adopted (figure2). The **FTIR study** revealed that the distinctive peaks and stretches of TSN pure Drugs were also found in TSN carries designate no negative discordance of TSN with carries used. The FTIR spectra of TSN pure and carriers were shown in figure 3.

When the TSN-SD assessed for the angel of repose was found to be 25 to 27 º i.e., 25.08±0.02 to 27.27±0.03º which authorizes excellent flow possessions. On the other hand, the compressibility index was less than 10 (1.157 to 1.502) and hausner ratio less than 1.09 (1.011 to 0.15), Demonstrating good compression assets while tableting. The flow properties of TSN-SD where briefed in table 3.

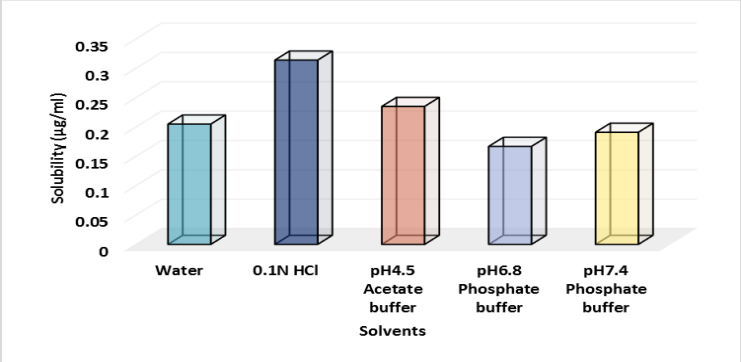


Fig1. The solubility of pure TSN in various solvents

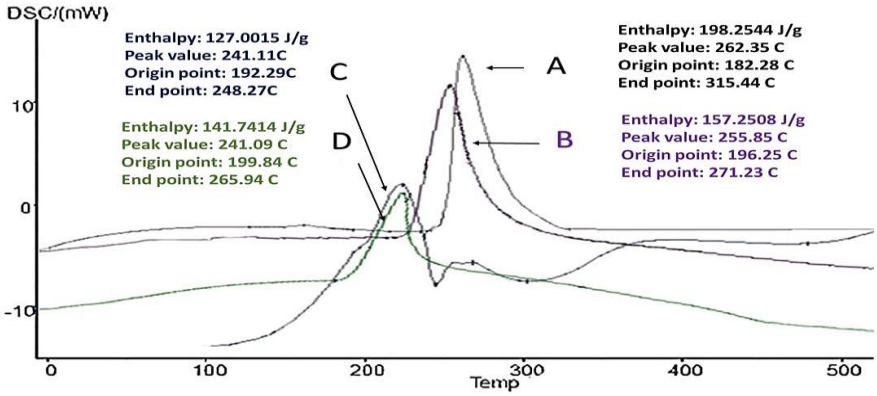


Fig 2. DSC thermograms of TSN (A) pure drug (B) PVPK 30 (C) Poloxamer 188 (D) HPMC K4M

