RESEARCH ARTICLE

Design Strategies for Improving Oral Bioavailability of Tizanidine: Solid Dispersion Approach

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ABSTRACT

Tizanidine is a poorly soluble drug that helps relax muscles and lower mild blood pressure. Solid dispersion of tinidazole may improve the solubility of the drug. The method involved mixing tizanidine with Soluplus in different amounts using a simple tumbling method for 15 minutes. The mixtures were then stored in a desiccator. These mixtures, in different ratios (5:5, 4:6, 3:7, 2:8), were dissolved in ethanol. Tablets were made using a tablet machine with direct compression. The tablets were tested for thickness, breakability, hardness, drug content, disintegration time, wetting time, how fast the drug was released, and stability. The optimized batch (F9) showed that the drug followed a steady release pattern, with an R^2 value of 0.984. Stability studies, done under specific conditions (40°C ± 2°C/75% ± 5%RH), showed no chemical or physical changes and no noteworthy drop in drug content. The pharmacokinetic study revealed that the height concentration (Cmax) was 97.53 ng/mL, and the drug's half-life was 1.75 hours. The formulation was optimized using a design that tested different combinations of two factors: the amount of crospovidone (superdisintegrant) and camphor (subliming agent). The goal was to improve disintegration time and friability.

Keywords: Tizanidine, Solid dispersion, Soluplus, Antihypertensive, Pharmacokinetic profile, Dissolution kinetics.

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INTRODUCTION

Tizanidine, an imidazoline derivative, acts as a non-selective α-2 adrenergic agonist.[1] It is commonly used as a muscle relaxant and a mild antihypertensive agent. By blocking nerve impulses that transmit pain to the brain, it helps manage muscle spasticity by temporarily relaxing muscle tone.[2] Tizanidine is short-acting and is usually taken up to three times daily, with doses spaced 6 to 8 hours apart. It has a half-life of about 3 hours and is metabolized primarily by the CYP1A2 enzyme.[3] The drug has a bioavailability of 34 to 40% and binds to plasma proteins at a rate of 30%.[4,5] A significant challenge in pharmaceuticals is improving the solubility of poorly aqueous soluble drugs.[6] Various methods have been developed to address this issue, such as micronization, inclusion complexation, and salt formation.[8-10] Among these, solid dispersion denotes a straightforward and effective technique.[11-16] This method involves reducing the drug particle size to enhance solubility and dissolution rate.[17-19] Solid dispersion allows for better dissolution and bioavailability when a drug is combined with soluble carriers. By reducing the particle size, solid dispersion often achieves improvements in dissolution that are difficult to attain with other methods.[20-23]

The optimization process used a 3^2 full factorial design with two factors at three levels, evaluating all possible combinations to refine the process parameters. The independent variables were: Factor A (amount of superdisintegrant crospovidone) and factor B (amount of subliming agent camphor). The dependent parameters were disintegration time and friability.

In this study, fast-dissolving TZD tablets were prepared using the solid dispersion technique. Solid dispersions were created via the solvent evaporation method, employing crospovidone as the carrier at various ratios.

MATERIALS AND METHODS

Tizanidine hydrochloride (TZD) was obtained from Sun Pharmaceutical Industries Ltd. As a gift sample, croscarmellose sodium (CCS) and crosspovidone were obtained as gift samples from DVM International and Isap. Tech, respectively. Other polymers and solvents which were used during the research were purchased from different companies.

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Preparation of Solid Dispersion of TZD

A Physical Mixture (PM) was prepared using a co-solvency method. TZD and soluplus were mixed in different ratios (5:5, 4:6, 3:7, and 2:8) by tumbling for 15 minutes. The homogeneous PM was stored in a desiccator. Each mixture was dissolved in anhydrous ethanol, and the organic solvent was evaporated by rotary evaporation. The samples were then dried in a vacuum dryer, ground, and sieved through a 60-mesh screen. This process was repeated three times.

Characterization of physical mixture and solid dispersion of tizanidine HCL

- *Percentage yield*

Prepared physical mixtures and solid dispersions were collected and weighed to determine practical yield from the following equation:[20]

$$\%Practical\ Yield = (Practical\ Mass\ of\ Solid\ Dispersion\ /\ (Theoretical\ Mass\ (Drug + Carrier)) \times 100$$

- *Determination of drug content*

Weighed 38 mg of tizanidine in solid dispersions/physical mixtures, transferred to a 500 mL volumetric flask, and added 70% of the total volume with distilled water. Shook to dissolve completely, then filled to the mark with distilled water. Measured the absorbance of this solution at the specified wavelengths against a reagent blank.[24]

- *Preparation of tablets containing SD of TZD*

The tablets were made using a direct compression method with a tablet punch machine (Model No. RTN-500, Rolex Scientific). This means the tablets were pressed from a mix of the drug and other ingredients without any extra steps like granulation. Initially, six trial batches were made to find the best superdisintegrants. Based on these results, more experiments were done to develop the best formulation. Each tablet had a solid dispersion of the drug (equal to the TZD dose), mannitol, MCC, starch, magnesium stearate, talc, and superdisintegrants. The weight of each tablet was kept the same in all batches, and 50 tablets were made for each batch. The effects of the superdisintegrants on the tablets' properties and how they dissolved were studied and discussed.

