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Original Article

Formulation and in-vitro evaluation of Tizanidine nanoparticle as a sublingual tablet

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ABSTRACT

Tizanidine (TZ) is a selective α2-adrenergic agonist used to relieve spasticity associated with spinal cord injury and multiple sclerosis. Despite its clinical utility, TZ is a Biopharmaceutics Classification System Class II drug with poor aqueous solubility and an oral bioavailability of about 13%, limiting efficacy. Polymeric nanotechnology was employed to enhance dissolution and absorption. TZ nanoparticles were prepared by a solvent–antisolvent method using carriers Soluplus® (SL) and Poloxamer 188 (PL188) with co-stabilizers such as PEG 200 and glycerol; TZ-NP formation succeeded with SL but not with PL188. The optimized formulation, F6 (TZ:SL 1:1 with glycerol at 50% w/w of SL), achieved a particle size of 89.88 nm, a narrow PDI of 0.2517, drug content 98.4%, and entrapment efficiency 98.5%. F6 delivered complete drug release within 75 minutes, far exceeding the 40% release from unformulated TZ. To enable rapid onset, F6 NP was lyophilized with 3% mannitol and incorporated into sublingual tablets with various superdisintegrants. The optimized tablet, SL3, disintegrated within 40 seconds and achieved 100% drug release within 5 minutes, indicating markedly improved dissolution and potential for enhanced bioavailability and patient compliance. This study demonstrates that Soluplus-based TZ nanoparticles, followed by lyophilization and sublingual formulation, offer a viable strategy to overcome TZ's solubility and bioavailability limitations, enabling faster onset of action and improved therapeutic outcomes.

Keywords: Tizanidine, Soloplus®, Poloxamers 188, PEG200, Glycerol

Introduction

Tizanidine, a centrally acting muscle relaxant, is classified as a Biopharmaceutics Classification System (BCS) Class II drug, characterized by poor aqueous solubility and limited oral bioavailability. These inherent physicochemical challenges adversely affect its therapeutic efficacy, necessitating innovative formulation strategies to enhance its dissolution and absorption.

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Nanotechnology offers a promising avenue to overcome such limitations; specifically, nanoparticle technology has demonstrated remarkable potential in improving the solubility and dissolution rates of poorly water-soluble drugs, thereby enhancing bioavailability and clinical outcomes [1].

Drawing parallels from recent advancements in nanoscale drug delivery, the application of polymers such as Soluplus and Poloxamer 188, combined with co-stabilizers like glycerol or polyethylene glycol (PEG 200), has been shown to reduce particle size and stabilize NP significantly. These stabilizers not only maintain physical stability but also facilitate increased drug dissolution and permeation. Applying these formulation principles to TZ-NP could effectively address its solubility barriers [2].

Moreover, converting TZ-NP into sublingual tablets represents an attractive strategy to further enhance bioavailability via bypassing hepatic first-pass metabolism and enabling rapid drug

onset through mucosal absorption. This dual approach promises to leverage both nanotechnology and sublingual delivery, achieving improved therapeutic benefits for patients requiring TZ [3].

Materials and Methods

Materials

Tizanidine (TZN) was supplied by Hyperchem. China. Poloxamer 188 (P188) was purchased from Eastman Chemical Company, USA. Soloplus ® (SL) Basf SE, Germany. Methanol and Ethanol were purchased from Sigma Aldrich, Germany. Glycerol (GL), PEG200 purchased from BDH, England.

Methods

Determining the saturated solubility of Tizanidine

One approach for assessing the solubility of the substance entails agitating an excessive quantity of the drug in a 10 mL plastic tube within a water bath shaker for 48 hours. In a 10 mL polypropylene tube, 10 mL of Buffer 6.8 was used to agitate the medication powder. The solution was filtered after 48 hours, and UV spectroscopy was used to analyse it at its maximum wavelength of 320 nm. Based on the results, the substance's solubility was then computed [4, 5].

Preparation of Tizanidine nanoparticles

TZ-NP was prepared via a bottom-up process known as the solvent anti-solvent method. 10 mg of the drug was dissolved in 3 mL of ethanol to create the organic phase, and 10 or 20 mg of various carriers [Soluplus®(SL) and Poloxamer 188(PL188)] were dissolved in 10 ml of deionised water (DW) based on the applied ratio, with various co-stabilizers (PEG 200 and glycerol (GL)) at varying percentages of 50% and 30% of the carrier's weight, as shown in **Table 1**. Subsequently, the organic phase was inserted into a 0.6 mm needle gauge syringe and attached to a syringe pump (Kelly Med, Germany). To evaporate the organic solvent, the organic phase was introduced dropwise to the aqueous phase at a rate of 1 mL/min while being stirred on a magnetic stirrer (Joan Lab, China) at 1000 rpm for 20 minutes [6, 7]. After preparation, the NPs were covered and left in a cool location overnight.

Table 1. Composition of Tizanidine-Loaded Nanoparticles (TZ NP).

FORMULA CODE	TZN mg	SLS mg	PL188 mg	*PEG200 %W/W	*PG %W/W	*GL %W/W	EtOH mL	DW mL	Speed rpm
F1	10	10		30%			3	10	1000
F2	10	10		50%			3	10	1000
F3	10	10			30%		3	10	1000
F4	10	10			50%		3	10	1000
F5	10	10				30%	3	10	1000
F6	10	10				50%	3	10	1000
F7	10	20		30%			3	10	1000
F8	10	20		50%			3	10	1000
F9	10	20			30%		3	10	1000
F10	10	20			50%		3	10	1000
F11	10	20				30%	3	10	1000
F12	10	20				50%	3	10	1000
F13	10		10	30%			3	10	1000
F14	10		10	50%			3	10	1000
F15	10		10		30%		3	10	1000
F16	10		10		50%		3	10	1000
F17	10		10			30%	3	10	1000
F18	10		10			50%	3	10	1000
F19	10		20	30%			3	10	1000
F20	10		20	50%			3	10	1000
F21	10		20		30%		3	10	1000
F22	10		20		50%		3	10	1000
F23	10		20			30%	3	10	1000
F24	10		20			50%	3	10	1000

*means the % w/w of the weight of the stabilizer used.

