Application of Plackett–Burman Screening Design for Formulation of Telmisartan Nanosuspension

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KEYWORDS

Telmisartan, Nanoprecipitation-Ultrasonication, Plackett–Burman Screening Design, Processing Parameters, Formulation Parameters.

ABSTRACT

Developing formulations for medications with low water solubility and low oral bioavailability presents significant challenges. Poor water solubility and a slow rate of dissolution are issues for the majority of newly developed and well-established biologically active compounds. Telmisartan (TM) is a BCS class-II medication characterized by low solubility as well as high permeability. The current study set out to determine crucial formulation and processing characteristics that could affect the nanosuspension's quality. Using the nanoprecipitation-ultrasonication process, a poorly soluble medication was converted into a nanosuspension formulation. In order to screen five independent factors—the amount of stabilizer (mg) (X2), the amount of Telmisartan (mg) (X1), the volume ratio of solvent to anti-solvent (X3), the speed of stirring (RPM) (X4), and the sonication time (min) (X5)—a total of eight experiments were created. The dependent factors used were saturation solubility (µg/ml) and mean particle size (nm). The acquired results demonstrated that, in comparison to all other stabilizers, the nanosuspension made with Poloxamer 407 has improved saturation solubility. The amount of telmisartan and the speed at which the mixture is stirred were also discovered to be potentia l formulation and processing parameters that exert considerable influence on the quality of the telmisartan nanosuspension.

1. INTRODUCTION

Formulating drugs that are poorly water soluble has always been a difficult task in the pharmaceutical industry and is a significant barrier to the creation of novel dosage forms. The solubility of 10% of currently available pharmaceuticals is approximately 1–10 µg/ml, whereas 40% of investigational drugs and 60% of synthetically generated compounds have similar solubility levels. (Keck and Muller, 2006; Kesisoglou F and Mitra, 2012; Verma et al., 2011). Drug solubility must be increased in order for the medication to be administered orally, pass through the GI tract, and reach the target tissue to have a pharmacological effect (Junghanns and Müller, 2008). Because cell membranes are phospholipidic, certain therapeutic compounds need a certain level of lipophilicity, although high lipophilicity is beneficial for permeability. It results in low aqueous solubility in the majority of cases (Kesisoglou et al., 2007). This leads to issues with delivery, including irregular absorption and limited oral bioavailability. Traditional methods like salt creation, complexation, co-solvents, micronization, or distribution through carriers like liposomes, solid-dispersions, etc. can all be used to increase drug solubility (Che et al., 2012). They frequently are unable to resolve the issue connected to bioavailability, nevertheless. For many years, micronizing poorly soluble medications has been utilized to boost their dissolving rate. However, at the low saturation solubility generally observed in BCS class II medications, the reduction of the drug to a micron size does not increase its solubility, and the strengthening of the dissolving properties does not provide considerable assistance. Consequently, nanonization has been used to treat BCS class II drugs.

Based on the Ostwald–Freundlich and Noyes–Whitney equations, a reduction in drug particle size to the nanoscale results in improved dissolving properties and an increase in saturation solubility. This could be attributable to the effective increase in particle surface area. The Ostwald-Freundlich equation directly explains the relationship between medication saturation solubility and particle size;

$$Log\frac{Cs}{C\alpha} = \frac{2\sigma V}{2.303RT\rho r}$$

Where, σ = Interfacial tension of substance,
C_S = Saturation solubility,
C_α = Solubility of the solid consisting of large particles,
R = Gas constant,
V = Molar volume of the particle material,
ρ = Density of the solid,
T = Absolute temperature,
r = Radius.

It is clear that when particle size (r) decreases, the saturation solubility of drug (CS) rises. However, this effect is more pronounced for materials whose mean particle size is less than 2 μm (Gao et al., 2008). The equation of Ostwald-Freundlich describes the connection between a compound-specific metric called saturation solubility (Cs) and particle size that depends only on solvent temperature. As a result, as particle size decreases, the drug's Cs increases significantly (Kesisoglou F and Mitra, 2012; Gao et. al., 2008). Due to its many uses, given their incredibly tiny particle size, nanosuspensions have emerged as a promising technique for the successful administration of hydrophobic drugs (Patil & Pandit, 2007).