- *Evaluation of TZD tablets*

The tablets were tested for friability, hardness, thickness, disintegration time, wetting time, drug content, dissolution, and stability. Hardness was measured with a Pfizer hardness tester by pressing the tablet between plungers and recording the force needed to break it. Thickness was measured with calipers during compression. Friability was assessed using a Roche friability by weighing two tablets, running them through 100 revolutions, and then re-weighing them after dust removal.[25-27] The percentage of friability was calculated using a specific formula.

$$F = (1 - W\_(0\ )/W)\ X\ 100$$

Here's a concise version

W_0 is the initial weight of tablets, and after testing W, the final weight. Six tablets per formulation were tested. For disintegration time, tablets were placed in 100 mL distilled water at 37 ± 2ºC, and the time to complete dispersion was measured using a digital disintegration apparatus. In the wetting time test, a folded tissue in a 6.5cm petri dish with 5 mL distilled water was used; the time for the tablet to fully wet was recorded. For drug content, tablets were weighed, crushed, diluted to 250 mL with phosphate buffer pH 6.6, filtered, and analyzed *via* UV spectrophotometry at 228nm (UV-1700 Shimadzu). The *in-vitro* dissolution study used a USP dissolution tester (Electrolab TDT-08 L), with 900 mL phosphate buffer pH 6.6 at 37 ± 0.5ºC and 50 rpm paddle speed.[28-30] Samples were withdrawn and analyzed after dilution, and filteration, by UV spectrophotometry at 228nm. Stability studies followed ICH guidelines, storing tablets at 40 ± 2ºC/75 ± 5% RH for three months in a stability chamber (Lab Care, Mumbai).

RESULTS AND DISCUSSION

Melting Point Determination by DSC Analysis.

The DSC thermogram of tizanidine HCl (Figure 1a) showed a sharp melting endotherm at 189.25°C with an enthalpy of 113.62 J/g. The thermogram of soluplus (Figure 1b) displayed a peak at 86.70°C (408.01 J/g).

Compatibility Studies

The IR absorption spectra of tizanidine were obtained and characteristic bands obtained were compared with the reference as depicted in Figure 2, which showed the characteristic peaks of some functional groups.[31-33] The FTIR spectral analysis of TZD (pure drug) reveals that characteristic absorption bands cm^{-1} appeared at 3242 (NH), 1530.95 (C=N), 1642.92 (C=N) and 747.89 (Ar-Cl) of drug (Figure 2) which are similar to the values, i.e., 3246 (NH), 1540 (C=N), 1647.28 (C=N) and 750 (Ar-Cl) mentioned in previous literature, confirmed that drug is tizanidine HCl (Figure 2a). Figure 2b of the solid dispersion does not exhibit any shifts or alterations in the characteristic bands. This indicates the compatibility of the chosen drug and solubilizer within the solid dispersion blend.

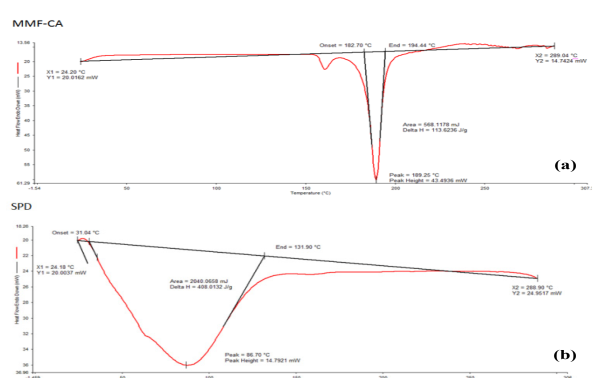

Figure 1: (a) Thermogram of tizanidine HCl (Pure Drug) and (b) Thermogram of Soluplus

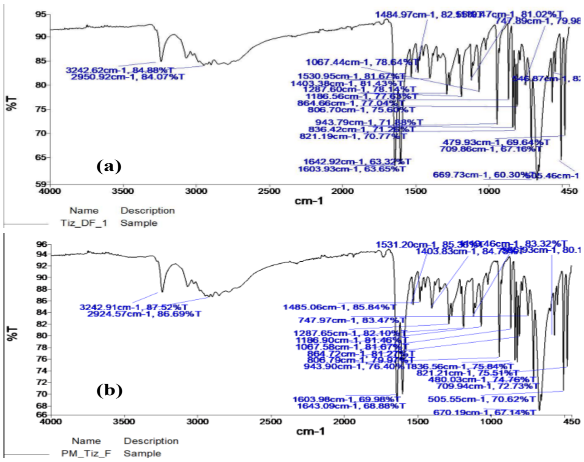

Figure 2: FTIR spectra of (a) pure drug tizanidine HCl and (b) Solid dispersion

Saturation Solubility Study

Solubility of tizanidine in distilled water and other solvents.

