Preparation And Characterization Nanoparticles To Improve Solubility Of Hydrophobic Drug

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Introduction

The challenge of poor solubility is a significant hurdle in the development of hydrophobic drugs, impacting their bioavailability and therapeutic efficacy. According to the Biopharmaceutical Classification System (BCS), approximately 40% of new chemical entities are classified as Class II drugs, which are characterized by low solubility and high permeability [1]. These solubility issues can lead to incomplete drug absorption, necessitating innovative formulation strategies to enhance the bioavailability of such compounds.

Nanoparticle technology has emerged as a promising approach to improve the solubility and dissolution rates of hydrophobic drugs. By reducing the particle size to the nanoscale, the surface area-to-volume ratio is significantly increased, promoting better solubility due to enhanced dissolution kinetics [2]. Various methods for preparing nanoparticles, including solvent evaporation, co-precipitation, and high-pressure homogenization, have been extensively studied [3]. Among these, the choice of preparation method plays a crucial role in determining the size, morphology, and stability of the nanoparticles.

Incorporating polymers and surfactants during the formulation process can further enhance the solubility of hydrophobic drugs. For example, the use of biocompatible polymers such as polyethylene glycol (PEG) and polyvinyl alcohol (PVA) can improve the stability and drug release characteristics of nanoparticles [4]. Additionally, surfactants can facilitate the dispersion of nanoparticles in aqueous media, promoting better solubilization.

The characterization of nanoparticles is essential to evaluate their physicochemical properties, including size, surface charge, morphology, and drug loading capacity. Techniques such as dynamic light scattering (DLS), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) are commonly employed for this purpose [5]. Understanding these characteristics is vital for predicting the behavior of nanoparticles in biological systems and optimizing their formulation for enhanced drug delivery.

This study aims to prepare and characterize nanoparticles designed to improve the solubility of a selected hydrophobic drug. By utilizing appropriate materials and methods, the goal is to enhance the bioavailability of the drug, ultimately leading to improved therapeutic outcomes.

Material and Methods

Material

The formulation of Telmisartan-loaded nanoparticles involved several key materials sourced from reputable suppliers. The active ingredient, Telmisartan, was obtained as a gift sample from a pharmaceutical company. Soya lecithin and stearic acid from Hi Media Pvt Ltd, Mumbai, served as stabilizers and surfactants to enhance solubility and stability. Tween 80 from Loba Chemie Pvt Ltd further improved drug dispersion. Di-potassium hydrogen orthophosphate from Hi Media acted as a buffering agent, while methanol, ethanol (from Loba Chemie and Jiangsu Huaxi International), and chloroform (Loba Chemie) were used as solvents. Finally, hydrochloric acid and sodium hydroxide from S. D. Fine Chem. Ltd. were employed for pH adjustment during the formulation process.

Methods

Preparation of Telmisartan loaded nanoparticles using solvent injection method

Nanoparticles were prepared by using solvent injection technique using ethanol as organic solvent [6-7]. Soya lecithin, drug and steric acid is dissolved in the ethanol in definite ratio and warmed to 70°C. To the phosphate buffer solution (pH 7.4) a definite amount of tween 80 is added to prepare aqueous phase and kept for stirring which is maintain at 70°C. The organic phase was added drop wise with stirring to the pre warmed aqueous solution with the help of hypodermic needle. The mixture was then sonicated (Ultra sonicator, Bath type, Electronic India) for varying time to obtain nanoparticles. The optimum parameters i.e. tween 80 concentrations in definite ratio and maximum sonication time resulted in maximum entrapment efficiency and controlled release were used for the preparation of nanoparticles using similar method. Twelve formulations were prepared by using different concentrations of tween 80 and sonication time to determine the effect of surfactant and sonication time on the potency of the nanoparticles.

