Solid Self Nanoemulsifying Drug Delivery System as carrier for the enhancement of bioavailability of Benidipine with Telmisartan.

Sheetal S. Buddhadev[1*], Kevinkumar C. Garala[2], Mukeshkumar Nariya[3], Mohamed Rahamathulla[4]

[1]School of Pharmaceutical Sciences, Atmiya University, Rajkot, Gujarat 360005, India: Faculty of Pharmacy, Noble University, Junagadh, Gujarat 362001, India; sheetal.buddhadev@ngivbt.edu.in

[2]School of Pharmaceutical Sciences, Atmiya University, Rajkot, Gujarat 360005, India; kevincgara-la@gmail.com

[3]Institute of Teaching and Research in Ayurveda, Institute of National Importance, Ministry of Ayush, Jamnagar, Gujarat 361008, India; mukeshnariya@gmail.com

[4]Department of Pharmaceutics, College of Pharmacy, King Khalid University, P. O. Box 62223, Al Faraa, Abha, Saudi Arabia; rahapharm@gmail.com

***Corresponding author: Email: sheetal.buddhadev@ngivbt.edu.in; Tel.: +91-9428419375**

Abstract

Background: Benidipine (BD) and Telmisartan (TEL), co-administered antihypertensive medicines in the BCS class II group, are characterized by inadequate bioavailability due to restricted water solubility. Self-nano emulsifying drug delivery systems (SNEDDS) offer efficient solubilization for weakly water-soluble medicines due to their ternary ingredients' solubilization and nanonization activity, driven by surfactant and cosolvent. SNEDDS formulations comprise surfactants and cosolvents that facilitate nano droplet dispersion.

Objective: This study seeks to investigate the antihypertensive activity of solidified self-nanoemulsifying drug delivery systems (S-SNEDDS) comprising BD and TEL.

Methods: Hypertension was produced in rats with oral 10% glucose treatment for three weeks. Animals were grouped: Group 1 as Normal control, Group 2 as Hypertensive control, Group 3 as Hypertensive treated with S-SNEDDS formulation of BD with TEL, and Group 4 as Hypertensive treated with conventional BD-TEL suspension. Rats with a mean blood pressure ≥150 mm Hg were selected. After baseline blood pressure measurement, Group 3 and 4 animals received oral doses of 4 mg BD and 40 mg TEL/kg from optimized S-SNEDDS and pure drug, respectively. Blood pressure was non-invasively monitored using a tail-cuff sensor and Biopack MP36 data gathering system at intervals of 0, 2, 6, 12, and 24 hours.

Results and Discussion: In contrast to the hypertensive control group, S-SNEDDS treatment contributed to a progressive blood pressure reduction, peaking at 45 minutes and persisting for 75 minutes. This reduction was statistically different from the control group, demonstrating superior hypertension control compared to BD-TEL suspension. The improved water solubility of BD and TEL due to surfactant presence, together with fast globule dispersion, absolutely contributes to the observed antihypertensive benefits of the SNEDDS formulation.

Keywords: Benidipine; Telmisartan; Solidified self-nanoemulsifying drug delivery systems

DOI: 10.48047/ecb/2023.12.6.288

Introduction

Cardiovascular diseases are major public health challenge. Hypertension is among the most important modifiable risk-factors for cardiovascular diseases. Many placebo-controlled trials and meta-analysis study of antihypertensive medication have shown that such treatment can prevent and postpone myocardial infarction and stroke. High blood pressure is responsible for 8.5 million deaths due to cardiovascular complications and kidney related problems [3, 4]. Hence, controlling normal blood pressure is essential.

Hypertension has a vital role in producing cardiovascular diseases (CVDs) such myocardial infarction and stroke worldwide. The worldwide burden of disease due to hypertension has dramatically risen from roughly 4.5% (nearly 1 billion adults) in 2000 to 7% in 2010, as revealed by WHO in 2008. This disorder leads to significant complications with substantial morbidity and mortality, accounting for at least 45% of heart disease-related death and 51% of stroke-related deaths, according to statistics published by WHO in 2008. Notably, hypertension contributes to an annual total of 9.4 million fatalities worldwide. In India, non-communicable diseases account for roughly 63% of total deaths, with 27% caused by cardiovascular disease, hurting 45% of those aged 40-69. Elevated blood pressure stands out as one of the major risk factors for CVDs [5, 6].