The solubility of tizanidine was determined in distilled water and other solvents also. The results denoted that the solubility of tizanidine was decreased as the pH of the system increased as shown in Figure 3. The maximum solubility was found to be 65.85 ± 2.01 mg/mL in 0.1N hydrochloric acid and the minimum in chloroform as 0.74 ± 0.012 mg/ml.

Formulation and Evaluation of Solid Dispersion

Phase solubility Study of TZD with Soluplus.

The phase solubility assay consisted of introducing 10 mg of tizanidine into a sealed glass vial filled with 10 ml of water with different doses of Soluplus® (0–10 mg/mL). The samples were subjected to sonication for 30 minutes at ambient temperature, followed by incubation in a water bath, stirring at 60 revolutions per minute at 37 ± 0.1°C for 48 hours. Following incubation, the filtrate was diluted with methanol and subjected to analysis by UV-Visible Spectrophotometry. The solubility of tizanidine rose as the concentration of Soluplus® increased, with concentrations of 2, 4, 6, 8, and 10 mg/mL correspondingly yielding values of 188.67, 229.17, 399.28, 484.64, and 621.87 µg/mL. Soluplus® functions as a Solubility Enhancer via the formation of micelles, therefore enhancing the dissolving and bioavailability of drugs in different formulations.31,32

Development of Physical combination and Solid dispersion of Tizanidine HCl

Preparation of Physical mixture (PM) of Tizanidine HCl.

PM was softly made by combining tizanidine and soluplus in varied ratios using simple tumble technique for 15 minutes. Furthermore, the produced homogenous PM was kept in a desiccator.

Preparation of Tizanidine HCl Solid Dispersion (HSD)

Mixtures of the active agent and polymer at weight-to-weight ratios of 5:5, 4:6, 3:7, and 2:8 were mixed together in a solution of anhydrous ethanol. The organic solvent was removed by rotary evaporation. Then, the resultant mixtures were further dried in a vacuum dryer. The dry materials were crushed and sieved through a 60-mesh screen to produce homogeneous particle sizes. Each experiment was done in triplicate.

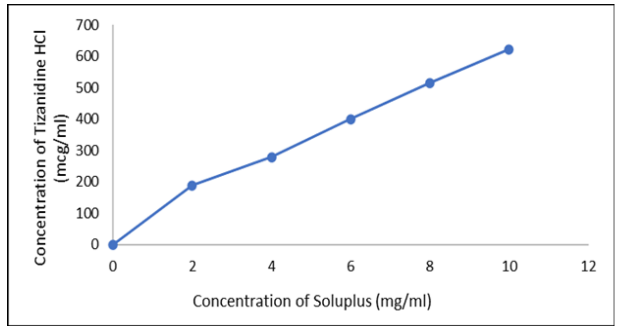

Figure 3: Phase solubility profiles of tizanidine HCl in water–soluplus mixtures

Characterization

Percentage yield

The practical yield of developed physical combinations and solid dispersions using soluplus were determined and the results, Active agent: polymer ratio (5:5, 4:6, 3:7, 2:8), Practical yield (%) of both PM and HSD decreased (75.81, 70.54, 65.49, and 61.32) and (77.95, 72.38, 68.85, 65.47) respectively (Table 1). The percentage yield was decreased with increasing the concentration of Soluplus in both physical combinations and solid dispersion.

Drug content

The drug content of the generated physical combination and solid dispersion was determined and results were depicted as increases in drug content with an increment of Soluplus ratios, as in Table 1. The findings revealed that the drug content was enhanced by increasing the concentration of Soluplus and the greatest value in a ratio of 2:8 (Drug:Soluplus).

Development of Solid Dispersion

Preparation of tablets

Firstly, six experimental batches were generated by utilizing two superdisintegrants to study the individual effect of the single superdisintegrant, which were further optimized by Central composite design (CCD). The prepared trial batches were also tested for pre-compression as well as post-compression characteristics (Table 2).

