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A Study of Nanosuspension for Poorly Soluble Telmisartan Drug

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ABSTRACT

Telmisartan is poorly water-soluble drugs belong to Biopharmaceutics Classification System (BCS) class II drug having very low solubility as well as low oral bioavailability. In this study, nanosuspension of Telmisartan was formulated using the antisolvent precipitation-ultrasonication method having different Solvent: Antisolvent Volume Ratio 1:8. Poloxamer 407 was used as Stabilizer in Telmisartan nanosuspension respectively. Plackett-Burman design was utilized to determine which factor has the biggest impact on the quality, stability, and effectiveness of the nanosuspension. Mean particle size and saturation solubility, was assessed using 3^2 complete factorial design and other metrics including cumulative percentage released (CPR) at two minutes, zeta potential, polydispersity index (PDI), and percent weighted drug content was also assessed. Formulations of Telmisartan nanosuspension batch TFD6 showed Mean Particle Size (nm) (Mean ± SD) (325.7 ± 6.6) and Saturation Solubility (µg/ml) (Mean ± SD (102.61 ± 1.34) respectively. Comparison was evaluated in-vitro dissolution of nanosuspension with marketed formulation and un-milled suspension.

Key Word: Nanosuspension, Telmisartan, antisolvent precipitation-Ultrasonication Method

1. Introduction

The problem is even more complicated for category II medicines, which are known to be poorly soluble in both aqueous and organic solvents. For such types of water-insoluble chemicals with high log P values, nanosuspension preparation is preferred [1]. A Nanosuspension is a colloidal dispersion of submicron-sized substance particles. Nanosuspensions are aqueous suspensions comprising one or more drug substances with submicron dimensions and the appropriate stabilizers. In this study, the term nanosizing refers to the reduction of disseminated drug

particles to the submicron range [2]. Preventing particle agglomeration or aggregation and crystal growth is the greatest challenge in nanosuspension technology. In nanosuspension technology, the drug is kept in the requisite crystalline state while the particle size is decreased, resulting in an increased dissolution rate and consequently enhanced bioavailability. Nanosuspensions can effectively formulate brick dust molecules for enhanced dissolution and absorption. In addition, Nanosuspensions have the following benefits: First, pharmaceuticals are no longer required to be soluble. secondly, a high drug loading can be achieved as a drug exists in the form of pure solids, which can significantly reduce the administration volume of a high dose; thirdly, nanosuspensions can increase the physical and chemical stability of drugs because they exist in the solid state; and finally, nanosuspensions can provide passive targeting and some more benefit as used for drugs with low water solubility, Improvement in biological performance as a result of the drug's high dissolution rate and saturation solubility, the potential for site-explicit conveyance through surface adjustment of nanosuspensions[3].

2. MATERIALS AND METHODS

Materials

Telmisartan were obtained as kind gift Sample from Alembic Research Centre, Vadodara. Poloxamer 188 and Poloxamer 407 were obtained as kind Gift Sample from Astron Research Centre, Ahmedabad. Polyvinyl alcohol was provided by Loba Chemie Pvt. Ltd., Mumbai. PVP K30 was provided by S. D. Fine Chemicals, Mumbai. Sodium Lauryl Sulphate was provided by Himedia Laboratories Pvt. Ltd., Mumbai. All the materials were used as an analytical grade.

Methods

a) Plackett-burman design (PB)

Plackett-burman design provided the interaction effects are nil or small, the Plackett-Burman design is effective for measuring main effects[4,5,6].

b) Optimization of other preliminary parameters

Telmisartan nanosuspension

Poloxamer 407 was used as a stabiliser to create telmisartan nanosuspension. Poloxamer 407 was chosen at three distinct dosages: 30, 40, and 50 mg. 50 mg of poloxamer 407 was chosen since it had the smallest mean particle size and highest saturation solubility.The antisolvent volume ratios of 1:4, 1:6, and 1:8 were used for solvent optimisation. the 1:8 solvent: antisolvent volume ratio was chosen because it had the shortest mean particle size and the

highest saturation solubility of the prepared nanosuspensions when tested using multiple evaluation parameters like mean particle size and saturation solubility.Once the drug particle precipitation had taken place in suspension, a probe sonicator was utilised to transform it into uniform nanosized particles. We chose to sonicate for periods of 10, 20, and 30 minutes. a sonication period of 30 minutes was chosen since it produced the smallest mean particle size and highest saturation solubility [7,8,9].

c) 3^2 factorial design

3^2 factorial design for TMNS

By changing Telmisartan concentrations and stirring rates, different formulations were created. Evaluation of the impact of both independent variables on the predetermined dependent variables, namely particle size and saturation solubility [7,10].

d) Evaluation of optimized batch

Evaluation parameter as well as Size of the particles and PDI, Zeta potential, Drug content, Saturation solubility and In-Vitro dissolution were performed [11].