Characterization of Tizanidine-loaded nanoparticles

Determination of the particle size and polydispersity index of TZ-NP

With a particle size analyser nano Laser (Malvern Zeta Sizer, Ultra rate Company, USA) at room temperature, the dynamic light scattering (DLS) approach was used to determine the size and distribution of TZ NP in all formulations. Particle size (PS) and polydispersity index (PDI) are among the metrics [8].

Entrapment efficiency measurement of TZ with the nanoparticle

The entrapment efficiency (%EE) is the proportion of the medication that is contained within the matrix of the nanoparticle. An Eppendorf tube is filled with 2 mL of nanosuspension to calculate the %EE. After centrifuging the tube for 20 minutes at 6000 rpm and 4°C, 1 mL of the supernatant was removed, and a UV spectrophotometer was used to determine the amount of free drug present. The following No. 2 formula was used to determine the %EE [9]:

$$\%EE = [(C\ initial - C\ free)/Cinitial\ ]100 \quad (1)$$

Where, %EE = Percentage of entrapment efficiency.

$Cinitial$ = Initial drug concentration or the theoretical drug content

$Cfree$ = Free drug concentration (unentrapped drug in the supernatant).

In-vitro dissolution of the selected TZ-NP

A dialysis membrane (MWCO 12000-14000 Da) containing 5ml of the chosen TZ NPs formula (equivalent to 5mg TZ) was attached to the paddle and placed in 500mL of phosphate buffer pH 6.8 with 0.2% w/v of Tween 80 at 37°C and 50 rpm to maintain the sink condition. However, only the chosen TZ NP formulas were subjected to the dissolution test using a USP type II dissolution apparatus based on the P.S., PDI, and EE% data. Five millilitres of the sample were taken out and replaced with new buffer at regular intervals of seven, fifteen, twenty, thirty, forty-five, sixty, seventy-five, and one hundred minutes in order to evaluate the drug's release. The cumulative percent release of the TZ was computed and displayed against time after the amount of Tizanidine released was determined spectrophotometrically at 230 nm [10].

Selection of the optimum formula

Based on the results of PS, PDI, %EE, and *in-vitro* release, only one formula was optimized and then subjected to Lyophilization.

Lyophilization of the optimized TZ-NP formula

The optimized formula was freeze-dried to obtain a dry powder using 3% w/v mannitol as a cryoprotectant. The Lyophilizer was equipped with eight round-bottom flasks, in each of which twenty milliliters of the optimized TZ NP was frozen in liquid nitrogen at −60°C for 10 minutes, followed by lyophilization under vacuum til dryness, as shown in **Figure 1**. The whole process took approximately 24 hours. The resulting dry powder was stored in a cool place and subjected to characterization [11].

Figure 1. Lyophilization process

Characterization of TZ-NP optimized formula.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy combined with the attenuated total reflectance (ATR) technique was used to detect any potential contact or complexation between the active ingredient and selected excipients, as well as TZ-excipient compatibility. Tinazidine, as a pure drug powder, and the optimized TZ NP, as a lyophilized formula, were each placed directly into the crystal area. Then, the pressure arm was placed above the sample and scanned over the range between 4000-400 cm-1 wavenumber [12].

Differential scanning calorimetry (DSC)

This device is frequently used to evaluate a drug's crystalline condition, especially when it's a lyophilised powder. It can also be used to assess the drug's physical compatibility with the formulation's excipients. All of the samples in this investigation were kept in aluminium pans that were not hermetically sealed. The pan was filled with pure TZ and lyophilised powder of the optimised formula, respectively, and heated at a rate of 10º °C per minute. The temperature was fixed between 20 and 350 oC, and the measurement was carried out with a dry nitrogen gas flow of 100 ml/min. The measurement was taken with the DSC-

Shimadzu 60 plus (Japan), and an empty aluminium pan served as a reference [13].

Morphological characterization

Field emission scanning electron microscope (FESEM)

Once the NP had been tuned, a drop of it was deposited on aluminum stubs and allowed to air-dry. To ensure the slide remained in place on the specimen holder, double-coated adhesive tape was used. It was followed by the application of gold to the slide using a sputter coater while the slide was placed in a vacuum for ten minutes. This action was performed to establish a consistent coating that enables the creation of high-quality images using scanning electron microscopy. To obtain the pictures using FESEM, several magnifications were employed [14].

Atomic force microscope (AFM)

Atomic Force Microscopy (AFM) characterizes nanoparticles by providing high-resolution, three-dimensional images and quantitative data on their size, shape, surface texture, and distribution. The technique utilizes a sharp tip to scan a surface, detecting interactions with nanoparticles to create detailed topography [15].

Preparation of Lyo-TZ NP as a sublingual tablet

The **Sublingual** tablets (SLTs) were prepared using the direct compression method as mentioned in **Table 2**. The weighed quantities of the Lyo TZ NP, equivalent to pure TZ, super disintegrants (CCS, SSG), binder (PVP), diluent (Mannitol), and lubricant (Magnesium stearate) were passed through a 60-mesh sieve to ensure uniform particle size. All ingredients, except magnesium stearate, were blended thoroughly in a mortar for 3 minutes to obtain a uniform powder mixture. Then, magnesium stearate was added just before compression. The final blend was compressed into tablets using a single-punch tablet compression machine equipped with 8 mm flat-faced punches [16].