Effect of formulation process variables

The effect of formulation variables such as Amount of Soya lecithin, Steric acid, Tween 80, Sonication time on the particle size was studied. From the results obtained, optimum level of those variables was selected and kept constant in the subsequent evaluations. However, molecular dispersion of the drug in the stearic acid matrix led to a reduction in the crystallinity of stearic acid. [8]

Table 1: Composition of nanoparticles by varying amount of Soya lecithin

Components	**Formulation code**		
	F1	**F2**	**F3**
Telmisartan (mg)	50	50	50
Soya lecithin (mg)	25	50	75
Steric acid(mg)	50	50	50
Tween 80(ml)	0.5	0.5	0.5
Sonication time (min)	6	6	6

Table 2: Composition of nanoparticles by varying amount of Steric acid

Components	**Formulation code**		
	F4	**F5**	**F6**
Telmisartan (mg)	50	50	50
Soya lecithin (mg)	50	50	50
Steric acid(mg)	25	50	75
Tween 80(ml)	0.5	0.5	0.5
Sonication time (min)	6	6	6

Table 3: Composition of nanoparticles by varying amount of Tween 80

Components	**Formulation code**		
	F7	**F8**	**F9**
Telmisartan (mg)	50	50	50
Soya lecithin (mg)	50	50	50
Steric acid(mg)	50	50	50
Tween 80(ml)	0.5	1.0	1.5
Sonication time (min)	6	6	6

Table 4: Composition of nanoparticles by varying sonication time

Components	**Formulation code**		
	F10	**F11**	**F12**
Telmisartan (mg)	50	50	50
Soya lecithin (mg)	50	50	50
Steric acid(mg)	50	50	50
Tween 80(ml)	1.0	1.0	1.0
Sonication time (min)	6	12	15

Evaluation of nanoparticles

Particle size and zeta potential

Particle size and zeta potential of the nanoparticles were measured by photon correlation spectroscopy using a Malvern Zetasizer[9].

Specification of Particle size and zeta potential Instrument

Model: ZetasizerPro
Measurement: Molecular size, Particle concentration, Particle size, Zeta potential
Particle size range: 0.3nm - 10µm
Technology: Dynamic Light Scattering

Entrapment efficiency

The entrapment efficiency of the drug was defined as the ratio of the mass of formulations associated drug to the total mass of drug [10]. Entrapment efficiency was determined by dialysis method. Nanoparticles entrapped Telmisartan were separated from the free drug by dialysis method. The above said formulations were filled into dialysis bags and the free Telmisartan dialyzed for 24 hours into 50 ml of phosphate buffer 7.4 saline. The absorbance of the dialysate was measured at 270nm against blank phosphate buffer 7.4 saline and the absorbance of the corresponding blank phosphate buffer 7.4 saline was measured under the same condition. The concentration of free Telmisartan could be obtained from the absorbance difference based on standard curve. Standard curve was made by measuring the absorbance at 232.0 nm for known concentrations of Telmisartan solution.

Drug content

From the prepared nanoparticles formulation 1ml of suspension is dissolved in the 10 ml of 7.4 PBS buffer and ethanol mixture [11-12]. The amount of Telmisartan was determined using UV spectrophotometer at 232nm. The placebo formulation prepared similarly to drug loaded nanoparticles was used as blank. The total drug content was calculated.

***In vitro* drug release in gastrointestinal fluids of different pH**

The prepared nanoparticles delivery system was evaluated for *In vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus [13-14]. The dissolution study was carried out in 900 ml dissolution medium (PBS pH 7.4) which was stirred at 100 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows: A weighed quantity of formulation (100 mg) was spread over the surface of dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml by PBS (pH 7.4). The samples withdrawn were assayed spectrophotometrically at 232 nm for Telmisartan and using UV visible spectrophotometer. The release of Telmisartan was calculated with the help of Standard curve of Telmisartan.

Results and Discussion

The formulation and evaluation of Telmisartan-loaded nanoparticles revealed significant findings regarding drug content, entrapment efficiency, particle size, and drug release profiles.

The results presented in Table 5 indicate a wide range of drug content among the various formulations, with formulation F11 showing the highest drug content at 95.23±0.98%. This suggests that the optimization processes effectively enhanced the drug loading capabilities of the nanoparticles. Similarly, Table 6 highlights the % entrapment efficiency, with formulation F11 achieving 83.36±0.14%, reflecting a strong ability to encapsulate Telmisartan. High entrapment efficiency is crucial for ensuring that a significant proportion of the drug is available for therapeutic action, minimizing loss during processing and administration.