Size of the particles and PDI

The generated nanosuspension's mean particle size and size distribution (polydispersity index) were measured using the Zetasizer (Zetatrac, Microtrac, Japan). The materials were properly diluted with water to an acceptable scattering intensity before the measurement and then re-dispersed by shaking. A nanosuspension's average particle size ranges from 200 to 1000 nm [13,14].

Zeta potential

Using the Zetasizer [Zetatrac, Microtrac, Japan] to measure the electrophoretic mobility of the particles, the Zeta Potential was evaluated in this work [15].

Drug content

The produced nanosuspension was divided into an aliquot (1 ml) and diluted with methanol before being filtered through a 0.2 m filter. A UV spectrophotometer was used to calculate the total drug content at the drug's maximum concentration [16].

Saturation solubility

Optioned nanosuspension's was placing in a vial and keeping it for 48 hours while stirring with a magnetic stirrer running at 100 RPM to assure saturation. An eppendorf tube containing 2 ml of nanosuspension was then filled, and it was centrifuged for 30 minutes at 10,000 RPM. After an

appropriate dilution with dissolution media that served as a blank, the supernatant was filtered through a 0.2 m syringe filter and subjected to UV-visible spectrophotometer analysis at the drug's maximum concentration (UV-1800, Shimadzu, Japan) [12,13].

In-Vitro dissolution

USP 24 paddle tool was used for an in-vitro dissolving research (ELECTROLAB TDT-06P). According to Dissolution was carried out at 37 °C with the paddle speed specified. The dissolving vessels received nanosuspension that was equal to a dose of the medication. 5 ml samples were taken at intervals of 2, 4, 6, 8, 10, 15, 30, 45, and 60 minutes, and they were promptly filtered through a 0.2 m syringe filter before being spectrophotometrically examined. 5 ml of brand-new medium was then added to the dissolving vessel [1,17].

Table 1. Dissolution conditions for nanosuspensions

Dissolution Condition	**Telmisartan Nanosuspension**
Dissolution media	Phosphate buffer pH 7.5
Volume of Dissolution media	900
Speed in RPM	75
Sampling Intervals	2, 4, 6, 8, 10, 15,30, 45, 60 mins
Dose of drug	40mg

e) Lyophilization of optimal batch nanosuspension

Mannitol (1:1, total solid: cryoprotectant) was used as a cryoprotectant to turn the nanosuspension into a dry powder using a lyophilizer. Samples were retained in the compartment for the lyophilization process with the temperature held at -80°C for 8 hours. After being transformed into dry powder over a period of 6 to 8 hours, the nanosuspension was taken out of the chamber and put in an airtight container for further use [11, 18].

f) Accelerated stability Study

According to ICH recommendations, accelerated stability investigations of lyophilized nanosuspension were carried out at 25+2°C and 60+5% RH for 6 months. Nanosuspension that had been lyophilized was enclosed in firm gelatin capsules. The samples were taken out and examined for particle size, saturation solubility, percent CPR at 2 minutes, and percent weight-to-weight of drug content at regular intervals (0, 1, 3, and 6 months) [19,20,21].

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3. RESULT AND DISCUSION

a) Plackett-burman design (PB)

The Plackett-Burman design is useful for measuring main effects as long as the interaction effects are zero or insignificant. The fact that the chosen response parameters varied widely. suggests that the independent factors had a considerable impact on them.