Table 2. Formulation of Lyo-TZ NP as sublingual Tablets

F. code / Ingredients (mg)	SL_1	SL_2	SL_3	SL_4
Lyophilized NP Powder	163	163	163	163
Sodium Starch Glycolate	-	5	10	-
Cross Carmellose	-	-	-	10
Mg Stearate	3	3	3	3
Avecil (101) q.s	200	200	200	200

Precompression evaluation of the prepared lyophilized TZ-NP with the other excipient for each sublingual tablet formula before compression

A certain weighed quantity of Lyo-TZ-NP, along with the required amounts of other excipients, was mixed to be processed into the precompression study. The properties measured included the Angle of Repose, Carr's Index, as follows:

Angle of repose

The angle of repose for each sublingual formula was measured using the funnel and petri dish method to assess flowability. Powder was poured through a funnel from a height of 2-4 cm onto a flat surface, forming a cone, with the height (h) and radius (r) measured to calculate the angle using the equation below. **Table 3** was used to predict the type of flow [17].

$$\tan\theta = {}^{h}/_{r} \qquad (2)$$

Table 3. Properties of Powder Flowability Measured By Angle of Repose

Flow property	The angle of Repose (Degree)
Excellent	<20
Good	20 – 30
Passable	30 - 34
Very Poor	>40

Determination of compressibility (Carr's) index and hausner's ratio

After filling a volumetric cylinder with a sample of each sublingual tablet formula to get an initial volume (V_0), the cylinder was tapped conventionally against a solid surface until a constant volume (V_f) was reached [18]. The following equation was then used to determine the compressibility index, which indicates the type of flow as listed in **Table 4**.

$$\text{Compressibility index} = [V_0 - V_f / V_0] \times 100 \qquad (3)$$

Table 4. Types of Flow According to Carr's Index

Type of flow	Carr's Index
Excellent	5-11
Good	12-17

Fair to passable	18-21
Poor	23-35
Very Poor	36-38
Extremely poor	>40

Post-compression evaluation of the prepared sublingual tablets after compression

Based on the previously described preparation method and the specific constituents outlined in **Table 2**, approximately 40 tablets of each formulation (SL1, SL2, SL3, and SL4) were produced. These tablets then underwent post-compression evaluation, including assessments of hardness, friability, weight variation, content uniformity, and in vitro disintegration, as mentioned below.

Hardness test

Three tablets were obtained for testing using an electronic hardness tester to measure their hardness. The average hardness of the three tablets was calculated. The required force, measured in kg/cm², to crush the tablets was used as an indicator of their hardness, which was determined to be [19].

Friability

Twenty tablets were pre-weighed and inserted into a Roche friabilator to conduct a friability test on the prepared tablets for four minutes at a rate of 25 revolutions per minute. Following the allotted time, the tablets were cleaned and weighed once again. The percentage of weight loss during rolling was used to calculate the friability. According to equation No. 3 [19], the SLTs pass the test if the weight loss is less than 1% of the initial tablet mass.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (4)$$

Content uniformity

After crushing and powdering one tablet of each recipe, 10 mg of the mix containing TZ was weighed, dissolved in 75 ml of ethanol, thoroughly smashed, and the amount was increased to 100 ml with ethanol before being filtered. Transfer 10 milliliters of the filtrate to a 100-milliliter flask containing methanol. Spectrophotometric analysis of the resulting solution was performed at the specified λmax [19].

In vitro disintegration test

The USP standard-defined test was utilized to investigate the TZ SLTs' disintegration time using the optimized formula. One tablet was placed in a basket with six holes and submerged in 900 milliliters of phosphate buffer 6.8 in a fixed motion that involved raising and lowering the tablet at 37°C for 30 cycles per minute. The time it took for the pills to completely dissolve and for no masses to remain in the basket was measured and noted (19).

Dissolution studies

The in vitro dissolution test for TZ-NP-SLTs was performed using USP dissolution apparatus Type II fitted with a paddle rotated at 50 rpm in 300 mL of the dissolution media, starting with PBS pH 6.8 for all the prepared SLTs, followed by 0.1N HCL only for the optimized SLT, all maintained at 37°C. At specific time intervals of 1, 2, 4, 6, 8, 10, 15, 20, 25, and 30 minutes, 5 mL samples were withdrawn and immediately replaced with an equal volume of fresh dissolution medium to maintain the sink condition. The collected samples were filtered using a 0.45 µm syringe filter and subsequently analyzed spectrophotometrically at a maximum wavelength of 290 nm (λmax) [20-22].

Statistical analysis

To determine whether the variations in the factors that were applied are significant at the level of ($P < 0.05$), highly significant at a level of ($P < 0.005$), and non-significant at the level of ($P > 0.05$), the research's findings were presented as the mean of three triplicate models ± (SD), and applying one way (ANOVA)using Microsoft Excel 2010.

Results and Discussion

Solubility of Tinazidine

Tizanidine free base is characterized by its inherently poor aqueous solubility, a hallmark of Biopharmaceutics Classification System (BCS) Class II drugs, which significantly impairs its oral bioavailability. In phosphate buffer at pH 6.8, its saturated solubility is notably low, approximately 0.5 mg/mL, and this solubility further diminishes with increasing pH due to limited ionization. To overcome these solubility challenges, Tizanidine was formulated into nanoparticles through a 1:1 ratio with SL and using glycerol as a co-stabilizer, resulting in a remarkable threefold enhancement in dissolution rate.

Particle size, polydispersity index, and entrapment efficiency of Tinazidine nanoparticles

The P.S., PDI, and EE% measurement for all formulas is shown in **Table 5**.