Pre-compression characteristics for experimental batches

Table 1: Determination of drug content in physical combination and solid dispersion of tizanidine HCl

Drug: Soluplus ratio	*Drug content (%)*		*Practical yield (%)*	
	PM	*HSD*	*PM*	*HSD*
5:5	96.06	97.57	75.81	77.95
4:6	96.78	98.15	70.54	72.38
3:7	97.38	98.70	65.49	68.85
2:8	98.35	99.67	61.32	65.47

1 PM: Physical mixture, HSD: Tizanidine solid dispersion.

Table 2: Determination of drug content in physical combination and solid dispersion of tizanidine HCl

Formulation code	*Bulk density (gm/cc)*	*Tap density (gm/cc)*	*Angle of repose (θ)*	*Carr's index (%)*	*Hausner's ratio*
T_1	0.631	0.691	27.51	8.683	1.095
T_2	0.678	0.729	25.32	6.995	1.075
T_3	0.662	0.698	26.55	5.157	1.054
T_4	0.668	0.715	25.43	6.573	1.070
T_5	0.679	0.719	27.23	5.563	1.058
T_6	0.679	0.727	28.23	6.602	1.070

Table 3: Determination of drug content in physical mixture and solid dispersion of tizanidine HCl

Formulation code	*Thickness (mm)*	*Weight variation*	*Hardness (kg/cm²)*	*Friability (%)*	*Disintegration time (sec)*
T_1	3.51	Passes	3.71	0.456	165
T_2	3.53	Passes	3.50	0.452	145
T_3	3.63	Passes	3.30	0.538	140
T_4	3.64	Passes	4.55	0.581	120
T_5	3.61	Passes	4.65	0.673	126
T_6	3.57	Passes	4.50	0.625	90

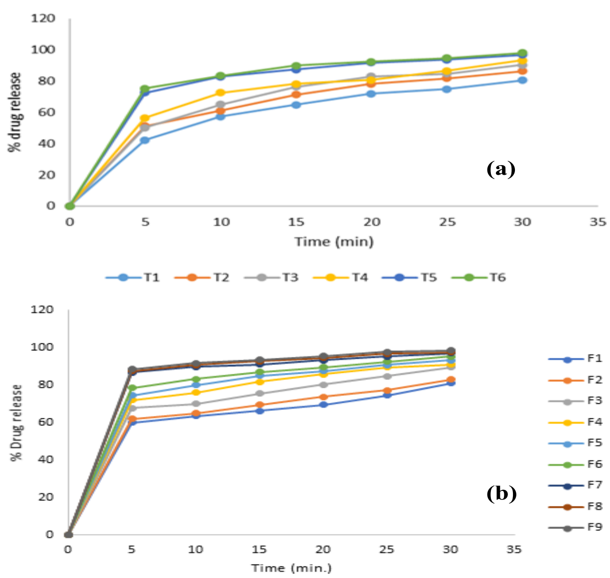

Figure 4: Comparative release profile of (a) trial batches of formulations T1-T6 and (b) desiged batches of formulations F1-F9 in acidic buffer pH 1.2

Pre-compression characteristics were measured as illustrated in Table 2.

Post-compression characteristics of trial batches

Post compression characteristics were measured as illustrated in Table 3.

In-vitro *dissolution studies of trial batches*

The prepared trial batches of Tizanidine solid dispersion tablets were determined for *in-vitro* dissolution study and results were depicted in Figure 4. *The in-vitro* dissolution profile of formulations T1- T6 in pH 1.2 Acidic buffer was found to be 90.38, 96.77, 98.19, 80.55, 86.34, and 90.27, respectively. Out of six trial batches, T3 shows maximum releases (98.19%) in 30 minutes.

Table 4: 3^2 Full factorial design layout

Formulation code	*Variable levels in coded form*		*Responses*	
	X1(Cross povidone)	*X2 (Camphor)*	*Disintegration time*	*%Friability*
F1	-1	-1	83	0.138
F2	-1	0	75	0.189
F3	-1	1	69	0.223
F4	0	-1	62	0.315
F5	0	0	53	0.355
F6	0	1	42	0.383
F7	1	-1	35	0.422
F8	1	0	32	0.456
F9	1	1	30	0.499
Coded values	Actual value			
	X1(%)	X2(%)		
-1	1	0		
0	3	2.5		
1	5	5		

Optimization by 3^2 factorial design

A 3² full factorial design was employed to optimize the variables in this study. Two independent formulation variables, cross povidone (1, 3, 5%) and camphor (0, 2.5, 5%), were tested at three levels, resulting in 9 experimental trials. The dependent variables were disintegration time (DT) and percentage friability (see Table 4).

Pre-compression (Micrometric) parameters for formulations of 3^2 factorial designs.

Pre-compression parameters were assessed for various blends (F1-F9) formulations. Based on trial batches (T1-T6), batch T6 was selected for a 3^2 full factorial design. Consequently, F1-F9 batches were evaluated for pre- and post-compression parameters (Table 5).