Table 2 - Layout and observed responses of Plackett - Burman design batches for TMNS (Preliminary screening formulations)

Batch Code	Amount of Telmisartan (mg) X1	Amount of Poloxamer 407 (mg) X2	Solvent: Antisolvent Volume Ratio X3	Stirring Speed (RPM) X4	Sonication Time (Min) X5	Saturation Solubility (µg/ml) (Mean ± SD)* Y1	Mean Particle Size (nm) (Mean ± SD)* Y2
TF1	20	50	1:8	800	30	70.22 ± 2.15	373.5 ± 9.9
TF2	10	50	1:8	1200	10	84.51 ± 1.96	130.3 ± 6.2
TF3	10	30	1:8	1200	30	78.18 ± 2.06	215.4 ± 6.9
TF4	20	30	1:5	1200	30	87.49 ± 1.15	112.7 ± 5.4
TF5	10	50	1:5	800	30	86.28 ± 0.98	123.7 ± 5.6
TF6	20	30	1:8	800	10	86.86 ± 1.84	124.9 ± 4.3
TF7	20	50	1:5	1200	10	84.27 ± 2.52	132.3 ± 4.7
TF8	10	30	1:5	800	10	60.68 ± 1.22	389.1 ± 7.2

* Indicates average of three determinations

Fig 1 and Fig 2 showed that stirring speed and the amount of Telmisartan had the greatest impact on mean particle size and saturation solubility.

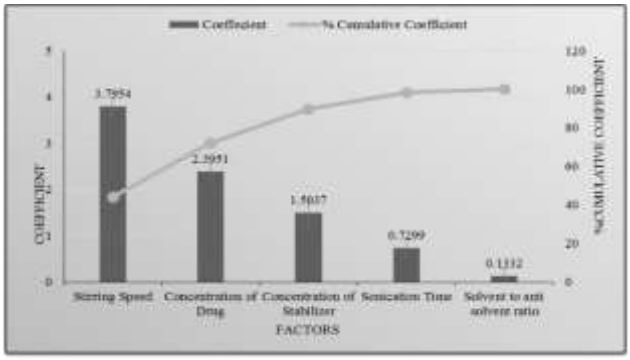

Fig 1. Pareto chart of the effect of independent variables on saturation the solubility of TMNS

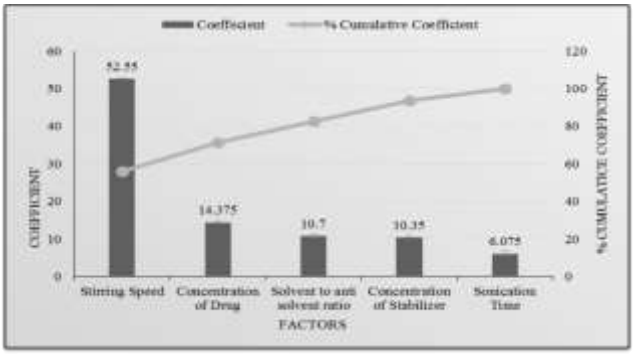

Fig 2. Pareto chart of the effect of independent variables on mean particle size of TMNS

b) Optimization of other preliminary parameters

Table 3 - Results of optimization of other preliminary parameters for TMNS

Batch Code	Preliminary Parameters		Mean Particle Size (nm) (Mean ± SD)*	Saturation Solubility (µg/ml) (Mean ± SD)*
TF9	Amount of Poloxamer 407 (mg)	30	304.3 ± 5.4	64.35 ± 1.14
TF10		40	228.1 ± 9.4	77.21 ± 1.54
TF11		**50**	**152.5 ± 7.6**	**82.18 ± 1.30**
TF12	Solvent to Antisolvent Volume Ratio	1:4	311.9 ± 4.0	79.72 ± 1.21
TF13		1:6	289.7 ± 8.7	77.26 ± 1.32
TF14		**1:8**	**254.4 ± 11.4**	**91.37 ± 1.54**
TF15	Sonication Time (min)	10	365.6 ± 9.2	62.28 ± 1.07
TF16		20	222.5 ± 6.9	69.24 ± 1.24
TF17		**30**	**180.4 ± 5.8**	**83.33 ± 1.37**

* Indicates average of three determinations

c) 3^2 factorial design

3^2 Factorial design for TMNS

By changing Telmisartan concentrations and stirring rates, different formulations were created. An evaluation of the impact of both independent variables on the predetermined dependent variables, namely particle size and saturation solubility, was conducted using a 3^2 complete factorial design, as shown in Table 4.