Angiotensin II Receptor Antagonists is the category under which telmisartan falls. It is a slightly yellowish or white crystalline powder having a melting range of 261-263°C. It is soluble in strong bases, weakly soluble in methyl alcohol, sparingly soluble in strong acids (apart from HCl), and almost insoluble in water. It is considered under BCS Class II medication because of its high permeability and limited solubility. After 40 mg, the absolute oral bioavailability is dosage dependant, varying by approximately 42%. The gastrointestinal system absorbs telmisartan quickly; the drug reaches its maximal plasma concentration between 0.5 and 1 hour after an oral dosage. The only one metabolite found in human urine and plasma is the glucuronide of the parent molecule, which is formed during the conjugation process of telmisartan to produce the pharmacologically inactive acyl-glucuronide. It is almost totally eliminated by bile, mostly as an unaltered medication. More than 99% of telmisartan is tendency to show plasma proteins binding. According to O'Neill et al. (2006), Sweetman (2009), telmisartan has an elimination half-life of approximately 24 hours (Stangier et al. 2000a and Stangier et al. 2000b).

Compounds with very poor water solubility are often thought to exhibit dissolution rate-limited absorption. In this situation, increasing water solubility is a worthwhile objective to raise therapeutic efficacy. The drug's surface area and solubility both affect how quickly it dissolves. As a result, increasing the drug's solubility will raise the dissolution rate, which will likewise increase as the drug's surface area increases (Hassan et al., 1990; Rania and Mohammed, 2008).

The objective of this study is to create Telmisartan nanosuspension using the nanoprecipitation followed by ultrasonication technique and to pinpoint crucial processing as well as formulation parameters that affect the product's quality.

2. MATERIALS AND METHODS

2.1 Materials

A gratis sample of telmisartan was received from the Alembic Research Centre in Vadodara, Gujarat, India. Astron Research Centre, Ahmedabad, sent gift samples of Poloxamer 188 and Poloxamer 407. The supplier of polyvinyl alcohol was Mumbai-based Loba Chemie Pvt. Ltd. For the study, S. D. Fine Chemicals in Mumbai provided Polyvinyl Pyrrolidone K-30, while Hi-media Laboratories Pvt. Ltd. in Mumbai provided Sodium Lauryl Sulphate. Double-distilled water was used throughout the investigation, and all other and solvents and chemicals employed were of analytical quality.

2.2 Selection of solvent and anti-solvent

It was investigated how soluble Telmisartan was in various solvents. In a specific gravity bottle, 10 ml of solvent was mixed with about 50 mg of the medication. This was sufficient to produce a saturated solution. These specific gravity bottles were shaken at 100 RPM for 24 hours at 25ºC in a cryo-static reciprocating shaker bath with a constant temperature. After that, the vials were opened, and solutions were filtered using Whatman filter paper. The absorbance of the solution was measured at 296 nm (λmax). This process was carried out three times. Based on the drug's solubility, excellent and inferior solvents were chosen (Shivakumar et al., 1999).

2.3 Preparation of Telmisartan nanosuspension (Xia et al., 2010)

Utilizing the nanoprecipitation–ultrasonication technique, telmisartan nanosuspension was created. At room temperature, tetamisartan was dissolved in methanol using sonication for five minutes. To create a range of anti-solvents, several stabilizers were dissolved in water. A 0.45μm filter was run through both solutions. The anti-solvent was cooled in an ice bath to less than 3°C. The drug solution was then quickly added to 40 ml of pre-cooled anti-solvent at varied rates using an overhead stirrer. This enabled the volatile solvent to evaporate at room temperature for five hours. The syringe was positioned with the needle straight into the stabilizer solution. Following the anti-solvent precipitation, the sample was promptly moved to a test tube and subjected to several ultrasonic probe treatments for varying durations (measured in minutes). When the liquid was

submerged, the 6 mm-diameter tip of the probe traveled downhill and reflected upward. 40 ml was the batch size used to prepare the nanosuspension.