Table 5: Results of precompression parameters for batches F1-F9

Formulation code	*Variable levels in coded form*		*Responses*		
	Bulk Density (gm/cc)	*Tapped density (gm/cc)*	*Angle of repose (θ)*	*Carr's index*	*Hausner's Ratio*
F1	0.659	0.705	28.28	6.524	1.06
F2	0.667	0.715	27.31	6.713	1.07
F3	0.669	0.727	26.45	7.977	1.08
F4	0.649	0.698	27.34	7.020	1.07
F5	0.667	0.729	27.65	8.504	1.09
F6	0.669	0.718	27.42	6.824	1.07
F7	0.667	0.715	26.55	6.713	1.07
F8	0.661	0.727	28.48	9.078	1.09
F9	0.685	0.729	25.35	6.035	1.06

Table 6: Result of post compression parameters for batches F1-F9

Formulation code	*Variable levels in coded form*		*Responses*		
	Thickness (mm)	*Weight variation*	*Hardness (kg/cm²)*	*Friability (%)*	*Disintegration time (sec)*
F1	3.75	Passes	3.55	0.138	83
F2	3.79	Passes	4.68	0.189	75
F3	3.68	Passes	5.05	0.223	69
F4	3.72	Passes	3.00	0.315	62
F5	3.73	Passes	5.00	0.355	53
F6	3.77	Passes	7.00	0.383	42
F7	3.71	Passes	3.00	0.422	35
F8	3.78	Passes	5.00	0.456	32
F9	3.76	Passes	7.00	0.499	30

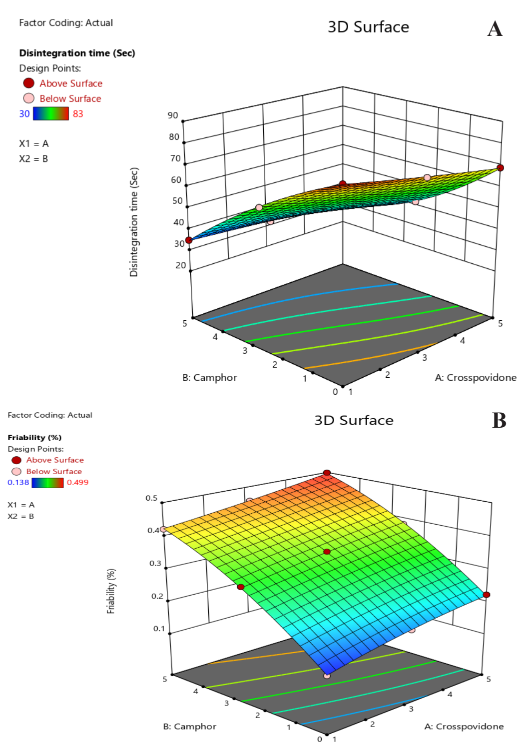

Figure 5: The influence, response surface graphs, of crospovidone and camphor concentration on (a) disintegration time and (b) % friability

Post-compression parameters for formulations of 3^2 factorial design.

The tablet formulation batches were evaluated for thickness, weight, hardness, and dissolution. Results are in Table 6.

In-vitro dissolution studies

The Tizanidine HCl solid dispersion factorial batches prepared were also assessed for *in-vitro* dissolution of formulations F1-F9 in pH 1.2 acidic buffer. The results reveal that the highest dissolution was observed in F9 (98.51%), while the lowest was in F1 (81.09%) after 30 minutes of study as depicted in Figure 4(b). All the designed batches were shown to release greater than 80%, so solid dispersion had higher solubility as compared to drug:soluplus mixture.

Numerical optimization solution for check point analysis.

Using the models you built in the analysis, numerical optimization will examine the design space for factor settings that fulfill the goals you specified. To begin, you must have good models (garbage in, garbage out). Then, you establish the objectives for each response. Finally, the software will provide a list of possible factor settings that will result in results that fit the criteria you specified. The experimentally measured parameters of disintegration time and %friability were shown in the optimal grafting (Table 7, Figures 5a and b).

Table 7: Independent factors and their goals

Name	*Goal*	*Lower limit*	*Upper limit*	*Lower weight*	*Upper weight*	*Importance*
A: Crospovidone	maximize	1	5	1	1	4
B: Camphor	maximize	0	5	1	1	3
Disintegration time	minimize	30	83	1	1	3
Friability	is in range	0.138	0.499	1	1	3

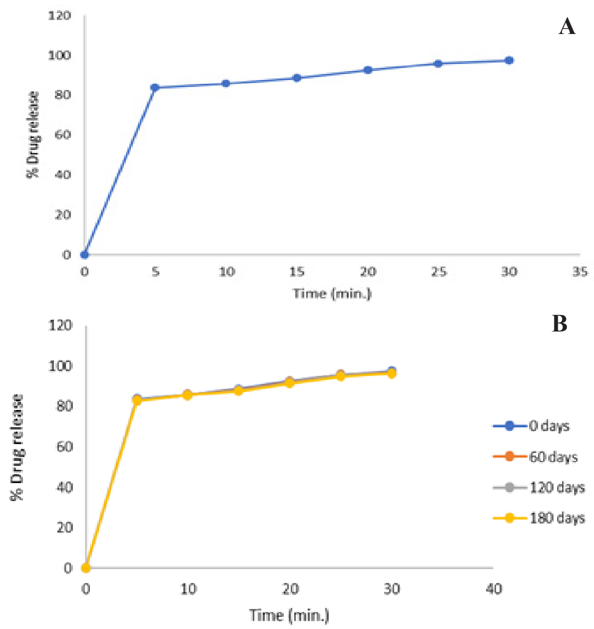

Figure 6: Percent (%) Drug release profile of (a) Optimized batch formulation and (b) Optimized batch of formulation at different time intervals of stability studies in pH 1.2 acidic buffer

The software-suggested optimum batch was formulated and assessed for various parameters.