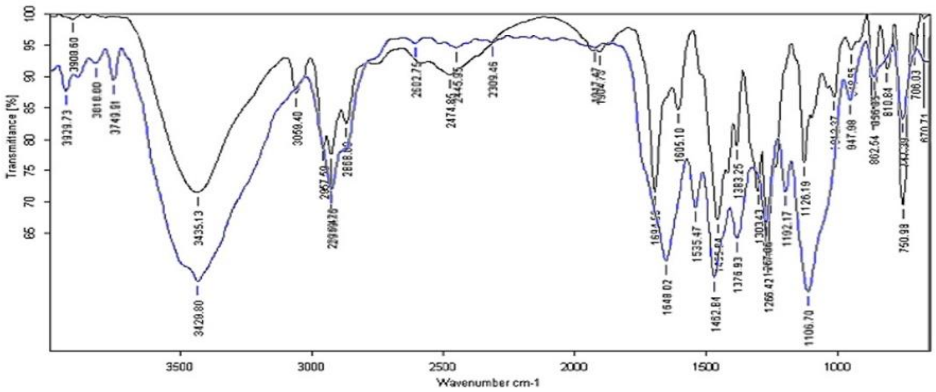


Fig 3. FTIR spectrum of Telmisartan with a polymer blend

Table 3 Flow character specifications of TSN-SD

Formulation	Flow properties				
	Angle of repose (^{0})	Bulk Density	Tapped Density	Carr's Index	Hausner Ratio
TPVP-5	25.25±0.04	0.485±0.01	0.491±0.03	1.221±0.02	1.012±0.02
TPVP-6	26.25±0.02	0.559±0.03	0.567±0.02	1.410±0.02	1.014±0.03
TPVP-7	27.22±0.02	0.425±0.02	0.431±0.01	1.392±0.03	1.014±0.01
TPVP-8	25.89±0.05	0.618±0.05	0.627±0.03	1.435±0.01	1.014±0.03
TPOX-5	25.45±0.03	0.625±0.02	0.634±0.02	1.419±0.01	1.014±0.02
TPOX-6	25.47±0.03	0.598±0.03	0.605±0.02	1.157±0.02	1.011±0.02
TPOX-7	26.21±0.01	0.625±0.01	0.633±0.05	1.263±0.02	1.012±0.01
TPOX-8	27.09±0.06	0.489±0.05	0.495±0.04	1.212±0.01	1.012±0.01
THPM-5	26.24±0.04	0.529±0.02	0.537±0.01	1.489±0.03	1.015±0.01
THPM-6	25.08±0.02	0.589±0.05	0.597±0.01	1.340±0.01	1.013±0.02
THPM-7	27.27±0.03	0.539±0.04	0.545±0.02	1.100±0.01	1.011±0.01
THPM-8	26.47±0.09	0.459±0.02	0.466±0.03	1.502±0.01	1.015±0.01
Values in mean ±SD; trials made (n=3)					

Table 4. Physical Characteristics for Tablets

Formulation	Physical parameter					
	Uniformity of weight (mg)	Hardness (cm^2)	Thickness (mm)	Friability (%)	Yield (%)	Assay (%)
TPVP-5	300.2±1.36	4.8±0.09	4.50±0.09	0.09±0.06	95.2±2.35	98.2±3.08
TPVP-6	302.5±2.65	5.6±0.06	4.50±0.08	0.18±0.02	96.4±3.61	95.3±0.94
TPVP-7	303.0±1.28	5.3±0.08	4.52±0.04	0.54±0.08	97.7±2.35	99.5±1.32
TPVP-8	300.7±2.37	5.9±0.08	4.51±0.02	0.29±0.07	95.4±4.25	99.8±2.39
TPOX-5	300.2±3.26	6.5±0.11	4.51±0.05	0.47±0.06	95.2±1.65	97.5±1.51
TPOX-6	300.4±4.27	7.8±0.24	4.50±0.01	0.39±0.05	96.8±2.25	97.8±1.64
TPOX-7	302.3±2.36	6.9±0.08	4.50±0.05	0.75±0.06	95.8±2.36	99.5±2.68
TPOX-8	303.2±2.36	7.5±0.04	4.50±0.03	0.56±0.02	98.7±1.26	98.7±0.67
THPM-5	302.2±1.28	5.8±0.04	4.51±0.02	0.84±0.05	97.2±4.15	99.9±3.26
THPM-6	300.9±3.58	5.9±0.04	4.51±0.02	0.74±0.04	98.2±2.84	97.4±1.25
THPM-7	300.7±3.25	6.7±0.11	4.50±0.02	0.49±0.02	97.2±1.85	98.4±0.63
THPM-8	301.8±1.37	6.8±0.25	4.51±0.05	0.51±0.03	96.7±2.25	98.7±2.36
Values in mean ±SD; trials made (n=3)						