2.4 Selection of stabilizer

Through the preparation of nanosuspensions (Table 1), various stabilizers, including Sodium Lauryl Sulphate, Polyvinyl Alcohol, PVP K-30, Poloxamer 407 as well as Poloxamer 188, were screened. Their saturation solubility, mean particle size, polydispersity index (PDI), and zeta potential were evaluated (Pandya et al., 2010).

Table 1: Formulating and processing parameters for selection of stabilizer for TMNS

Batch Code	Stabilizers	Amount of Stabilizers (mg)	Amount of Telmisartan (mg)	Stirring Speed (RPM)	Stirring Time (h)	Sonication Time (min)	Solvent: Antisolvent Volume Ratio
TF1	PVP K30	30	10	800	4	20	1:8
TF2	Polyvinyl Alcohol	30					
TF3	Sodium Lauryl Sulphate	4					
TF4	Poloxamer 407	30					
TF5	Poloxamer 188	30					

2.5 Plackett-Burman Design

The Plackett-Burman design is typically employed in the first stages of research because it is a good strategy for screening a large number of variables suspected to be impacting major product features or quality. A fractional factorial design called the Plackett-Burman design works well for calculating and assessing the impact of processing variables (Gacula, 1993; Paun, J.S., 2016).

Five parameters were chosen through a review of the literature to influence the formulation of Telmisartan nanosuspension. This design was used to identify the element that most affects the nanosuspension's quality, stability, and efficacy. To screen for five independent parameters, eight experiments were created: X_1 stands for amount of telmisartan in milligrams; X_2 for amount of poloxamer 407 in milligrams; X_3 for volume ratio of solvent: anti-solvent; X_4 for speed of stirring in revolutions per minute; and X_5 for time of sonication in minutes (Paun, J.S., 2016). The dependent factors chosen were the mean particle size in nm and the saturation solubility in µg/ml. Table 2 below displays the coded and uncoded values for the various independent components.

Table 2: Layout and observed responses of Plackett - Burman design batches

Batch Code	Amount of Telmisartan (mg) X_1	Amount of Poloxamer 407 (mg) X_2	Solvent: Antisolvent Volume Ratio X_3	Stirring Speed (RPM) X_4	Sonication Time (Min) X_5	Saturation Solubility (µg/ml) (Mean ± SD)* Y_1	Mean Particle Size (nm) (Mean ± SD)* Y_2
TF6	20 (+)	50 (+)	1:8 (+)	800 (-)	30 (+)	70.21 ± 2.14	373.3 ± 9.8
TF7	10 (-)	50 (+)	1:8 (+)	1200 (+)	10 (-)	84.50 ± 1.98	130.1 ± 6.4
TF8	10 (-)	30 (-)	1:8 (+)	1200 (+)	30 (+)	78.19 ± 2.05	215.5 ± 6.8
TF9	20 (+)	30 (-)	1:5 (-)	1200 (+)	30 (+)	87.48 ± 1.14	112.8 ± 5.1
TF10	10 (-)	50 (+)	1:5 (-)	800 (-)	30 (+)	86.29 ± 0.97	123.8 ± 5.7
TF11	20 (+)	30 (-)	1:8 (+)	800 (-)	10 (-)	86.88 ± 1.85	125.0 ± 4.2
TF12	20 (+)	50 (+)	1:5 (-)	1200 (+)	10 (-)	84.26 ± 2.51	132.5 ± 4.5
TF13	10 (-)	30 (-)	1:5 (-)	800 (-)	10 (-)	60.69 ± 1.21	389.2 ± 7.1

* Indicates average of three determinations

Mean particle size and a saturation solubility study were used as evaluation criteria for the aforementioned batches of nanosuspensions. The following formulae were used to compute the net effect of each individual element based on the saturation solubility value and the mean particle size value:

Effect of $X_1 = [(Y_1+Y_4+Y_6+Y_7)-(Y_2+Y_3+Y_5+Y_8)]/8$

Effect of $X_2 = [(Y_1+Y_2+Y_5+Y_7)-(Y_3+Y_4+Y_6+Y_8)]/8$

Effect of $X_3 = [(Y_1+Y_2+Y_3+Y_6)-(Y_4+Y_5+Y_7+Y_8)]/8$

Effect of $X_4 = [(Y_2+Y_3+Y_4+Y_7)-(Y_1+Y_5+Y_6+Y_8)]/8$

Effect of $X_5 = [(Y_1+Y_3+Y_4+Y_5)-(Y_2+Y_6+Y_7+Y_8)]/8$ (Paun, J. S. (2016)

Two crucial parameters were found to have the most impact on the features of the product after the net effect of the various parameters was calculated. These two factors can be chosen for product optimization using an appropriate experiment design.

2.6 Evaluation of Nanosuspensions

2.6.1 Saturation solubility

The prepared nanosuspension's saturation solubility was tested by filling a vial with the suspension and shaking it for 48 hours at 100 RPM with the aid of a magnetic stirrer. After that, an Eppendorf tube containing 2 ml of the nanosuspension was subjected to centrifugation for 30 minutes with 10,000 rpm. Before being subjected to an analysis at 296 nm using a UV-visible spectrophotometer [UV-1800, Shimadzu, Japan] the supernatant was diluted appropriately with Phosphate Buffer having pH 7.5, which was employed as a blank, and then filtered through a 0.2µm syringe filter. Every sample was examined three times. Saturation solubility was computed using the calibration curve (Muller et al., 2001).

2.6.2 Particle size and PDI

Using Zetasizer [Zetatrac, Microtrac, Japan], which employs the principle of light diffraction the size distribution (polydispersity index) and mean particle size of the produced nanosuspension were ascertained. Before measuring, the samples were shaken to re-disperse them and suitably diluted with water to achieve the desired scattering intensity (Shinde and Hosmani, 2014).

2.6.3 Zeta potential

The particle surface electric charge is measured by the Zeta potential, which shows the physical stability of colloidal systems. Aqueous dispersions exhibit long-term electrostatic stability when their zeta potential values are greater than |30mV|. In order to calculate the Zeta Potential, the electrophoretic mobility of the particles was assessed in this work using Zetasizer [Zetatrac, Microtrac, Japan]. (Shinde and Hosmani, 2014).

3. RESULT AND DISCUSSION

3.1 Selection of solvent and anti-solvent

The selection of solvent and anti-solvent was based on telmisartan's solubility in a variety of solvents and their combinations.

Table 3: Results of selection of solvents for TMNS

Drug	Solvents	Solubility (mg/ml) (Mean ± SD)*
Telmisartan	Methanol	3.329 ± 0.23
	N-Butanol	1.975 ± 0.18
	Alcohol: Butanol (1:1)	1.235 ± 0.095
	Alcohol	0.877 ± 0.052
	Alcohol:2-Propanol (1:1)	0.609 ± 0.033
	Ethyl Acetate	0.562 ± 0.046
	Iso-propanol	0.094 ± 0.0021
	Water	0.012 ± 0.0041

*Indicates average of three determinations

Based on its lowest solubility (0.012 ± 0.0041 mg/ml) in water and its maximum solubility (3.329 ± 0.230 mg/ml) in methanol, the medication was selected as an anti-solvent and a solvent, respectively.

3.1 Selection of stabilizer

A variety of stabilizers, including Poloxamer 188, Poloxamer 407, Sodium Lauryl Sulphate, Polyvinyl Alcohol, and PVP K-30, were utilized to create nanosuspensions, which were then measured for zeta potential, saturation solubility, mean particle size, and polydispersity index (PDI) (Paun and Tank, 2016).