Antihypertensive are a class of drugs that are used to treat hypertension (high blood pressure). Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many classes of antihypertensive, which lower blood pressure by different mechanisms. Among the most important and most widely used drugs are thiazide diuretics, calcium channel blockers, Angiotensin-converting enzyme inhibitors (ACE), angiotensin II receptor antagonists (ARBs), and beta blockers.

For most patients with systemic hypertension, long-term medication treatment is indicated and is beneficial. There is strong evidence to suggest that antihypertensive medications offer protection against complications of hypertension. Fortunately, a number of medicines are available to accomplish successful treatment of hypertension conditions. While it is usual to commence treatment with a single medicine, a proper mix of drugs is often necessary to manage blood pressure adequately. Different studies indicated that combination therapy with medicines having a different mechanism of action assists in the effective and speedy management of blood pressure. Combining different types of antihypertensive medicines together is one significant approach for obtaining blood pressure control in most hypertensive individuals. Most of the benefits of combination therapy in contrast with monotherapy include a synergistic effect of each medicine's therapeutic effects and a reduction of side effects due to a lower dose of each drug [7].

Benidipine and Telmisartan are the suggested combinations of calcium channel blockers (CCBs) with angiotensin receptor blockers (ARBs) for the therapy of hypertension because of their anti-proteinuria properties [8]. Benidipine, a powerful and long-acting calcium channel blocker, functions by blocking three subtypes of calcium channels (L, N, and T) and showed a kidney protective effect. It also demonstrated a cardio-preventive effect due to enhanced nitric oxide generation with greater vascular selectivity [9]. Telmisartan, an azole class angiotensin II receptor antagonist, functions by decreasing the release of aldosterone by reversibly binding angiotensin II to the AT1 receptor found on vascular smooth muscle and adrenal glands. Thereby arterial blood pressure is lowered by decreasing the overall vascular resistance. Telmisartan also showed PPAR-γ agonistic function, which has positive effects on carbohydrate metabolism and antidiabetic property [10-11].

However, the effectiveness of Benidipine with It as an anti-hypertensive drug was disputed by its poor water solubility and low absorption after oral administration. Benidipine is the medicine of BCS class II with poor oral bioavailability. Benidipine has a considerable proportion of hepatic first-pass metabolism and a high lipophilicity (log P of 4.28). Similarly, Telmisartan is a BCS class II drug with poor solubility and high permeability. It is practically insoluble in water (0.0035 mg/mL) and has a high log P 7.7 with barely 50% oral bioavailability [12]. Telmisartan is often used with other antihypertensive drugs such as calcium channel blockers in scenarios of hypertension with renal failure settings. In order to enhance the bioavailability and solubility of Benidipine with Telmisartan solid self-emulsifying drug delivery devices were developed.

The self-nano emulsifying drug delivery system (SNEDDS) is receiving interest in pharmaceutical companies due to the success of medications like Norvir ®, Sandimmune ®, Fortavase ®, and Neoral ®. SNEDDS mixes medicines (typically water-insoluble), lipids, surfactants, and cosurfactants to generate small oil-in-water nanoemulsions (particle size < 100 nm) when exposed to mild agitation or digestive processes in the GI tract. This improves drug solubility, absorption, and intestinal lymphatic transfer [13,14]. Mechanisms include improved cell absorption, greater paracellular trafficking, and suppression of cellular activities. SNEDDS has been found to improve oral absorption of numerous medicines by utilizing distinct pathways. Recent findings highlight its applicability to increasing the oral bioavailability of weakly water-soluble medicines [15, 16].

Self-nano emulsifying drug delivery systems (S-SNEDDS) of Benidipine with Telmisartan were developed by systematically utilizing a quality-by-design (QbD)-based paradigm. Utilizing Eucalyptus Oil, Kolliphor EL, and Transcutol P, BD with TEL-SNEDDS were created. Box-Behnken design (BBD) was used to construct and optimize many variables for BD using TEL-SNEDDS. S-SNEDDS were generated utilizing the adsorption process and evaluated using FTIR, DSC, SEM and PXRD. As compared to the pure drug and the commercial product, optimized S-SNEDDS of BD and TEL revealed a drug release rate of > 95% within 60 minutes for both BD and TEL.

The goal of the present research work is to investigate the pharmacodynamics activity of S-SNEDDS of Benidipine with Telmisartan in Albino rats. The Pharmacodynamics efficacy of solid SNEDDS of Benidipine with Telmisartan was investigated and compared to the pure drug and

market sample of Benidipine with Telmisartan (Benidip T 4mg/40mg Tab, Precia Pharma Pvt Ltd, Thane, India.