When the TSN-SD assessed for the angel of repose was found to be 25 to 27 º i.e., 25.08±0.02 to 27.27±0.03º which authorizes excellent flow possessions. On the other hand, the compressibility index was less than 10 (1.157 to 1.502) and hausner ratio less than 1.09 (1.011 to 0.15), Demonstrating good compression assets while tableting. The flow properties of TSN-SD where briefed in table 3. The Yield of TSN-SD was observed to be good (≥90), and TPOX-7 has a good to yield 95.8±2.36%, The TSN-SD tablets were seeming to have a uniforms in size, shape, pale white colored, odorless with a smooth surface. The tablets were found to have a uniform in thickness, ranged from 4.50±0.01 to 4.52±0.04 mm, and weight and ranged from 300.2±1.36 to 303.0±1.28 mg. the loss on friability was between 0.18±0.02 to 0.84±0.02%, which is ≤ 1%, and the hardness was ranged from 5.8±0.02 to7.8±0.02 (≥4 kg/cm^2) representing that the tablets bearing significant mechanical strength and the TSN content was also found to be uniform (95.3±0.94 to 99.9±3.26). All these valuves were explained in table 4.

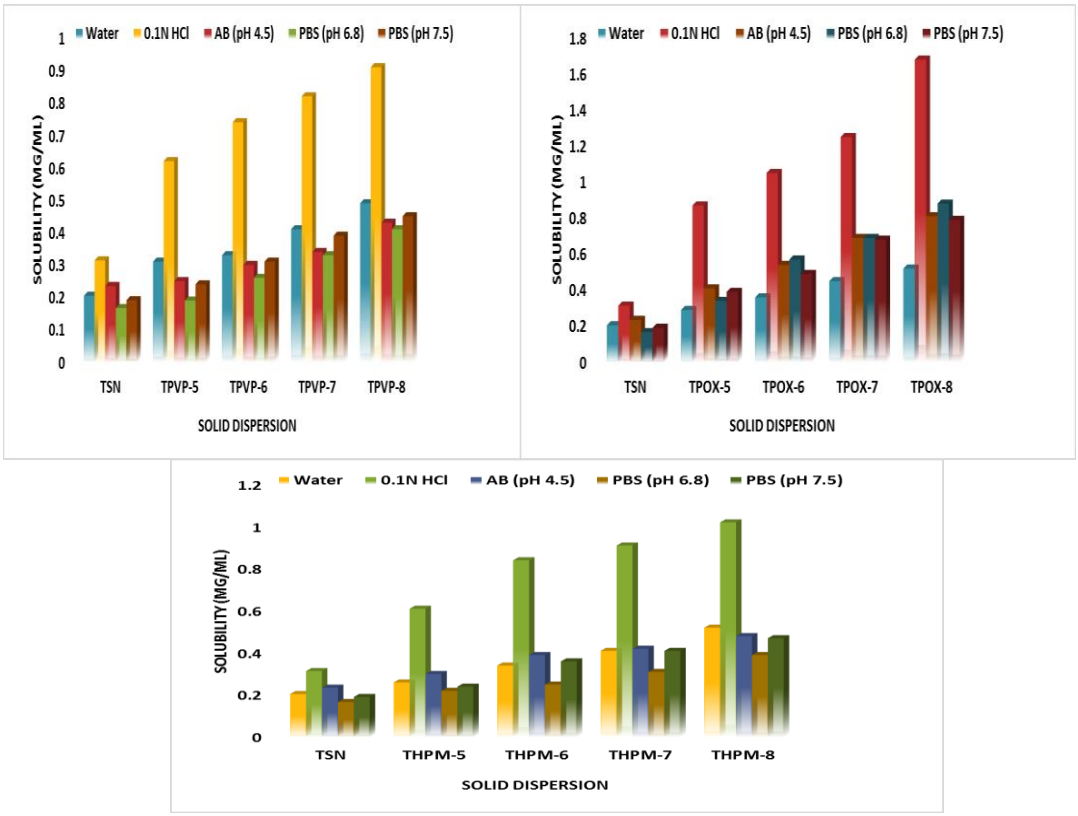
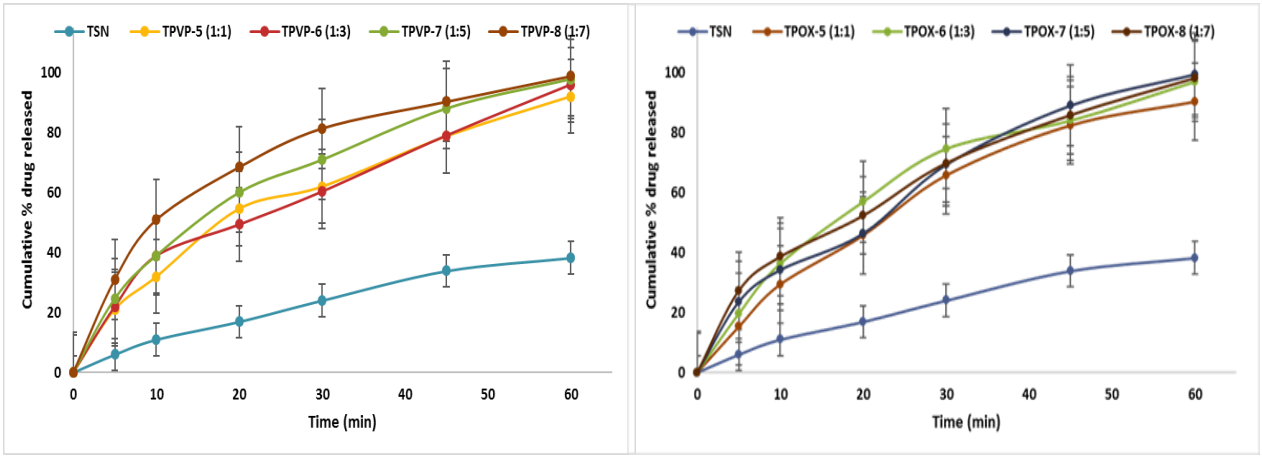