Table 4: Results for selection of stabilizer for TMNS

Batch Code	Stabilizer Used	Saturation Solubility (µg/ml) (Mean ± SD)*	Mean Particle Size (nm) (Mean ± SD)*	PDI (Mean ± SD)*	Zeta Potential (mV) (Mean ± SD)*
TF1	PVP K-30	39.51 ± 1.47	360.0 ± 3.8	1.077 ± 0.14	19.85 ± 1.38
TF2	Polyvinyl Alcohol	58.46 ± 2.55	214.8 ± 5.1	0.742 ± 0.21	17.60 ± 1.25
TF3	Sodium Lauryl Sulphate	36.09 ± 0.84	85.60 ± 4.8	1.255 ± 0.34	-16.68 ± 1.41
TF4	**Poloxamer 407**	**76.38 ± 1.02**	**276.5 ± 5.1**	**0.673 ± 0.11**	**-22.82 ± 1.02**
TF5	Poloxamer 188	48.61 ± 0.97	380.0 ± 6.4	1.423 ± 0.41	-15.34 ± 0.97

*Indicates average of three determinations

The findings of the first trial batches used to choose the stabilizer are displayed in Table 4. Poloxamer 407 had the maximum solubility (76.38 ± 1.02 µg/ml) according to Table 4 results. Among all stabilizers, this one had the lowest

PDI value (0.63 ±0.11), indicating a restricted range of particle size (276.5 nm) and size dispersion. The zeta potential of batch TF5, which was -22.82 mV, this aqueous dispersions were shown to be electrostatically stable over time (Paun and Tank, 2016).

3.3 Plackett-Burman design

Several formulation and processing parameters that could offer low mean size of particle and high saturation solubility were screened using the Plackett-Burman design. Five independent variables were chosen, as indicated in table 4: the amount of poloxamer 407 (mg) (X_2), the amount of telmisartan (mg) (X_1), the volume ratio of solvent: anti-solvent (X_3), the speed of stirring (RPM) (X_4), and the time of sonication (Min) (X_5). The dependent variables chosen were saturation solubility (µg/ml) as well as mean particle size (nm).

The chosen response parameters had a broad range of change, as indicated in table 5, indicating that the independent factors significantly influence the dependent parameters.

Table 5: Coefficient Values of dependent variables

Factors	Coefficient from Saturation solubility	Coefficient from Particle size
Concentration of Drug (X_1)	2.39	14.37
Concentration of Stabilizer (X_2)	1.50	10.35
Solvent to anti solvent ratio (X_3)	0.13	10.70
Stirring Speed (X_4)	3.79	52.55
Sonication Time (X_5)	0.72	06.07

The saturation solubility value and the mean particle size value from equations were used to compute the net effect (Co-efficient) of each individual factor.

It is evident from the Pareto chart in Figures 1 and 2 that the amount of telmisartan (X_1) and stirring speed (X_4) had the greatest effects on saturation solubility as well as mean particle size. Together, the amount of telmisartan (X_1) and the pace at which the products were stirred (X_4) caused a cumulative impact on product quality of over 70%.

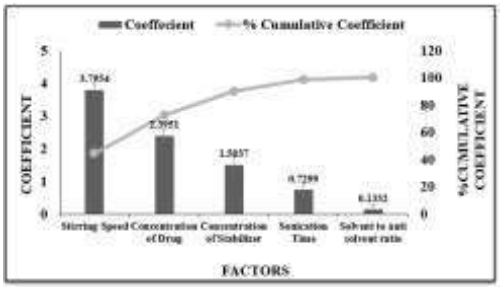

Figure 1: Pareto chart of the saturation solubility of TMNS

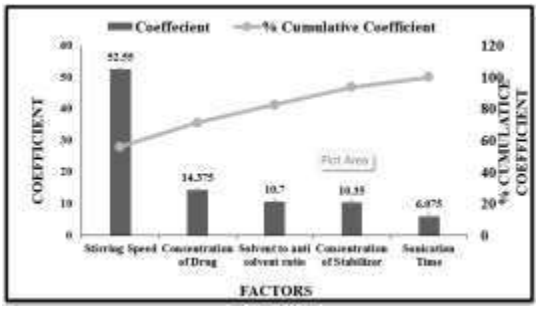

Figure 2: Pareto chart of mean particle size of TMNS

4. CONCLUSION

The data obtained demonstrated that, in comparison to all other stabilizers, the nanosuspension made with Poloxamer 407 had better saturation solubility. The results also showed that drug concentration and stirring speed were promising formulation parameters that significantly impacted the quality of the Telmisartan nanosuspension.

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