Material and Method

Benidipine and Telmisartan were gift samples from Nikishan Pharmaceuticals and Torrent Research Center, respectively. Koliphore EL and Transcutol P were supplied by BASF and Gattefose in Mumbai, India. Chemicals, such as Eucalyptus oil and D-Fructose were purchased from S.D. Fine Chem and Loba Chemie, India. Water, which underwent repeated distillation, served as the solvent throughout the entire experiment. The only additional substances utilized in this research were of analytical grade. Empty hard gelatin capsules were voluntarily provided by Torrent Research Center.

Method

Antihypertensive evaluation

Animals: Wistar albino rats were obtained from Animal house.

Ethical clearance for the experiments: The study has been approved by Institutional Animal Ethics Committee in 20th IAEC Meeting at Accuprec Research Labs Pvt Ltd, Ahmedabad (ARL/PT/712/2022).

Husbandry conditions:

a. **Housing:** Animals were housed in a polypropylene cage with a stainless steel grill on top. The bedding material was dry wheat husk (post hulled) that was changed every morning hours during acclimatization periods.

b. **Acclimatization:** The animals were acclimatized for one week prior to the start of the experiment.

c. **Environment:** Animals were exposed to 12 hours day and night cycles with a standard temperature of 23±3°C and the relative humidity was 50–60%.

d. **Diet:** The animals were fed with standard rat pellet feed provided by Keval sales Corporation, Vadodara throughout study period. The drinking water was provided in polypropylene bottles with stainless steel sipper tube at all times.

Drugs:

1. Standard drug of Benidipine and Telmisartan
2. Capsule of SNEDDS of Benidipine with Telmisartan containing 4 mg of Benidipine and 40 mg of Telmisartan and other adsorbent.
3. Market sample of Benidipine with Telmisartan (Benidip T 4mg/40mg Tab, Precia Pharma Pvt Ltd,

Dose fixation: The drug dose was derived from the previously mentioned dose of Benidipine and Telmisartan for animal studies.

Route of drug administration: The drugs were administered through oral route to respective groups and were prepared in distilled water (vehicle) as per dose level and same was administered in a uniform volume of 5 ml/kg body weight of albino rats.

Drug schedule: The test drug and vehicle were administered orally between 09:00 am to 09:30 am.

Experimental Protocols

Thirty Wistar albino rats of adult size of either sex in weight ranging from 220 to 240 g were obtained from the Animal house. They were kept in groups and each group consists of six animals. Each group was kept in clean poly-acrylic cages.

Systolic blood pressure and mean arterial pressure were measured on the 1st day of experiment before being induced using (66% w/v) D-Fructose, and was stated as an initial blood pressure. Rats with systolic blood pressure ≤ 120 mmHg, Mean blood pressure ≤ 100 mmHg and diastolic blood pressure ≤ 91 mmHg were considered normotensive and were selected for the study [17, 18].

The blood pressure was measured non-invasively by tail cuff sensor method using BioPack MP36 data acquisition system (NIBP200A- Small animal tail non-invasive Blood Pressure System) (BIOPAC System Inc., USA). The rats were trained to stay in the rat holders in a constant temperature chamber in a calm and non-aggressive state during blood pressure measurement. The rat was nonaggressive in a low-stress environment and allowed to enter the holder freely at least 15 min before blood pressure measurements. The nose of albino rats made to protrude through the front of the nose cone for easy breathing and the tail of the albino rats was protracted to exit of the restrainer through the rear opening of the rat holder. The rat was warmed by using digital Animal heating controller and Tail heating unit, the room temperature was maintained about 32±1°C, reduce stress and the blood flow to the tail was enhanced to acquire a blood pressure signal. The rat never had its head bent sideways or its body compressed against the back hatch. The animal's temperature was monitored throughout the experiment [19, 20]. A tail-cuff lined with a thin, inflatable rubber bladder, a light source, and a photocell sensor, was placed at the base of the tail. The tail-cuff was inflated and deflated automatically. During the measurement, three individual readings were obtained in a rapid sequence and the average of the three readings was reported as the measurement.

The dietary induction of hypertension in Wistar albino rats was employed using 10% w/v fructose in drinking water (equivalent to a diet containing 66% fructose) for 3 week for the rapid production of fructose-induced hypertension in Wistar albino rats, which was associated with elevated levels of plasma insulin, glucose, and triglycerides as explained in figure 1. The normal control group of rats had free access to water and normal standard diet palette feed ad libitum [21, 22].