Table 5. Particle size and PDI data of the prepared TZ NP

FORMULA CODE	D-P RATIO	PHYSICAL STABILITY	P. SIZE nm	PDI	EE%
F1	1:1	Stable	69.82	0.2234	35.5
F2	1:1	Stable	97.81	0.2963	47.4
F3	1:1	Stable	160.4	0.3612	37.2

F4	1:1	Stable	66.66	0.2031	12.7
F5	1:1	Stable	296.4	0.4462	39
F6	1:1	Stable	89.88	0.2517	98.5
F7	1:2	Stable	92.03	0.297	45.2
F8	1:2	Stable	89.47	0.2631	80.5
F9	1:2	Stable	88.64	0.2806	91.5
F10	1:2	Stable	106	0.2926	75
F11	1:2	Stable	84.7	0.2688	85
F12	1:2	Stable	95.01	0.2328	32
F13	1:1	unstable	--------	--------	--------
F14	1:1	stable	584.1	0.7784	--------
F15	1:1	unstable	--------	--------	--------
F16	1:1	unstable	--------	--------	--------
F17	1:1	unstable	--------	--------	--------
F18	1:1	unstable	--------	--------	--------
F19	1:2	unstable	--------	--------	--------
F20	1:2	stable	664.1	0.4621	--------
F21	1:2	unstable	--------	--------	--------
F22	1:2	unstable	--------	--------	--------
F23	1:2	unstable	--------	--------	--------
F24	1:2	stable	1444	1.08	--------

Effect of carrier type and concentration on the particle size, PDI, and entrapment efficiency % of the prepared TZ NP

The correlation between polymer or carrier type and concentration on nanoparticle characteristics such as particle size, polydispersity index (PDI), and entrapment efficiency (EE%) is well-documented and plays a crucial role in the formulation outcome.

Different polymers also have varying molecular weights and hydrophobic/hydrophilic balances, which affect their ability to stabilize nanoparticles and control size distribution. For example, more hydrophilic polymers may lead to smaller particle sizes because of better steric stabilization.

Regarding the first stabilizer or carrier, **Soloplus (SL), as shown in Table 5:**

The P.S typically increases with increasing polymer concentration due to the higher viscosity of the polymer solution, which hinders efficient droplet breakup during nanoparticle formation, leading to larger particles. **The PDI**, which reflects the uniformity of particles, tends to decrease with the use of suitable polymers and optimal concentrations that stabilize nanoparticle formation by preventing aggregation. Excessive polymer concentration, however, can increase PDI due to viscosity-induced aggregation or heterogeneous nucleation [23].

The Entrapment efficiency (EE%), indicating the percentage of drug encapsulated within nanoparticles, is generally enhanced at moderate polymer concentrations since an adequate polymer matrix provides better drug encapsulation. However, very high polymer amounts can reduce EE as polymer chains may hinder drug incorporation or lead to phase separation. The carrier type influences EE since polymers with specific interactions (e.g., hydrogen bonding or hydrophobic forces) with the drug retain the drug more efficiently [24].

Regarding the second stabilizer or carrier, **Poloxamer (POL 188):**

The failure and instability of Tinazidine nanoparticles prepared using Poloxamer 188 (P188), resulting in large particle sizes in the micrometer range, can be attributed to several key factors related to the physicochemical properties and interactions of P188 with the drug and polymer matrix.

Poloxamer 188, although commonly used as a stabilizer, has a relatively high molecular weight (~7500 Da) and specific molecular architecture that influences its stabilizing ability. Compared to other surfactants like Polysorbate 80 (PS80), P188 tends to produce nanoparticles with higher crystallinity and less durable physical stability, leading to rapid melting and aggregation. This is because P188 shows a sharp glass transition temperature (Tg) peak indicative of fast melting behavior, making the nanoparticles prone to fusion and growth beyond nanoscale dimensions during processing or storage [25].

Moreover, P188 exhibits an antiplasticizing effect that increases rigidity but also increases crystallinity of the nanoparticle matrix, which can hamper uniform drug encapsulation and lead to structural instability. The drug-polymer-stabilizer interactions with P188 are strong due to its high molecular weight, but they may promote phase separation or aggregation under certain conditions, causing larger particle formation in the micrometer range.

Additionally, the hydrophilic-lipophilic balance (HLB) and hydrophobic side chains of P188 affect its emulsifying and steric stabilization efficacy. P188 has less effective steric hindrance compared to surfactants with longer hydrophobic chains, resulting in weaker prevention of particle agglomeration [26].

Effect of co-stabilizer type and concentration on the particle size, PDI, and entrapment efficiency % of the prepared TZ NP

The use of different types and concentrations of co-stabilizers such as PEG 200, glycerol(GL), and propylene glycol (PG) in the formulation of TZ NP with SL at ratios like 1:1 or 1:2 significantly influences key nanoparticle parameters, including particle size, polydispersity index (PDI), and entrapment efficiency (EE%).

PEG 200, due to its relatively low molecular weight and excellent miscibility with water, acts as a solubilizing agent that can reduce particle size and PDI by promoting better dispersion and preventing aggregation, as shown with F1 and F2. Glycerol, a viscous polyol, can increase the viscosity of the medium and thus may lead to an increase in particle size but can enhance EE% by stabilizing drug molecules within the formulation, as shown with F5 and F6. PG behaves similarly to glycerol but generally imparts slightly less viscosity, helping to balance particle size and EE%, as shown with F3 and F4. Increasing the concentration of these cosolvents typically improves drug

solubility and entrapment but may also promote particle growth or aggregation, increasing PDI if not optimized [27, 28].

So an optimal type and concentration of co-solvent enhances nanoparticle stability by finely balancing drug solubilization, particle size reduction, and encapsulation efficiency.

In-vitro drug release for TZN nanoparticles

Depending on the P.S., PDI, and EE% data mentioned in **Table 5**, only F6, F8, F9, and F11 of TZ NPs were selected to pass through the in vitro release test, as shown in **Figure 2**.