As indicated in Table 7, the optimized formulation F11 had a particle size of 256 nm, which is favorable for enhancing the bioavailability of poorly soluble drugs. Smaller particle sizes generally correlate with improved solubility and faster dissolution rates, as they provide a larger surface area for interaction with the dissolution medium. The zeta potential of -10.7 mV suggests that the nanoparticles possess moderate stability; while a higher absolute zeta potential indicates better stability, this level is sufficient to prevent significant agglomeration during storage.

The cumulative drug release data in Table 8 demonstrate a gradual release of Telmisartan from the nanoparticles over time. After 12 hours, 98.78% of the drug was released in phosphate buffer (pH 7.4), indicating that the nanoparticles are capable of delivering a high percentage of the drug effectively. This sustained release profile can lead to improved therapeutic outcomes by maintaining drug concentrations within the therapeutic range over an extended period.

The regression analysis presented in Table 9 shows the different kinetic models applied to the drug release data. The Pappas plot yielded the highest correlation coefficient ($R^2 = 0.9834$), suggesting that the release of Telmisartan from the nanoparticles follows a more complex diffusion mechanism rather than simple first or zero-order kinetics. This finding highlights the potential for sustained release characteristics of the optimized formulation.

Result for drug content of nanoparticles

Table 5: Result of drug content of nanoparticles

S. No.	Formulation Code	Drug Content
1	F1	62.26±0.25
2	F2	68.78±0.45
3	F3	72.56±0.23
4	F4	69.98±0.45
5	F5	73.23±0.36
6	F6	71.36±0.25
7	F7	78.36±0.36
8	F8	79.98±0.31
9	F9	80.25±0.45
10	F10	83.69±0.58
11	F11	95.23±0.98
12	F12	72.23±0.96

Table 6: Result for entrapment efficiency of drug loaded nanoparticles

S. No.	Formulation Code	% Entrapment Efficiency
1	F1	78.98±0.25
2	F2	73.25±0.32
3	F3	74.65±0.45
4	F4	73.25±0.12
5	F5	78.98±0.25
6	F6	74.45±0.26
7	F7	79.98±0.65
8	F8	80.21±0.48
9	F9	78.98±0.54
10	F10	80.45±0.32
11	F11	83.36±0.14
12	F12	78.21±0.49

Table 7: Particle size and Entrapment efficiency of Optimized nanoparticles formulation F11

Formulation Code	Particle size (nm)	% Entrapment Efficiency	Zeta potential (mV)	% Drug Content
F11	256	83.36±0.14	-10.7	95.23±0.98