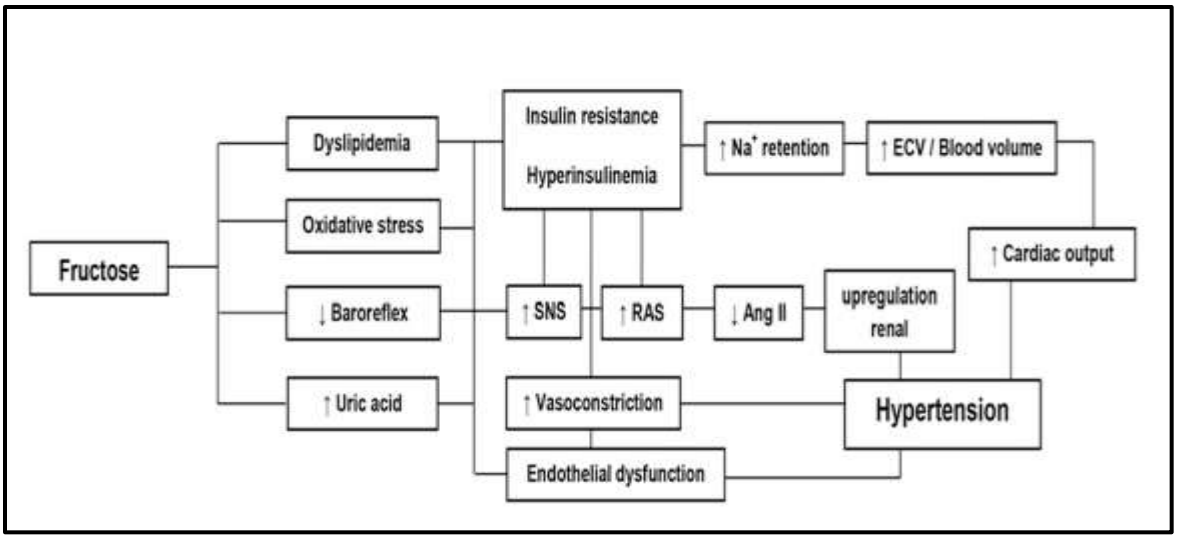

Figure1: Proposed mechanisms for hypertension resulting from fructose in the diet; Ang II, angiotensin II; ECV, extracellular volume, RAS, renin- angiotensin system; SNS, sympathetic nervous system.

Male Wistar rats were randomly divided into groups with six animals (n = 6). Normal control rats (Group 1) received distilled water ad libitum only, negative control rats (Group 2) received 66% w/v D-Fructose ad libitum only, positive control rats (Group 3) received S-SNEDDS of Benidipine with Telmisartan 4mg/40mg BD with TEL/kg/day , (Group 4) received standard Benidipine with Telmisartan (4mg/40mg BD with TEL/kg/day) while Group 5 received Market sample of Benidipine with Telmisartan (Benidip T 4mg/40mg Tab)

Table 1: Study design

Groups	Treatments	No. of animals
G1	Normal control group	1-6
G2	Hypertensive control (Disease Control)	7-12
G3	Hypertensive treated with formulation (S-SNEDDS of Benidipine with Telmisartan)	13-18
G4	Hypertensive treated with standard Benidipine with Telmisartan	19-24
G5	Market sample of Benidipine with Telmisartan (Benidip T 4mg/40mg Tab)	25-30

After 3 weeks, again systolic and diastolic blood pressure was measured as per above mentioned procedure by using BioPack data acquisition system which was representing to hypertension stage in rats except control group. All the rats with a systolic blood pressure of 150 mm Hg were selected. After recording the initial blood pressure of rats, Group 2 to Group 5 were administered orally test

drugs as mentioned below to respective groups and the fall of blood pressure in albino rats was measured at different time.

Table 2: Evaluation Parameters for Pharmacodynamics study:

Sr. No	Parameters	Measured at
1	Body weight	Prior to First dose administration and at least at weekly interval thereafter
2	Food Consumption	At least at weekly interval
3	Clinical Signs and Mortality	At least once a day
4	Detailed Clinical Observation	Once weekly
5	Blood Pressure measurement	Using Tail Cuff Method as and when required.

SBP and MAP were measured on the 1st day of experiment before hypertension being induced using (66% w/v) D-Fructose, and was stated as a BP_0. Rats with $SBP_0 \leq 120$ mmHg, $MAP_0 \leq 100$ mmHg and $DBP0 \leq 91$ mmHg were considered normotensive and were given (66% w/v) D-Fructose except those served as normal control. Then BP was measured after administration of drug at 2,6,12 and 24 hrs. using BioPack data acquisition system. Every measurement was taken in triplicate and the average value was reported.