The variation in the in vitro release of Tizanidine (TZ) from the prepared nanoparticles (NPs) formulations F6, F8, F9, and F11 can be linked to differences in the drug-to-carrier ratio, as well as the type and concentration of the co-stabilizer used.

Formulation F6, with optimal drug-to-carrier ratio and co-stabilizer concentration, achieved the highest release of 70-80% within 30 min and complete release (100%) by 100 min. In contrast, F8, F9, and F11 showed slower release profiles, reaching only 40-61% release within 30 min and maximum release between 55 95% at 100 min. This indicates that higher carrier content or suboptimal co-stabilizer amount may retard drug release by enhancing matrix density or particle agglomeration, reducing surface area available for dissolution [29].

The drug-to-carrier ratio influences the drug encapsulation and matrix compactness; higher polymer or carrier ratios generally retard release due to thicker diffusion barriers. The co-stabilizer type and concentration impact the nanoparticle surface characteristics and stability, affecting drug release kinetics [30].

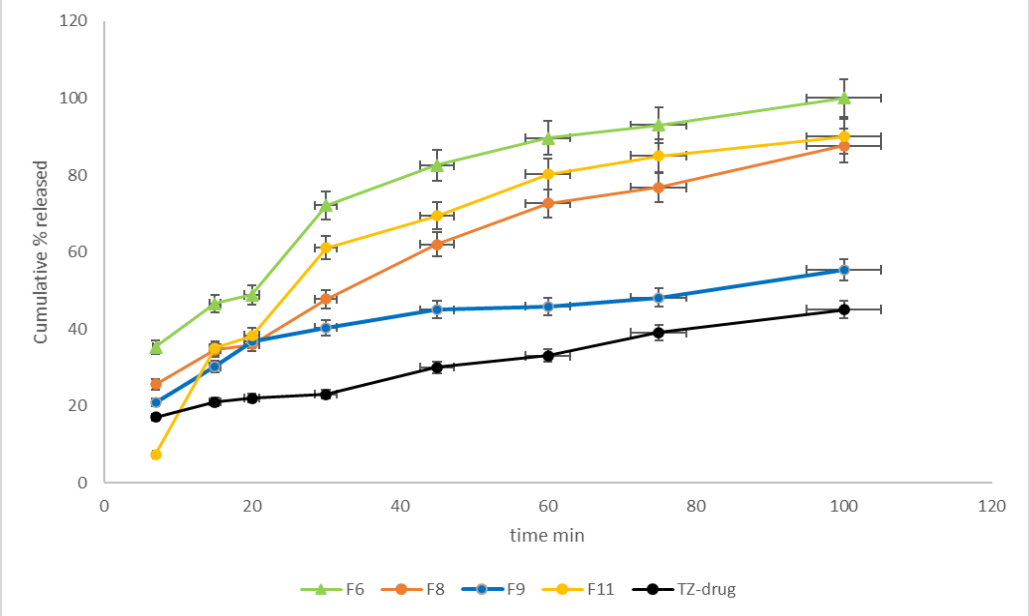


Figure 2. The release profile of F6, F8, F9, and F11 TZ NPs.

Optimization of the best formula

Depending on the previous results of P.S., PDI, EE%, and the release profile, F6 was optimized as the best TZ NP to be lyophilized after preparation of 160 ml, each 5ml containing 10 mg of TZ (dose). 4.8 g of mannitol (3%) was weighed and added, then kept in the lyophilizer overnight. Finally, the gained granules were subjected to characterization.

Characterization of the Lyophilized TZ NP

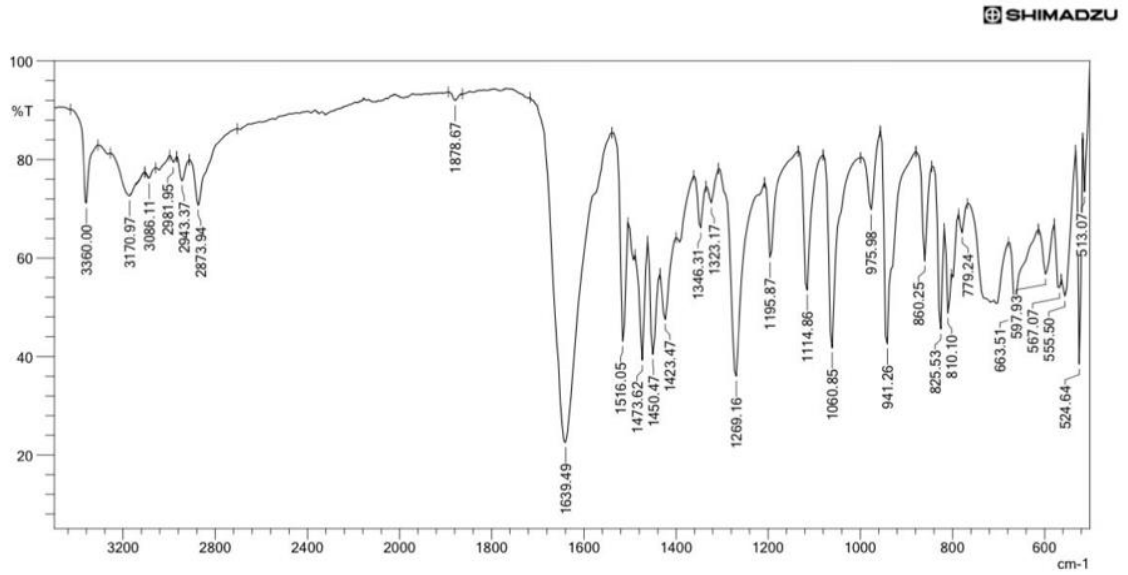
Compatibility analysis of the drug and excipient using FTIR

Figure 3a represents the FTIR spectrum of pure Tizanidine, which typically exhibits characteristic peaks such as broad absorption bands around 3379 and 3271 cm^{-1} corresponding to N-H stretching vibrations from amine groups, peaks near 2935, 2920, and 2881 cm^{-1} assigned to aliphatic C-H stretching, and a sharp peak at 1735 cm^{-1} indicative of C=O stretching possibly from the drug or excipient matrix. Additional peaks between 1651 and 1431 cm^{-1} correspond to aromatic C=C stretching and bending vibrations. Peaks observed at lower wavenumbers (1300-500 cm^{-1}) relate to various fingerprint region functionalities, confirming molecular identity [31].