Fig 4.Solubility details of TSN SD'S prepared with (A) PVP K30 (B) Poloxamer-188 (C) HPMC K4M



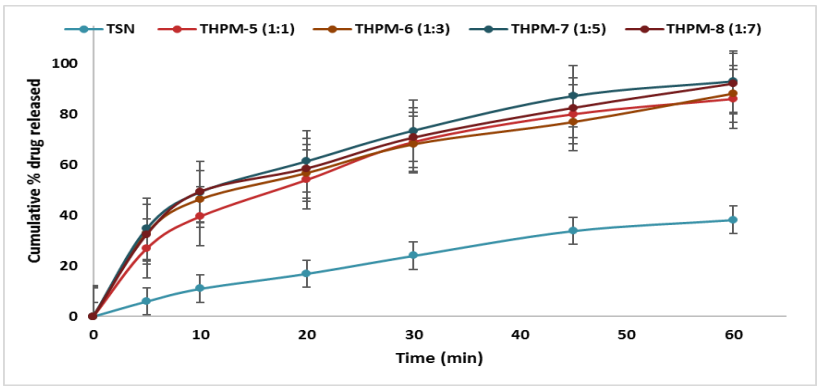


Fig5. In vitro dissolution profile of TSN with PVP K30, Poloxamer-188, HPMC K4M

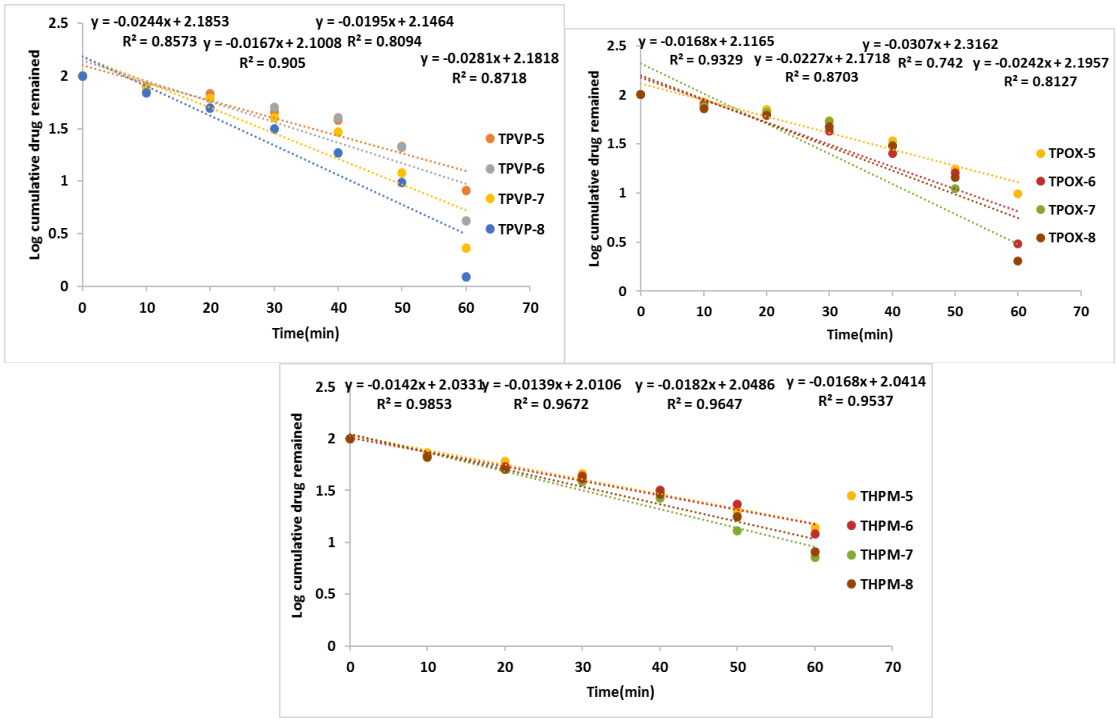


Fig 6.First-order release kinetics of TSN with PVP K30,Poloxamer-188,HPMCK4M

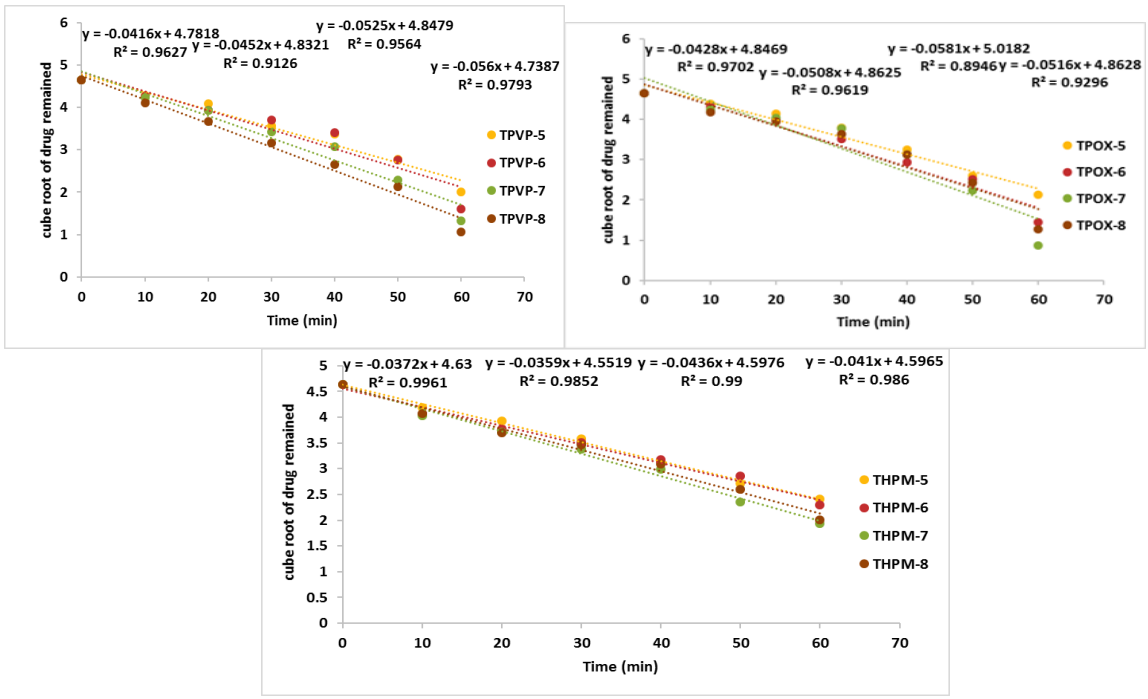


Fig7. Hixson Crowell's plots of TSN with PVP K30, Poloxamer-188, HPMC K4

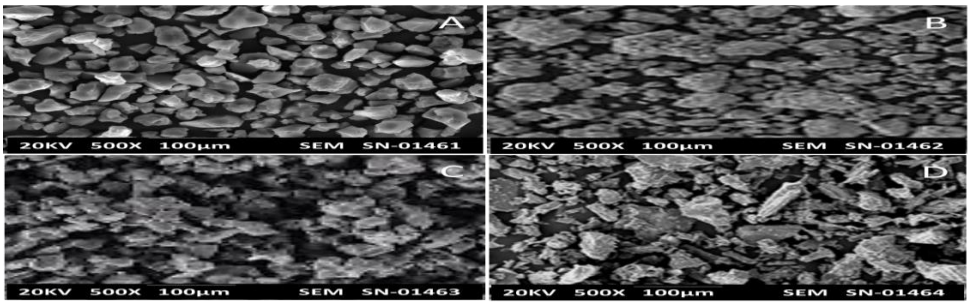


Fig 8: SEM analysis of TSN-SD with A) Pure Drug B) PVPK30 C) Poloxamer-188 D) HPMCK4

The solubility of TSN was found to be good in 0.1N HCL and diminished with an increase in PH of the buffer. Among them, TPOX- 7 signified good solubility in 0.1 N HCL. The entire description of solubility was embodied in figure 4. TSN followed Beers Lamberts law at 2 to 10µg/Ml. The regression (R^2 value detected to be 0.0923× + 0.0788. The TSN determined by plotting the calibration curve of the TSN. TSN released from the tablets were firstly by eruption less than 10 mints and the end of 1hr the TSN was released in zero order. The dissolution of prepared tablets was found good in SD with TSN: Poloxamer -188 at the ratio of 1:5 (figure 5), which followed zero order. The kinetic study reveal that the TSN – SD followed first order release kinetics and illustrated in figure 6 and 7.