Statistical Analysis

All experimental data's were expressed as mean values (measurement of BP or % relaxation) ± S.E.M and were subjected to bio statistical interpretation by SPSS windows version 20 statistical packages all the way through a one-way ANOVA followed by post-hoc test (Dunnett's 't' test) for multiple comparisons of the mean differences and responses of different drugs and extracts. Statistical significance of $P < 0.05$ were considered as level of significance [23].

Results and Discussion

When fructose delivery was utilized to induce hypertension in experimental rats, the efficacy of this induction was evident in Group II, III, IV, and V rats, as displayed by the highly significant differences ($p < 0.01$) in blood pressure (BP) compared to the negative control Group I, as depicted in Figure 2. Group I served as the negative control and demonstrated normal blood pressure values. The hypertensive model rats in Group I, treated with 66% w/v D-Fructose, displayed a considerable increase in systolic blood pressure (SBP) by 40 mmHg, diastolic blood pressure (DBP) by 20 mmHg, and mean arterial pressure (MAP) by 30 mmHg from their basal levels as we can noticed from table 3.

Conversely, the positive control groups receiving pure Benidipine with Telmisartan (BD with

TEL) as individual drugs, self-emulsifying drug delivery systems (S-SNEDDS) of BD with TEL, and the market sample of Benidipine T 4mg/40mg Tab, all administered concurrently with 66% w/v D-Fructose, effectively mitigated the rise in SBP, DBP, and MAP among the fructose-consuming rats as shown in figure 3. The observed effects were statistically significant, underlining the promise of these interventions in avoiding fructose-induced hypertension.

Table 3: Pharmacodynamic study of Benidipine with Telmisartan on different group (mean values ± SD)

Treatments	**Blood pressure (mm Hg)**					
	Blood pressure	**0 hr.**	**2 hrs.**	**6 hrs.**	**12 hrs.**	**24 hrs.**
Normal control (G1)	Systolic	117.0±1.633	110.33±2.201	103.83±1.851	101.00±2.477	110.83±3.683
	Mean	92.67±1.232	89.89±0.901	87.50±0.576	85.44±1.219	89.17±1.468@
	Diastolic	80.50±1.408	79.50±0.885	79.33±1.174	77.67±1.706	78.33±2.155
Hypertensive control (G2)	Systolic	162.67±1.667@	155.50±1.648@	155.50±1.821@	153.33±2.860@	152.33±3.833@
	Mean	126.22±1.655@	121.94±1.703@	117.83±1.659@	120.78±1.833@	115.28±2.140@
	Diastolic	108.00±1.770@	105.17±2.040@	99.00±1.966@	104.50±2.754@	98.50±2.262@
Benidipine+ Telmisartan SNEDDS (G3)	Systolic	159.33±1.085	133.33±1.667*	122.83±1.493*	119.50±2.766*	124.50±3.423*
	Mean	124.55±1.207	102.55±1.472*	98.17±1.765*	97.61±1.013*	100.94±2.147*
	Diastolic	107.17±2.023	87.17±1.922*	79.85±2.386*	83.50±1.996*	89.17±2.482$
Standard Benidipine + Telmisartan (G4)	Systolic	156.83±2.183	137.83±1.515*	127.17±1.424*	126.50±2.045*	131.33±2.654*
	Mean	123.28±2.296	105.94±1.013*	101.72±1.679*	99.83±1.964*	103.11±1.703*
	Diastolic	106.50±2.705	90.0±1.633*	89.00±2.309*	86.50±2.884*	89.00±2.840$
Market sample of BD with TEL (G5)	Systolic	155.47±2.105	135.07±1.145*	129.30±2.005*	128.90±1.945*	129.10±2.125*
	Mean	122.98±1.967	105.10±1.217*	102.90±1.523*	100.17±1.125*	101.90±1.859*
	Diastolic	105.50±2.712	89.80±1.853*	89.20±2.106*	88.18±2.853*	88.10±2.107*

Data: Mean±SEM (n=6)

@P<0.01, when compared to normal control group; $P<0.05, *P<0.01, when compared to hypertensive control group (Annova followed by Dunnett's multiple't' test)