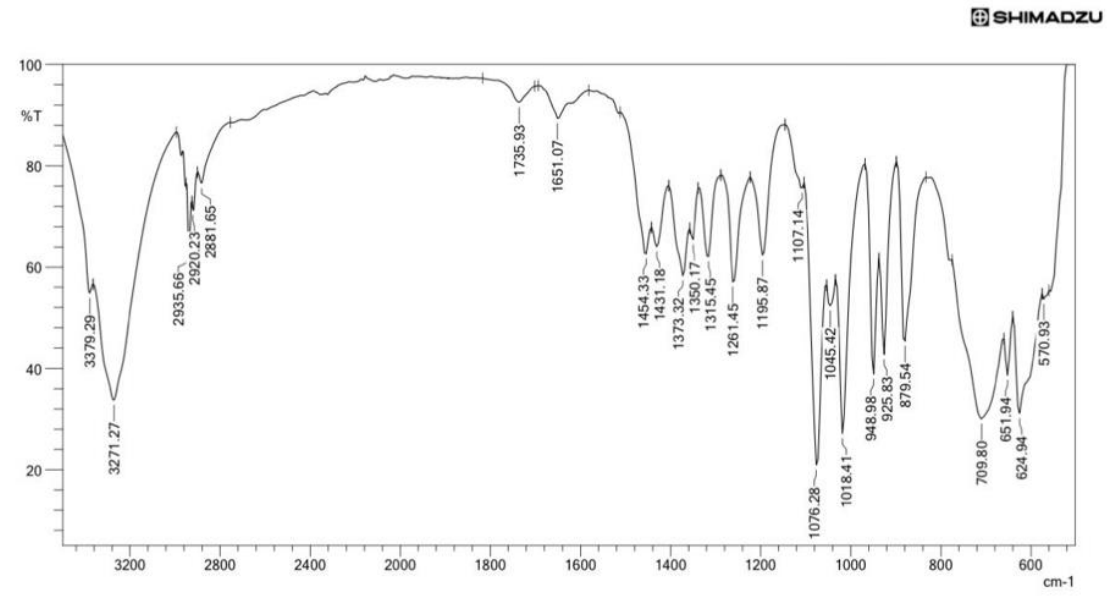
The FTIR spectrum of the prepared Tizanidine nanoparticles (NPs) shows these characteristic drug peaks preserved with minor shifts or intensity changes, indicating physical entrapment rather than chemical interaction or new bond formation. No new peaks or disappearance of diagnostic absorption bands occur, demonstrating compatibility between Tizanidine and the polymers/excipients such as Soluplus, surfactants, or cryoprotectants used in formulation. The slight shifts can be attributed to drug-excipient interactions like hydrogen bonding or encapsulation within the nanoparticle matrix, which do not

alter the drug's chemical structure but may influence peak intensities [32].

This FTIR compatibility confirms that the excipients do not chemically alter or degrade Tizanidine during nanoparticle preparation, ensuring chemical stability and efficacy of the formulation [33-35].



a)

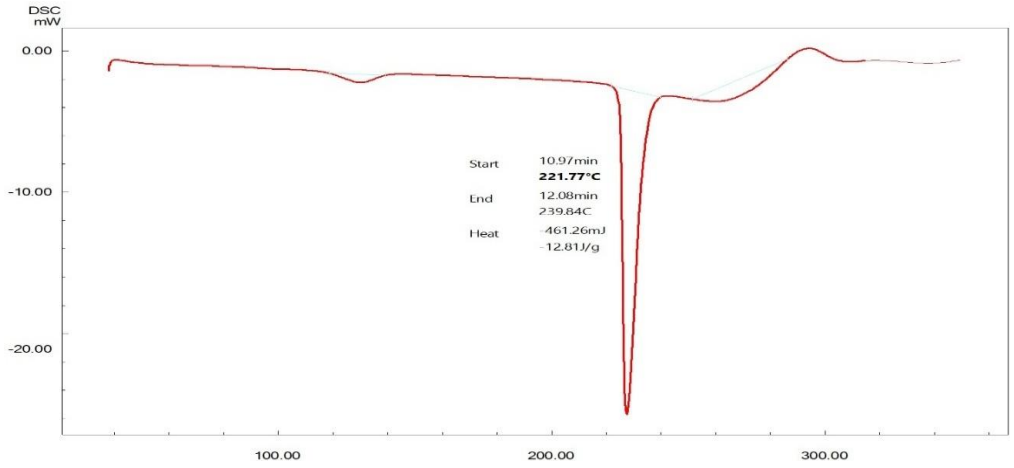


b)