Table 4 - Layout and observed responses of 3^2 factorial design for TMNS

Batch Code	Level of Amount of Telmisartan X1	Level of Stirring Speed X2	Mean Particle Size (nm) (Mean ± SD)* Y1	Saturation Solubility (µg/ml) (Mean ± SD)* Y2
TFD1	-1	-1	465.2 ± 8.8	63.16 ± 0.99
TFD2	-1	0	384.1 ± 4.9	71.41 ± 0.86
TFD3	-1	1	365.6 ± 8.2	84.92 ± 1.06

TFD4	0	-1	429.9 ± 7.3	83.52 ± 1.13
TFD5	0	0	344.1 ± 6.8	86.58 ± 1.09
TFD6	**0**	**1**	**325.7 ± 6.6**	**102.61 ± 1.34**
TFD7	1	-1	405.3 ± 5.9	74.28 ± 0.98
TFD8	1	0	334.2 ± 8.1	83.32 ± 1.22
TFD9	1	1	314.5 ± 9.2	93.04 ± 1.17
Translation of Coded Levels in Actual Units				
Variables Level		**Low (-1)**	**Medium (0)**	**High (1)**
X1		10 mg	15 mg	20 mg
X2		800 RPM	1000 RPM	1200 RPM

* Indicates average of three determinations

Table 5 - Other evaluation parameters of factorial batches of TMNS

Batch Code	CPR at 2mins (% w/w) (Mean ± SD)*	PDI (Mean ± SD)*	Zeta Potential (mV) (Mean ± SD)*	Drug Content (%w/w) (Mean ± SD)*
TFD1	92.18±1.85	0.528± 0.040	17.37±1.83	95.21±1.03
TFD2	101.25±2.26	0.921± 0.113	-28.11 ±2.07	97.51±1.12
TFD3	88.63±1.57	0.788± 0.083	-15.32 ±1.49	100.96±1.85
TFD4	97.93±1.92	0.967± 0.102	-18.09±1.09	99.83±0.55
TFD5	93.34±1.43	0.846± 0.063	27.77±2.16	96.10±0.20
TFD6	**98.26±1.39**	**0.461± 0.039**	**-29.97 ±1.88**	**99.57±0.82**
TFD7	96.27±2.06	0.421± 0.052	-18.21 ±1.56	94.11±0.74
TFD8	93.58±1.00	0.715± 0.069	-19.03 ±1.62	92.13±0.59
TFD9	91.23±1.10	0.644± 0.044	19.26±1.73	93.27±0.69

* Indicates average of three determinations

Table 6 - Formulation and process parameters for an optimized batch of TMNS

Amount of Telmisartan	15 mg
Amount of Poloxamer 407	50 mg
Solvent: Antisolvent Volume Ratio	1:8
Stirring Speed	1200 RPM
Stirring Time	4 h
Sonication Time	30 mins
Amount of lyophilizer (1:1, Total Solid: Mannitol)	65 mg

Particle size and PDI

Particle size and PDI of TMNS

Fig 3 displays the improved batch's particle size distribution. The optimized batch's mean particle size is 328.10±9.8 nm and its PDI value was 0.475.

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Zeta potential

Zeta potential of TMNS

The improved formulation's zeta potential, which met the zeta potential criteria, was observed to be -30.37±2.53mV

Drug content

Drug content of TMNS

By using a UV-Visible spectrophotometer at 296 nm to measure the total drug content, it was discovered to contain 99.56% by weight of Telmisartan.