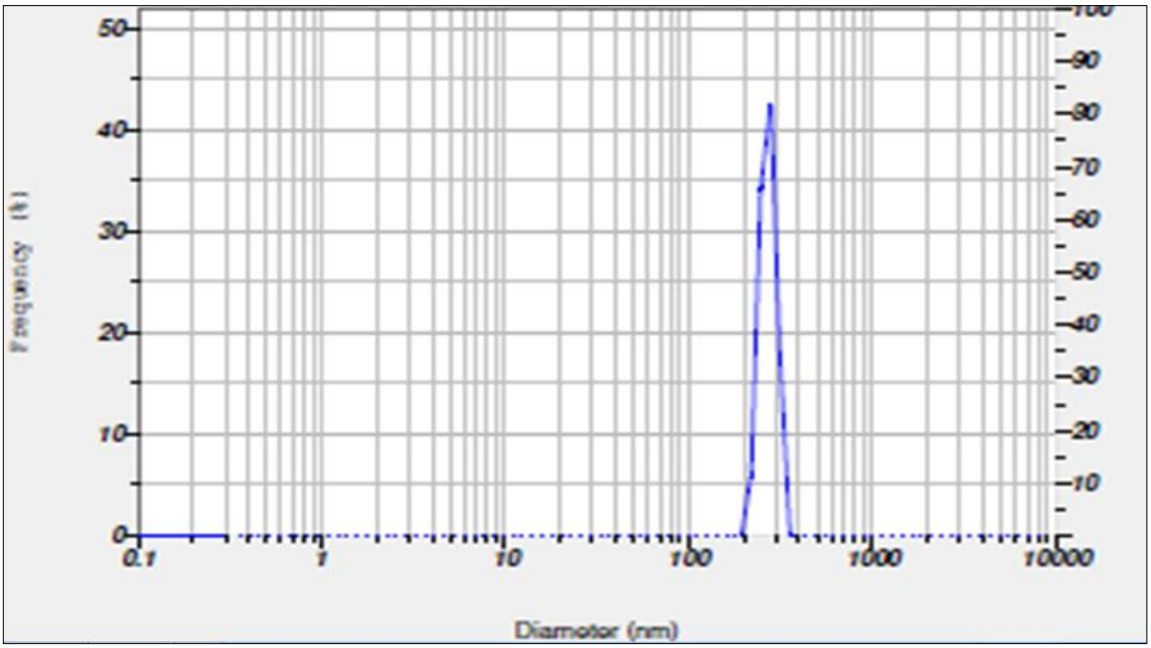

Figure 1: Particle size of Optimized nanoparticles

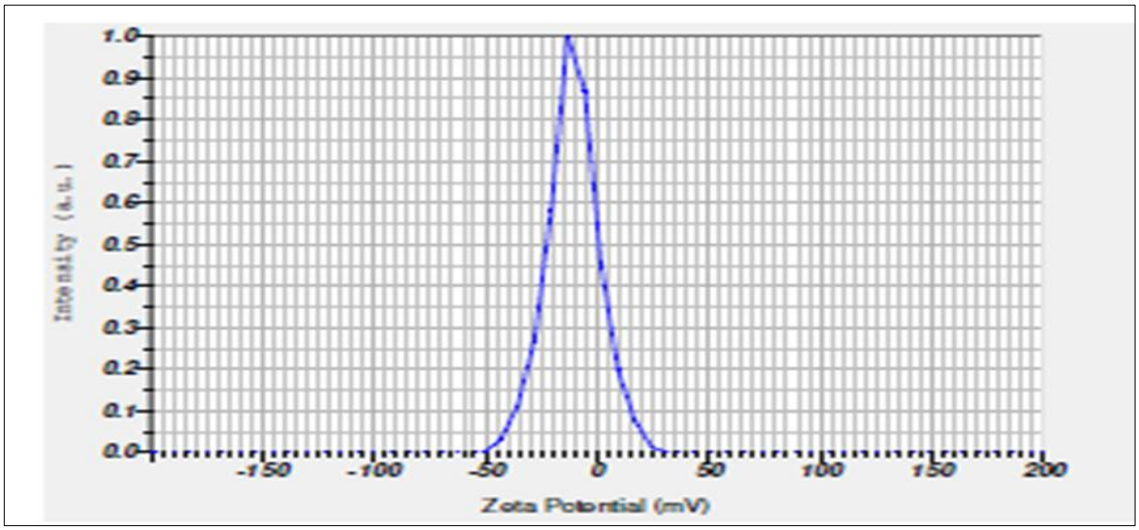

Figure 2: Zeta potential of Optimized nanoparticles

Table 8: Cumulative % drug release of Telmisartan loaded nanoparticles

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release
1	Phosphate Buffer (pH 7.4)	1	16.65
2		2	23.32
3		3	36.45
4		4	44.65
5		5	59.98
6		6	68.85
7		7	76.65
8		8	85.54
9		9	92.23
10		10	94.47
11		12	98.78

Table 9: Regression analysis data of nanoparticles formulation

Formulation	Zero order	First order	Pappas plot
F11	$R^2 = 0.9520$	$R^2 = 0.9263$	$R^2 = 0.9834$

Conclusion

The formulation of Telmisartan-loaded nanoparticles demonstrated promising results regarding drug content, entrapment efficiency, and sustained release profiles. The optimized formulation (F11) exhibited excellent characteristics that can enhance the solubility and bioavailability of hydrophobic drugs, making it a suitable candidate for further development in drug delivery applications.

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