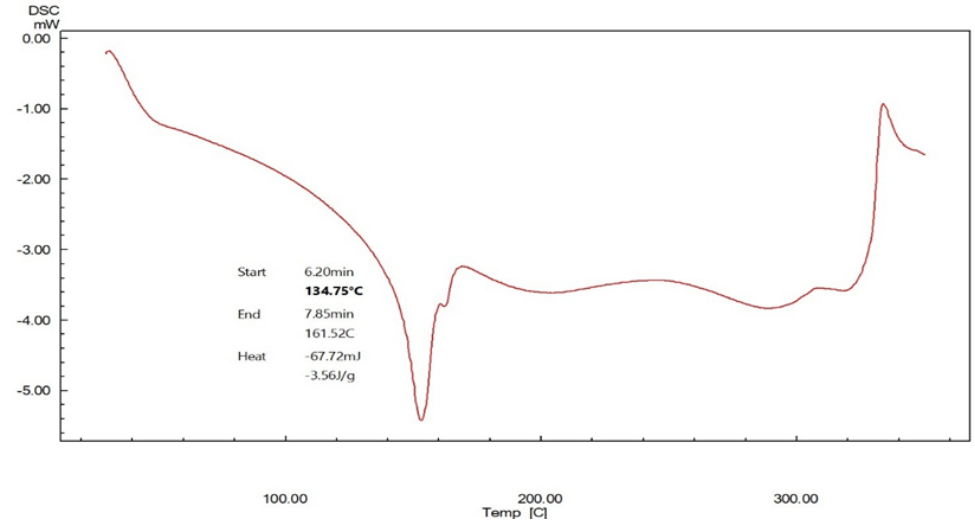
Figure 3. FTIR spectrum of: a) pure TZ, b) Lyophilized TZ NPs(F6)

Differential scanning calorimetry (DSC) for crystallinity specification

Figures 4a and 4b illustrates the thermal behavior of the pure drug TZ, and the optimized formula F6, demonstrating a sharp endothermic peak at 221°C corresponding to TZ as a free base, indicating its purity and anhydrous crystalline structure [36-39]. The thermogram of F6 (Lyo-TZ-NP) shows that the endothermic peak has vanished, which may suggest that the drug is no longer in its crystalline form and is likely entrapped in an amorphous state within the nanoparticle [40].



a)

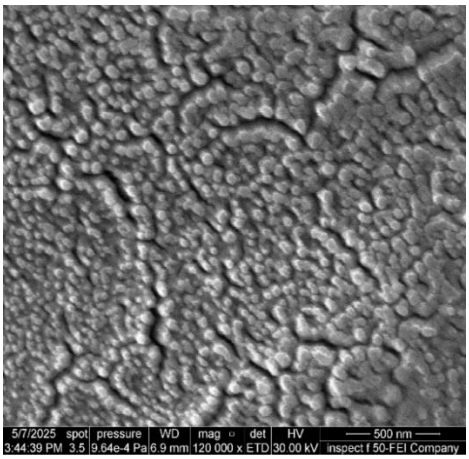


b)

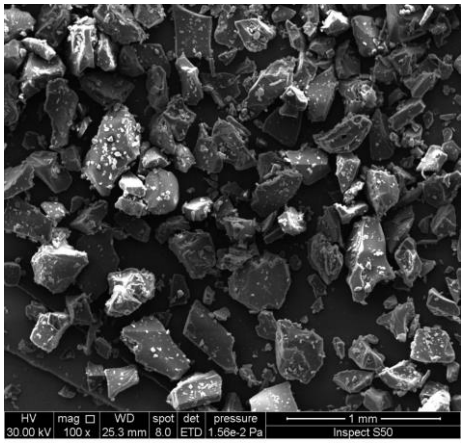
Figure 4. Differential scanning calorimetry (DSC)of the: a) Pure TZ, b) Optimized F6(TZ-NP)

Morphological Characterization by AFM and FESEM

Nanoparticles exhibited uniform, spherical morphology, smooth surface, and consistent size by FSEM and AFM, indicating successful formulation and stability [41].



a)



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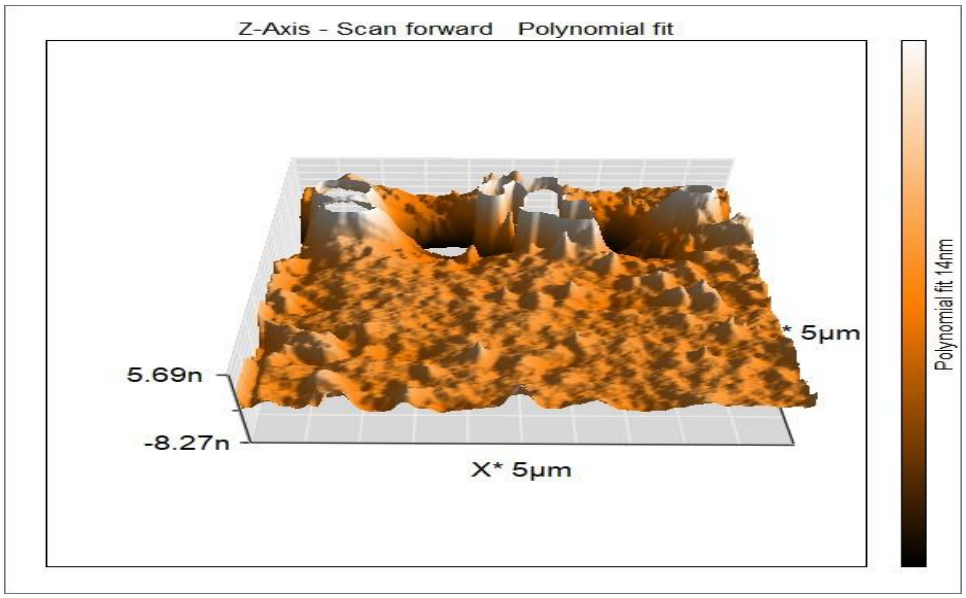

c)

Figure 5. Morphological characterization: a) F6 by FSEM, b) F6 by AFM, C) Pure TZ

Precompression Evaluation of the Prepared Lyophilized TZ-NP with the other Excipient for each Sublingual Tablet Formula Before Compression

Precompression evaluation tests, as mentioned in **Table 6**, indicated improved flowability and compressibility of the **Ly-TZ-NP,** as shown by a decreasing angle of repose and Carr's index from SL1 to SL4 [42].