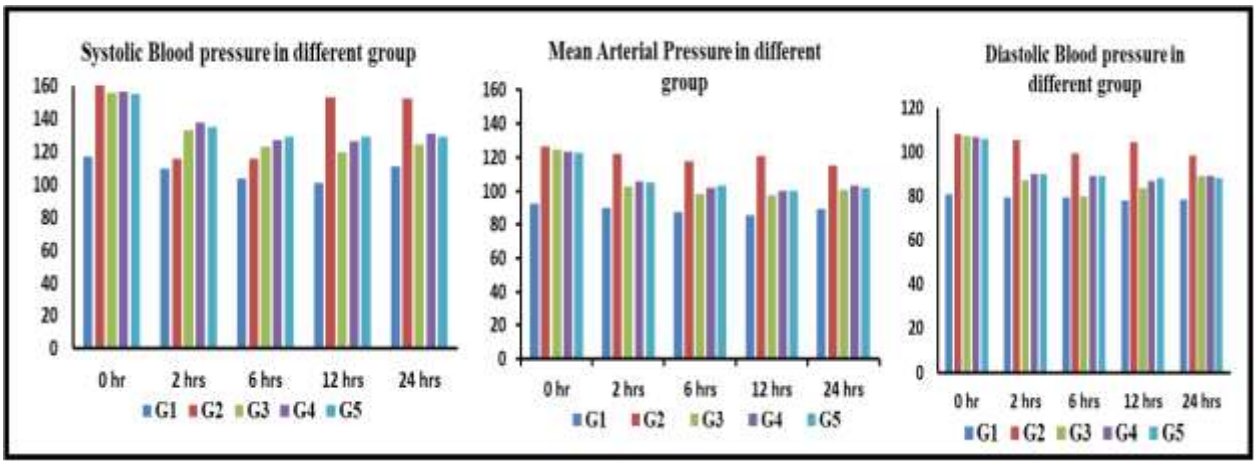

Figure 2: Systolic blood pressure, Mean Arterial pressure and Diastolic blood pressure values before and after drug treatment to different group (n=6rats/group)

The data reveal that S-SNEDDS exhibited higher bioavailability compared to both the suspension form of pure BD with TEL and the market sample Benidip T 4mg/40mg Tab. This heightened bioavailability can be due to the improved solubility of BD obtained with the S-SNEDDS formulation. This difference in hypertensive response is indicative of the better drug solubility and absorption kinetics produced by the S-SNEDDS formulation.

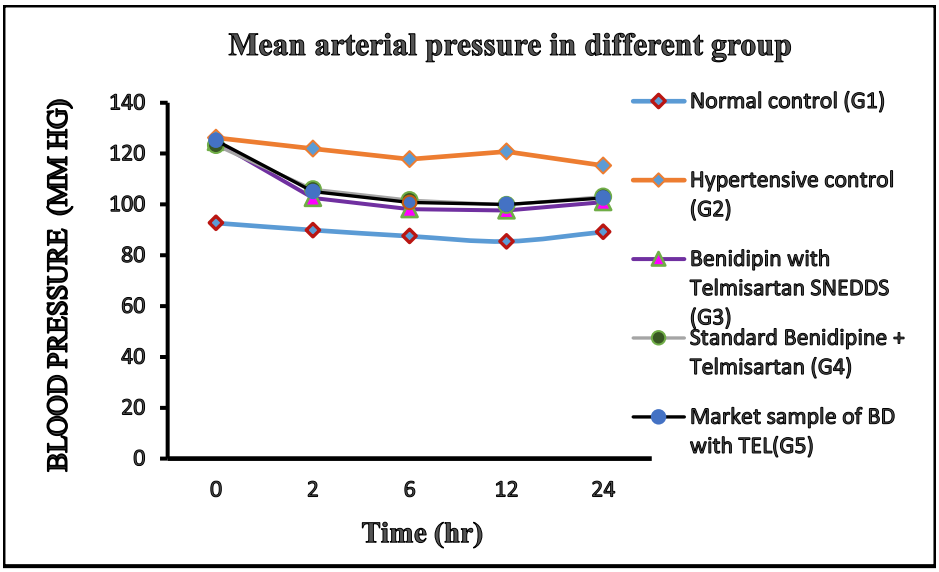

Figure 3: Mean arterial pressure in different group

The addition of surfactants in the S-SNEDDS formulation likely contributed to the heightened aqueous solubility of BD and promoted the fast dispersion of drug globules. This behavior is consistent with the ability of SNEDDS to deliver drug molecules at the nanoscale scale, hence increasing the surface area available for oral absorption. This accords with the assumption that smaller particle sizes and increased surface area lead to improved dissolving behavior and enhanced absorption [24, 25].

These results were verified by dissolution investigations, which underlined the importance of particle size on medication absorption disparities. The results from this research supported the hypothesis that variations in absorption are mostly driven by the dissolving behavior of medicines with various particle sizes.