The SEM analysis revealed that SD with PVP K30 and Poloxamer -188 produce an amorphous SD. In case of Poloxmer-188, which acts as a crystal inhibitor, this may be the reason for the enhancement of dissolution. The SEM analysis images were represented in figure 8.

SUMMARY

Compression assets of prepared SD. The yield of TNS-SD was found enhanced (up to 98.9± 1.95) compared to other approaches using PVP K-30[26] .The TNS – SD tablets were found to have uniformity in physicochemical constraint including the loss on friability was below I% with >4Kg/cm² hardness, the uniformity in TNS drug content. This rapid dissolution needed to assist in enhancing the release of TNS from the SD. [27] The prepared SD showed good TNS release within 10 mints, which might be due to the solubility enhancing stuff of Poloxamer-188 when combined with TNS. The release rate was significantly increased when the TNS: Poloxamer -188 ratio was at 1:5 similar observations were also reported by Shamsuddin at al. [29] The TNS release from all the SD followed first-order kinetics, as the plot observed in between log percentage drug remaining versus time was found to be linear with a coefficient of correlation (R^2=0.992). The correlation coefficient of correlation (r) values of the first order release model are found to be 0.9912-0.9964, which is slightly higher compared to the Hixson-Crowell`s cube root model. Hence, the release of drug from the SD followed mainly first-order kinetics compared to the Hixson – Crowell cube root law. The SEM analysis revealed that SD with PVPK30 andPoloxamer-188 produces an amorphous SD. This may be the reason for the enhancement of dissolution.

CONCLUSION

The study discovered that the solid dispersion prepared by Poloxamer– 188 were good carrier for elevating the solubility of Telmisaran by making solid dispersion the LPOX -7 formulation with 1:5 proportion of Telmisartan and Poloxamer -188 made by the solvent evaporation methodology were good in elevation of in vitro dissolution of Telmisartan and it followed first-order kinetics.

Author's contributions statement:

Nazemoon Reddy conceived the presented idea, developed the theory and performed the computations. Swarnalatha Dugasani and Devanna Nayakanti verified and corrected the manuscript. All authors discussed the results and contributed to the final manuscripts

Conflicts of interest: Conflicts of interest declared none.

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