The predicted solution for the optimized batch entails factor A set at 5.00 and factor B also at 5.00. The percentage friability stands at 0.496, with the disintegration time (DT) recorded at 29.80 seconds. Achieving a desirability score of 1.000, this configuration is deemed highly favorable. Consequently, it has been selected for further consideration and implementation.

A checkpoint batch (optimized formulation) was selected at X1= 5.0 andX2=5.0% to confirm the predicted replies of percentage friability and disintegration time. The F9 batch has the same composition as of predicted solution and nearer values of dependent factors, i.e., disintegration time and %friability. Thus, formulation F9 was considered as an optimized batch for further studies. Further, the *in-vitro* dissolution profile of the optimized dosage batch was shown to be 97.50 ± 0.25 in 30 minutes (Figure 6a).

The mechanism of drug dissolution was determined with prepared Tizanidine HCl solid dispersion (2:8) and were separately put to kinetic models, i.e., zero-order, first-order, Korsmeyer-Peppas with Higuchi. The release kinetic study of the optimized batch (F9) revealed that the drug has followed the zero-order release as showing maximum R2 (0.984).

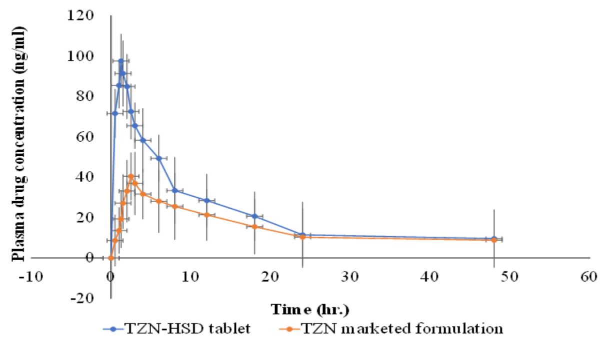

Figure 7: Pharmacokinetic profile of tizanidine HSD tablet and tizanidine marketed tablet

Stability study of optimized formulation

Stability studies were conducted in accordance with ICH guidelines under accelerated conditions (40 ± 2°C/75 ± 5% RH), revealing no discernible physicochemical alterations. Additionally, no significant drop in Tizanidine HCl content was observed. Observations from the stability studies over a period of 180 days under accelerated conditions (40 ± 2°C/75 ± 5% RH) for appearance, %friability, and disintegration time (in seconds) indicated consistent results with no change, 0.496 and 0.495, 29.80 and 29.79, respectively. These findings affirm that the optimized batch of the formulation remained stable throughout the duration of the stability studies.

Release profile of optimized batch of formulation.

The drug release was assessed at intervals of 0, 60, 120, and 180 days, revealing release percentages of 97.50, 96.88, 96.65, and 96.42, respectively. Notably, no variations in the release of the drug were observed. This indicates that the optimized batch of the formulation remained stable, maintaining a consistent release profile even after 180 days of accelerated stability studies (Figure 6b).

In-vivo study

A bioequivalence study was conducted to compare the pharmacokinetics of tizanidine from a hydrotropic solid dispersion (HSD) formulation with a conventional zanaflex tablet. The pharmacokinetics were assessed using HPLC to measure tizanidine levels in rabbit plasma and to evaluate the *in-vivo* performance of the HSD tablet. A crossover study design was employed, using oral solutions of zanaflex and HSD tablets administered to albino rabbits. Plasma concentration-time profiles of the formulations were analyzed, and the pharmacokinetic parameters are detailed in Figure 7.

PK solver was used to analyze the pharmacokinetic parameters of TZN in HSD tablets. Results showed a Cmax of 97.53 ng/mL and an average half-life (t½) of 1.75 hours. In comparison, the standard marketed tablet had a Cmax of 40.45 ng/mL and a t½ of 3.5 hours. The HSD tablets demonstrated a 2-fold increase in bioavailability and approximately a 2-fold reduction in half-life, indicating a significant rise in plasma concentration after buccal administration.

CONCLUSION

The results from this study, following the administration of the oral solution, were lower than those reported by Henney, H.R. *et al*. (2008) for buccal TZN. This suggests that TSD tablets offer an improved pharmacokinetic profile compared to the oral solution. However, the observed tmax values (1.25 hours for TSD tablets and 2.5 hours for marketed tablets) align with the findings of Galal M. and colleagues (2014). The AUC0-24 and AUC0-∞ values were 1095.56 ng h/mL and 1278.386 ng h/mL, respectively. These higher values indicate enhanced release and bioavailability compared to the standard TZN-marketed tablets. Additionally, these results were more favorable than those reported by Muhammad Zaman and his research team.