Statistical analysis was performed using one-way ANOVA followed by Dunnett's post hoc test, with statistical significance defined at $p < 0.05$. Moreover, the normotensive rats provided S-SNEDDS of BD with TEL displayed a noteworthy drop ($p < 0.05$) in systolic blood pressure, mean arterial blood pressure, and diastolic blood pressure. This observation further highlights the potential antihypertensive efficacy of the S-SNEDDS formulation even in normotensive situations.

Conclusion

Fructose-induced hypertension was significantly counteracted by the administration of S-SNEDDS of BD with TEL, revealing its remarkable potential in preventing and lowering hypertension. The increased bioavailability, solubility, and dissolving properties of the S-SNEDDS formulation provide mechanistic insights into its greater efficacy compared to typical suspension formulations and market samples. Further inquiry into the underlying processes of S-SNEDDS-mediated drug transport and its prospective clinical implications offers promise for addressing hypertension and related cardiovascular disorders.

While the present study underlines the potential benefits of S-SNEDDS, it is vital to acknowledge the necessity for additional exploration. Additional research employing varied models would be needed to corroborate these findings and validate the constancy of the reported antihypertensive effects. As research continues, further efforts to understand the specific mechanisms and clinical importance of S-SNEDDS-mediated intervention offer enormous potential in enhancing our ability to combat hypertension and its accompanying cardiovascular problems successfully.

Acknowledgments

The authors thankful to Faculty of Pharmacy, Noble University, Junagadh, and School of Pharmaceutical Science, Atmiya University, Rajkot for providing the facilities to carry out the research work. We are also thankful to Accuprec Research Labs Pvt. Ltd., Ahmedabad, for carrying out a pharmacological study successfully.

Institutional Review Board Statement:

The animal study protocol was approved by the IAEC of 20th Institutional Animal Ethics Committee, Accuprec Research Labs Pvt. Ltd., Ahmedabad dated 7/10/2022 (letter No. ARI/PT/712/2022.)

Conflicts of Interest: No conflict of interest was declared by the authors.

References

1) Tinawi, M. (2022). New Trends in the Diagnosis and Management of Hypertension. Cureus, 14(2), e22393. https://doi.org/10.7759/cureus.22393
2) Beaney, T., Schutte, A. E., Tomaszewski, M., Ariti, C., Burrell, L. M., Castillo, R. R., Charchar, F. J., Damasceno, A., Kruger, R., Lackland, D. T., et al. (2018). May Measurement Month 2017: An Analysis of Blood Pressure Screening Results Worldwide. The Lancet Global Health, 6, e736–e743.
3) Mancia, G., Facchetti, R., Bombelli, M., Grassi, G., & Sega, R. (2006). Long-term Risk of Mortality Associated with Selective and Combined Elevation in Office, Home, and Ambulatory Blood Pressure. Hypertension, 47, 846–853.
4) Mills, K. T., Bundy, J. D., Kelly, T. N., Reed, J. E., Kearney, P. M., Reynolds, K., Chen, J., & He, J. (2016). Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies from 90 Countries. Circulation, 134, 441–450.
5) Ettehad, D., Emdin, C. A., Kiran, A., et al. (2016). Blood Pressure Lowering for Prevention of Cardiovascular Disease and Death: A Systematic Review and Meta-analysis. The Lancet, 387, 957-967.
6) Zhang, Y., & Moran, A. E. (2017). Trends in the Prevalence, Awareness, Treatment, and Control of Hypertension Among Young Adults in the United States, 1999 to 2014. Hypertension, 70, 736-742.
7) Kalra, S., Kalra, B., & Agrawal, N. (2010). Combination Therapy in Hypertension: An Update. Diabetology & Metabolic Syndrome, 2, 44.
8) Kang, W. K., Yun, H. Y., & Kwon, K. I. (2005). Assessing the Bioequivalence of 4 and 8 mg Benidipine Tablets in Healthy Volunteers after a Single Oral Dose. Journal of Clinical Pharmacy and Therapeutics, 30, 85–90.
9) Yun, H. Y., Yun, M. H., Kang, W., & Kwon, K. I. (2005). Pharmacokinetics and Pharmacodynamics of Benidipine Using a Slow Receptor-Binding Model. Journal of Clinical Pharmacy and Therapeutics, 30, 541–547.
10) Wienen, W., Entzeroth, M., Meel, J. C. A., et al. (2000). A Review on Telmisartan: A Novel, Long-acting Angiotensin II-receptor Antagonist. Cardiovascular Drug Reviews, 18, 127–154.
11) Deppe, S., Tekade, M., Pandey, V., & Nagaraja, S. H. (2020). Self-Microemulsifying Drug-Delivery System: Ongoing Challenges and Future Ahead. In Drug Delivery Systems (pp. 393–454). Academic Press.