Table 6. Precompression Study of the flow property (mean± SD)

Formula code	Angle of repose	Carr's index
SL_1	42 ± 0.01	22.1 ± 0.5
SL_2	36.5 ± 0.04	20.9 ± 0.2
SL_3	31.4 ± 0.01	18.6 ± 0.11
SL_4	25.9 ± 0.02	14.9 ± 0.12

Post-compression evaluation of the prepared sublingual tablets after compression

As shown in **Table 7**, all formulated tablets demonstrated acceptable hardness values ranging from 2.5 to 3.5 kg/cm², ensuring mechanical integrity for handling and packaging. Friability percentages were within acceptable limits (<1%), highlighting the tablets' resistance to breakage during transport. Disintegration times improved notably with the addition of superdisintegrants; SL1 showed the longest time (3 minutes), while SL3 and SL4 tablets disintegrated rapidly within about 40-55 seconds, which is favorable for the quick onset of action via sublingual delivery. Content uniformity was consistent across all formulations (>98%), ensuring dose accuracy [42].

Overall, SL3 and SL4 exhibited an optimal balance between mechanical strength and rapid disintegration, making them preferred formulations for enhanced patient compliance and therapeutic effectiveness [43-49].

Table 7. Post-compression parameter for the direct compression method (mean± SD)

Formula code	Hardness	%Friability	Disintegration time (min)	% Content
SL_1	3.5 ±0.4	0.67	3 ± 0.3	98.8
SL_2	3.3 ±0.2	0.60	1 ± 0.1	98.9
SL_3	3.0 ±0.3	0.5	40 sec ± 0.5	99.5
SL_4	2.5 ±0.1	0.1	55 sec ± 0.5	99.8

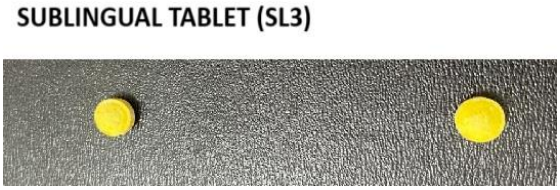

Figure 6. The selected Lyophilized Tinazidine Nanoparticles compressed as a sublingual tablet (SL3).

In vitro dissolution of the prepared Sublingual tablets

Figure 7 illustrates the in vitro dissolution profiles of the prepared SLT formulations in comparison with the F6 (TZ-NP) and pure TZ powder. The dissolution profile comparison reveals that raw Tizanidine powder (TZ) shows the slowest and lowest drug dissolution. Nanoparticles before lyophilization (F6) exhibit slightly improved dissolution due to enhanced surface area [50]. The sublingual tablets without superdisintegrant (SLT1) show low dissolution, reflecting slower tablet disintegration. In contrast, SLT2, SLT3, and SLT4, formulated with increasing

amounts of superdisintegrants, demonstrate significantly enhanced dissolution rates, achieving near-complete release rapidly due to faster tablet disintegration and improved drug wettability.

SLT3 displays the best dissolution, highlighting the critical role of superdisintegrants in promoting rapid drug release from lyophilized nanoparticle tablets [51].

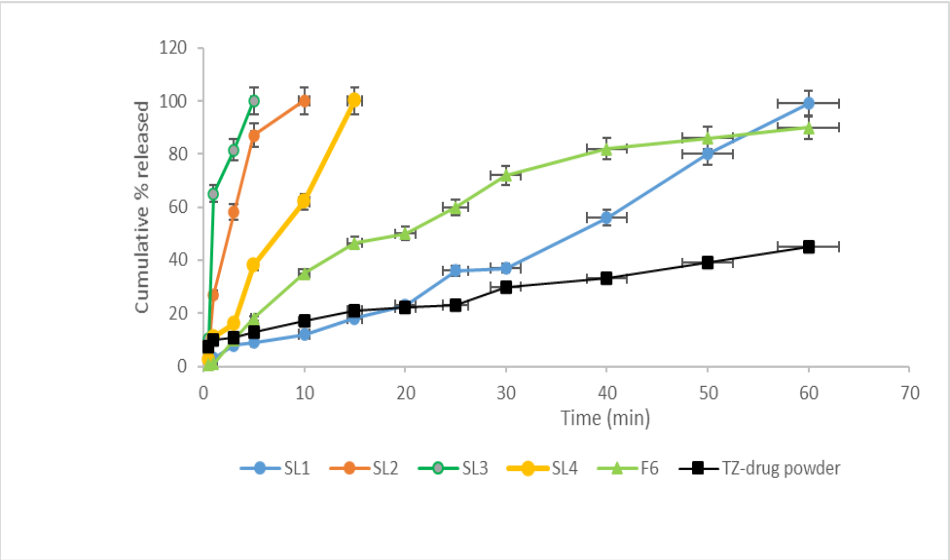

Figure 7. The release profile of TZ(PURE DRUG), TZ NPs(F6), and SLT1-SL4.

Conclusion

This study successfully enhanced the solubility and dissolution of Tizanidine, a poorly soluble BCS Class II drug, by preparing nanoparticles using Soluplus and glycerol via the solvent anti-solvent method. The optimized formulation (F6) achieved a small particle size with high drug content and entrapment efficiency, demonstrating complete drug release within 75 minutes. Transforming F6 nanoparticles into lyophilized sublingual tablets with superdisintegrants produced SL3 tablets exhibiting rapid disintegration within 40 seconds and complete dissolution in just 5 minutes. This formulation approach offers a promising strategy for improving Tizanidine's bioavailability and therapeutic efficacy, enhancing patient compliance with a rapid onset of action.

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Ethics statement: None

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