REFERENCES

1. Leiphart JW, Dills CV, Levy RM. Alpha-2-adrenergic receptor subtype specificity of intrathecally administered tizanidine used for analgesia for neuropathic pain. J of Neurosurgery. 2004;101(4):641-7. Doi.org/10.3171/jns.2004.101.4.0641
2. Zhu LL, Wang YH, Zhou Q. Tizanidine: Advances in pharmacology & therapeutics and drug formulations. Journal of Pain Research. 2024;1257-71. Doi.org/10.2147/JPR.S461032.
3. Mohsen AM, El-Hashemy HA, Salama A, Darwish AB. Formulation of tizanidine hydrochloride–loaded pro vesicular system for improved oral delivery and therapeutic activity employing a 2^3 full factorial design. Drug Delivery Translational Research. 2023;13(2):580-92. Doi.org/10.1007/s13346-022-01217-3
4. Sinha S, Thapa S, Singh S, Dutt R, Verma R, Pandey P, Mittal V, Rahman MH, Kaushik D. Development of biocompatible nanoparticles of tizanidine hydrochloride in orodispersible films: *In-vitro* characterization, Ex-*vivo* permeation, and cytotoxic study on carcinoma cells. Current Drug Delivery. 2022;19(10):1061-72. Doi.org/10.2174/1567201819666220321111338
5. Malanga G, Reiter RD, Garay E. Update on tizanidine for muscle spasticity and emerging indications. Expert Opinion on Pharmacotherapy. 2008;9(12):2209-15. Doi.org/10.1517/14656566.9.12.2209
6. Pardhi E, Vasave R, Srivastava V, Yadav R, Mehra NK. Nanocrystals technologies in biomedical science: Bench to beside the clinic. Drug Discovery Today. 2024:103913. Doi.org/10.1016/j.drudis.2024.103913
7. Kumar N, Dureja H, Chandra A. Enhancement of drug dissolution of erlotinib tablets by micronization technique using pharmaceutical experimental design. Journal of Pharmaceutical Research International. 2021;33(51):70-8. Doi.org/10.9734/jpri/2021/v33i51A33470
8. Semalty A. Cyclodextrin and phospholipid complexation in solubility and dissolution enhancement: a critical and meta-analysis. Expert Opinion on Drug Delivery. 2014;11(8):1255-72. Doi.org/10.1517/17425247.2014.916271
9. Bhalani DV, Nutan B, Kumar A, Singh CK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines 2022;10(9):2055. Doi.org/10.3390/biomedicines10092055
10. Serajuddin AT. Salt formation to improve drug solubility. Adv Drug Delivery Reviews. 2007;59(7): 603-16. Doi.org/10.1016/j.addr.2007.05.010
11. Hermans A, Milsmann J, Li H, Jede C, Moir A, Hens B, Morgado J, Wu T, Cohen M. Challenges and strategies for solubility measurements and dissolution method development for amorphous solid dispersion formulations. AAPSJ. 2022;25(1):11. Doi.org/10.1208/s12248-022-00760-8
12. Nakkala RK, Maddiboyina B, Bolisetti SC, Roy H. Duloxetine hydrochloride enteric-coated pellets in capsules with delayed release: formulation and evaluation. Smart Sci. 2023;11(3):434-446. Doi.org/10.1080/23080477.2023.2191496
13. Pandi P, Bulusu R, Kommineni N, Khan W, Singh M. Amorphous solid dispersions: An update for preparation, characterization, mechanism on bioavailability, stability, regulatory considerations and marketed products. Intenational Journal of Pharmaceutics. 2020;586:119560. Doi.org/10.1016/j.ijpharm.2020.119560
14. Maddiboyina B, Nakkala RK, Kokkilagadda VK. Preparation and evaluation of esomeprazole enteric coated tablets. IJPPR. 2020;18(1):16–30.
15. Zhang X, Xing H, Zhao Y, Ma Z. Pharmaceutical dispersion techniques for dissolution and bioavailability enhancement of poorly water-soluble drugs. Pharmaceutics. 2018; 10(3):74. Doi.org/10.3390/pharmaceutics10030074
16. Sood S, Maddiboyina B, Rawat P, Garg AK, Foudah AI, Alam A, Aldawsari HM, Riadi Y, Singh S, Kesharwani P. Enhancing the solubility of nitazoxanide with solid dispersions technique: formulation, evaluation, and cytotoxicity study. J Biomater Sci Polym Ed. 2021 Mar;32(4):477-87. Doi: 10.1080/09205063.2020.1844506
17. Wang X, Zhang L, Ma D, Tang X, Zhang Y, Yin T, Gou J, Wang Y, He H. Characterizing and exploring the differences in dissolution and stability between crystalline solid dispersion and amorphous solid dispersion. AAPS PharmSciTech. 2020; 21:1-15. Doi.org/10.1208/s12249-020-01802-0
18. Maddiboyina B, Jhawat V, Nakkala RK, Desu PK, Gandhi S. Design expert assisted formulation, characterization and optimization of microemulsion based solid lipid nanoparticles of repaglinide. Prog Biomater. 2021;10(4):309-20. DOI: 10.1007/s40204-021-00174-3
19. Giri BR, Kwon J, Vo AQ, Bhagurkar AM, Bandari S, Kim DW. Hot-melt extruded amorphous solid dispersion for solubility, stability, and bioavailability enhancement of telmisartan. Pharmaceuticals. 2021;14(1):73. Doi.org/10.3390/ph14010073
20. Sharma U, Saroha KA. Review of hydrotropic solubilization techniques for enhancing the bioavailability of poorly soluble drugs. International Journal of Toxicology. 2024;43(1):63-71. Doi.org/10.1177/10915818231216414
21. Vasam M, Maddiboyina B, Talluri C, *et al*. Formulation, characterization, and Taguchi design study of eplerenone lipid-based solid dispersions integrated with Gelucire. BioNanoSci. 2023;13:576–587. Doi.org/10.1007/s12668-023-01102-4
22. Ainurofiq A, Putro DS, Ramadhani DA, Putra GM, Santo LD. A review on solubility enhancement methods for poorly water-soluble drugs. Journal of Pharmaceutical Sciences. 2021;10(1):137-47. Doi.org/10.4103/jrptps.JRPTPS_134_19
23. Maddiboyina B, Nakkala RK, Sivaraman G. Biomass-derived