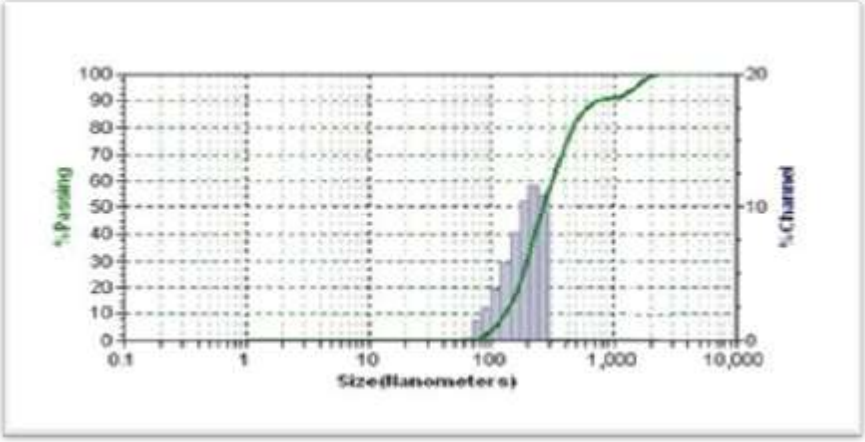

Fig 3. Particle size graph for TMNS

Saturation solubility

Saturation solubility TMNS

Telmisartan nanosuspension from an improved batch and pure drug had a saturation solubility of 100.18 µg/ml and 3.53 µg/ml**,** respectively.

In-Vitro dissolution

In-Vitro dissolution of TMNS

Fig 4 shows the dissolving profiles for nanosuspension, unmilled (pure drug) suspension, and the commercial formulation (Inditel 40 Tablet). Whereas the cumulative percentage of drug release from un-milled suspension and commercially prepared suspension revealed 16.42% and 77.09% at 60 minutes, respectively, in nanosuspension, more than 102.61% of the medication was released within 2 minutes.

Accelerated stability study

According to the results of the accelerated stability investigation, lyophilized telmisartan nanosuspension was both physically and chemically stable when kept at 25±2°C and 60±5% RH for six months. Results of mean particle size, saturation solubility, cumulative percentage release at 2 minutes, and percent weight of drug content are shown in Table 7. All of these metrics showed a small shift with a bias of less than 5%, which was not significant. Results from the optimised batch before and after the stability investigation, as per ICH guidelines, showed a minor difference.

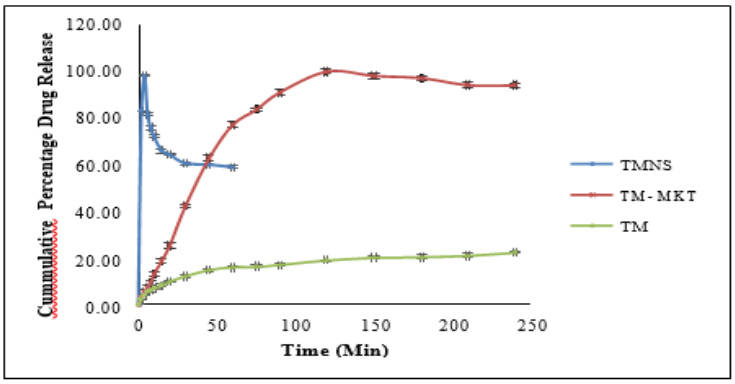

Fig 4. Comparison of in-vitro dissolution of telmisartan nanosuspension with marketed formulation and un-milled suspension.

Table 7 - Results of accelerated stability study of TMNS

Sr. No.	Storage condition for stability study	Time Period (months)	Evaluation Parameters			
			Mean Particle Size (nm) (Mean ± SD)*	Saturation Solubility (µg/ml) (Mean ± SD)*	CPR at 2mins (%w/w) (Mean ± SD)*	Drug Content (%w/w) (Mean ± SD)*
1	25°C ± 2°C and 60% ± 5% RH	0	328.1 ± 5.5	100.17 ± 2.2	98.26 ± 0.86	99.54 ± 0.54
2		1	339.3 ± 4.9	99.29 ± 1.81	97.98 ± 0.80	98.85 ± 0.53
3		3	356.4 ± 8.3	98.74 ± 1.66	97.12 ± 0.88	97.67 ± 0.48
4		6	385.5 ± 9.9	98.18 ± 1.72	96.54 ± 0.47	96.98 ± 0.90

*Indicates average of three determinations

4. CONCLUSION

Telmisartan Nanosuspension were developed by using antisolvent precipitation-ultrasonication method with help of Plackett-Burman design and 3^2 complete factorial design. Nanosuspension

was evaluated by different parameters as well as Mean Particle Size, polydispersity index (PDI), Zeta Potential, Drug Content, Saturation Solubility, CPR at 2 mins. In-vitro dissolution was performed for prepared Telmisartan nanosuspension and Comparison were performed with marketed formulation and un-milled suspension.

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