Abstract

Benidipine (BD), a dihydropyridine calcium channel blocker indicated in hypertension angina therapy, presents challenges with oral bioavailability owing to hepatic first-pass metabolism and high lipophilicity (log P of 4.28).In order to boost its bioavailability, numerous approaches, such as solid dispersions and nanosuspensions, have been investigated. Similarly, telmisartan (TEL), an angiotensin II receptor antagonist for hypertension, has problems with oral bioavailability owing to low solubility and high permeability. It is frequently administered together with other antihypertensive medicines, such as calcium channel blockers, for the treatment of hypertension with renal failure.

Despite the excellent therapeutic use of both medications, BD and TEL experience different pharmacological issues due to their low solubility, as they both belong to BCS class II. Thus, in order to obtain the primary therapeutic advantages from the combination of BD and TEL in a single carrier, the smart drug delivery technique, i.e., the lipid-based drug delivery system, has been utilized in the present investigation in order to improve the bioavailability of both medications. The most advantageous lipid-based drug delivery methodology that may address the above-described challenges is SNEDDS. The goal of the present study is to evaluate the possibility of creating solid SNEDDSs as potential carriers for the oral administration of Benidipine and Benidipine (BD) with Telmisartan (TEL), applying the Quality by Design (QbD) approach.

Based on pre-formulation and risk assessment studies, the maximal drug solubility in each oil, surfactant, and co-surfactant was selected. Ternary phase diagrams were generated for BD with Labrafil M 2125 CS (oil), Kolliphor EL (surfactants), and Transcutol P (co-surfactant) at 1:1, 2:1, and 3:1 ratios for determining the largest region for the creation of thermodynamically stable nanoemulsions. Similarly, utilizing Eucalyptus Oil, Kolliphor EL, and Transcutol P, the BD with TEL SNEDDS was created. The oil phase, the screened surfactant, and the co-surfactant have been employed for creating phase diagrams of BD with TEL in differing weight ratios of 1:1, 2:1, 3:1, 1:2, and 1:3.

The central composite design has been selected for BD, and the Box-Behnken design (BBD) has been generated for BD with TEL to optimize various variables. Zeta potential, drug concentration, resistance to dilution, pH, refractive index, viscosity, thermodynamic stability, and cloud point were further examined in the most efficient formulation. Optimized formulation BD14 contained Benidipine (4mg), Labrafil M2125 Cs (30%), Kolliphor EL (45%), and Transcutol P (50%), which had a globule size of 156.20 ± 2.40 nm, PDI of 0.25, zeta potential of -17.36 ± 0.18 mV, self-emulsification time of 65.21 ± 1.95 sec, % transmittance of 99.80 ± 0.70%, and drug release of 92.65 ± 1.70% at 15 min. Similarly, BD with a TEL formulation was further investigated. The optimized formulation BT11 contained Benidipine (4mg), Telmisartan (40 mg), Eucalyptus oil (60%), Kolliphor EL (35%), and Transcutol P (10%), which had a globule size of 175.12±2.70 nm, a PDI of 0.226, a zeta potential of −24.98 ± 0.18 mV, a self-emulsification time of 53.00±2.10 sec, a % transmittance of 99.6±0.3%, and a drug release of 92.65±1.70 at 15 min.

S-SNEDDS have been generated utilizing the adsorption process and investigated with FTIR, DSC, SEM, and PXRD. Neusilin US2, L-SNEDDS: Adsorbent (1:1.5), was selected as the carrier for pores in a mixture with excellent flow rate, flow ability, highest drug content, and drug release in order to facilitate further exploration of BD14 and BT11.

In contrast to the percentages of 58.80% and 60.15% for the pure drug BD and a commercial specimen of BD, L-SNEDDS and S-SNEDDS of BD14 demonstrated that BD released more than 85% of its contents after 15 minutes and 100% after 60 minutes (f2< 50). Similarly, in contrast to the percentages of 50.1% and 58.1% for the pure drug BD, a commercial specimen of BD with TEL, L-SNEDDS, and S-SNEDDS of BT11 showed that BD released more than 85% of its contents after 15 minutes and 100% after 60 minutes (f2< 50). Similarly, when compared to the percentages of 48.7% and 59.8% for the pure drug TEL and a commercial specimen of BD with TEL, L-SNEDDS and S-SNEDDS of BT11 demonstrated that TEL released more than 85% of its contents after 15 minutes and 100% after 60 minutes (f2< 50). The release of drug kinetics of L-SNEDDS of BD14, BT11, and S-SNEDDS of BD14, BT11, follow 1st-order kinetics, which shows the drug release from the porous matrix corresponds to the amount of drug remaining in its interior.

The pharmacodynamics study results reveal that S-SNEDDS of BD and BD with TEL displayed greater bioavailability compared to both pure BD and BD with TEL medicines. After six months of storing at $40\pm2°C$ and $75\pm5\%$ relative humidity, the BD-loaded S-SNEDDS of BD14 samples and the BD with TEL-loaded S-SNEDDS of BT11 exhibited no observable changes in emulsification efficacy, size of the globules, percentage of transmission, or release of the drug over a period of fifteen minutes. These results indicate that BD14 and BT11 in the boosted S-SNEDDS display chemical and structural stability. Consequently, research demonstrates that the production of oral S-SNEDDS of benidipine and benidipine with telmisartan may be advantageous for boosting BD and BD with TEL's water solubility, as well as the future delivery technique that may deliver both drugs to treat hypertension for enhanced treatment.