mesoporous carbon nanomaterials for drug delivery and imaging applications. In: Biomass-Derived Carbon Mater. 2022. p. 129–46. Doi.org/10.1002/9783527832903.ch6
24. Ghatmale R, Pathan VT. Formulation and evaluation of sublingual tablet of edoxaban by solid dispersion method. International Journal of Pharmaceutical Sciences Review and Research. 2023;1(2):115-28. Doi.org/10.5281/zenodo.8019467
25. Mohapatra D, Kumar DN, Shreya S, Pandey V, Dubey PK, Agrawal AK, Sahu AN. Quality by design-based development and optimization of fourth-generation ternary solid dispersion of standardized *Piper longum* extract for melanoma therapy. Drug Delivery Translational. Research. 2023;13(12):3094-31. Doi.org/10.1007/s13346-023-01375-y
26. Sohn JS, Choi JS. Development and evaluation of febuxostat solid dispersion through screening method. Saudi Pharmaceutical Journal. 2023;31(9):101724. Doi.org/10.1016/j.jsps.2023.101724
27. Maddiboyina B, Shanmugapriya J, Rasala S, Sivaraman G. In bioinspired nanomaterials: synthesis and emerging applications. Materials Research Forum LLC. 2021;111:63-95. DOI: https://doi.org/10.21741/9781644901571-3
28. Eisa AM, El-Megrab NA, El-Nahas HM. Formulation and evaluation of fast dissolving tablets of haloperidol solid dispersion. Saudi Pharmaceutical Journal. 2022;30(11):1589-02. Doi.org/10.1016/j.jsps.2022.09.002
29. H. Roy, B. Maddiboyina, SA. Rahaman, PK. Singh, AK. Tripathi, SK. Srivastava, R. Chaubey, VK. Theendra, KR. Sankula, Implementation and effect estimation by Taguchi orthogonal array design for Metoprolol Sustained Release Tablets. Smart Sci., 11 (2023) 649–660. Doi.org/10.1080/23080477.2023.2236778
30. Maddina BY, Asthana GS, Asthana A. A review of current scenario of spirulina drug delivery systems. World J Pharm Sci. 2016;4:86-9.
31. Maddiboyina B, Jhawat V, Sivaraman G, Sunnapu O, Nakkala KR, Naik HM, Gulia M. Formulation development and characterization of controlled release core-in-cup matrix tablets of venlafaxine HCl. Curr Drug Ther. 2020;15(5):503-11. Doi.org/10.2174/1574885515666200331104440
32. Attia MS, Elshahat A, Hamdy A, Fathi AM, Emad-Eldin M, Ghazy FES, Chopra H, Ibrahim TM. Soluplus® as a solubilizing excipient for poorly water-soluble drugs: recent advances in formulation strategies and pharmaceutical product features. Journal of Drug Delivery Science and Technology. 2023:104519. Doi.org/10.1016/j.jddst.2023.104519
33. Singh C, Yashwant, Gupta AK, Garg V. Formulation Development and Evaluation of Divalproex Sodium Extended-release Tablets. International Journal of Drug Delivery Technology. 2022;12(4):1769-1773.DOI: 10.25258/ijddt.12.4.46