12) Aristote, B., Buya, B., Beloqui, A., & Memvanga, P. (2020). Self-Nano-Emulsifying Drug-Delivery Systems: From Development to Current Applications and Challenges in Oral Drug Delivery. Pharmaceutics, 12(12), 1194.
13) Tran, P., & Park, J. S. (2021). Recent Trends of Self-Emulsifying Drug Delivery System for Enhancing the Oral Bioavailability of Poorly Water-Soluble Drugs. Journal of Pharmaceutical Investigation, 51, 196-218.
14) Truong, D. H., Tran, T. H., Ramasamy, T., et al. (2015). Development of Solid Self-Emulsifying Formulation for Improving the Oral Bioavailability of Erlotinib. AAPS PharmSciTech, 17(1), 466-473.
15) Sharma, P. K., Kumar, A., & Shukla, V. K. (2022). DOE Optimized Self-Nanoemulsifying Drug Delivery System (SNEDDS) Based Cilnidipine Formulations for Bioavailability Augmentation: Physical Characterization and Pharmacodynamic Assessment. Journal of Pharmaceutical Negative Results, 13(5), 1465-1467.
16) Alaribe, C. S., & Momoh, R. (2021). The Antihypertensive Effect of N-Hexane and Aqueous Ethanolic Extracts of the Sclerotium of Pleurotus tuber-regium in Sodium Chloride Induced Albino Rats. International Journal of Medical, Biological and Pharmaceutical Sciences, 13(3), 14-24.
17) Geleta, B., Makonnen, E., Debella, A., & Tadele, A. (2016). In Vivo Antihypertensive and Antihyperlipidemic Effects of the Crude Extracts and Fractions of Moringa stenopetala (Baker f.) Cufod. Leaves in Rats. Frontiers in Pharmacology, 7, 97.
18) Jalal, D. I., Smits, G., Johnson, R. J., & Chonchol, M. (2010). Increased Fructose Associates with Elevated Blood Pressure. Journal of the American Society of Nephrology, 21, 1543-1549.
19) Dornas, W. C., Lima, W. G., Pedrosa, M. L., & Silva, M. E. (2015). Health Implications of High-Fructose Intake and Current Research. Advances in Nutrition, 6, 729-737.
20) Shah, S. M. A., Naqvi, S. A. R., Munir, N., Zafar, S., Akram, M., & Nisar, J. (2020). Antihypertensive and Antihyperlipidemic Activity of Aqueous Methanolic Extract of Rauwolfia Serpentina in Albino Rats. Dose-Response, 18(3), 1559325820942077.
21) Patel, P., Pailla, S. R., Rangaraj, N., Cheruvu, H. S., Dodoala, S., & Sampathi, S. (2019). Quality by Design Approach for Developing Lipid-Based Nanoformulations of Gliclazide to Improve Oral Bioavailability and Anti-Diabetic Activity. AAPS PharmSciTech, 20(2), 45.
22) Dornas, W. C., de Lima, W. G., Pedrosa, M. L., & Silva, M. E. (2015). Health Implications of High-Fructose Intake and Current Research. Advances in Nutrition, 6, 729–737. doi:10.3945/an.114.008144.
23) Shah, S. M. A., Naqvi, S. A. R., Munir, N., Zafar, S., Akram, M., & Nisar, J. (2020). Antihypertensive and Antihyperlipidemic Activity of Aqueous Methanolic Extract of Rauwolfia Serpentina in Albino Rats. Dose-Response: An International Journal, 18(3), 1559325820942077. doi:10.1177/1559325820942077.

24) Patel, P., Pailla, S. R., Rangaraj, N., Cheruvu, H. S., Dodoala, S., & Sampathi, S. (2019). Quality by Design Approach for Developing Lipid-Based Nanoformulations of Gliclazide to Improve Oral Bioavailability and Anti-Diabetic Activity. AAPS PharmSciTech, 20(2), 45.
25) Rani, E. R., & Radha, G. V. (2023). Investigation of In Vivo Bioavailability Enhancement of Iloperidone-Loaded Solid Self-Nanoemulsifying Drug Delivery Systems: Formulation and Optimization Using Box-Behnken Design and Desirability Function. Journal of Pharmaceutical Innovation, 1-17.