Section A-Research paper

DEVELOPMENT AND CHARACTERIZATION OF AZILSARTAN MEDOXOMIL LOADED SOLID DISPERSION OF POORLY WATER-SOLUBLE ANTIHYPERTENSIVE DRUG

Sanjeev Kumar [1, 2*], Tanveer Naved[1], Sanjar Alam[3]

[1]Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Uttar Pradesh, 201303, Uttar Pradesh, India.

[2]KIET Group of Institutions (KIET School of Pharmacy,) Muradnagar, Ghaziabad, U.P, India

[3]R.V Northland Institute, Dadri, Greater Noida-II, Gautam Budh Nagar, Uttar Pradesh 203207

Abstract

The development and characterization of solid dispersion formulations of Azilsartan medoxomil (AZM) is an important approach to enhance the dissolution rate and oral bioavailability of this poorly water-soluble antihypertensive drug. The aim of this research was to develop modified dosage form of poorly water-soluble antihypertensive drug Azilsartan medoxomil, with the goal of improving their solubility and bioavailability. Azilsartan medoxomil with low water solubility, was selected for the study. Various formulations were prepared using method, including solid dispersion. The prepared formulations were characterized using various techniques, including Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). The results showed that the modified dosage forms significantly improved the solubility and dissolution of the poorly water-soluble antihypertensive drugs by using solid dispersion. The solid dispersion formulation AZLC2 was found to be the most effective in improving the solubility and dissolution of the drugs. Overall, the study demonstrated the potential of modified dosage forms for improving the bioavailability and efficacy of poorly water-soluble drugs, which could lead to improved therapeutic outcomes for patients with hypertension.

Keywords: Antihypertensive drugs, Modified dosage forms, Solid dispersion, Solubility enhancement.

Introduction

Hypertension, commonly known as high blood pressure, is a chronic medical condition affecting a significant proportion of the world population[1]. It is a major risk factor for several cardiovascular and renal diseases, making its control and management crucial for improving patient outcomes[2]. Antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics, are commonly used to treat hypertension. However, some of these drugs are poorly soluble in water, which limits their bioavailability and therapeutic efficacy. To overcome this challenge, researchers have focused on developing modified dosage forms that can improve drug solubility, dissolution rate, and bioavailability [3]. Such modified forms include solid dispersions, nanoparticles, liposomes, and others. These formulations offer several advantages, such as increased drug absorption, reduced side effects, and improved patient compliance[4]. Azilsartan medoxomil are medications used to treat hypertension, or high blood pressure[5]. Azilsartan is an

angiotensin II receptor blocker (ARB), which works by blocking the action of a hormone called angiotensin II that constricts blood vessels and raises blood pressure[6]. On the other hand, is a prodrug that is metabolized in the body to produce the active form of azilsartan. On the other hand, is much less water-soluble, with a solubility of only 0.0037 mg/mL at room temperature[7]. This means that medoxomil is much less likely to dissolve in water and may be more difficult to administer as a medication[5][8]. To improve the water solubility of medoxomil, it is often formulated as a salt, such as the calcium salt or potassium salt[9]. These salt forms are more water-soluble than the parent medoxomil molecule, which can make them easier to dissolve and administer as medications[10][11]. The use of solid dispersions has gained significant attention in recent years due to their ability to enhance the dissolution rate and bioavailability of poorly soluble drugs. Beta-cyclodextrin is a commonly used carrier system for the preparation of solid dispersions[12]. It has good solubility, is biocompatible, and has been approved by regulatory agencies for use in pharmaceutical formulations[13]. In this context, the development and characterization of a solid dispersion of azilsartan medoxomil loaded with Beta-cyclodextrin could potentially lead to improved drug solubility and dissolution rate, leading to better therapeutic outcomes[14]. Therefore, this study aims to develop and characterize a solid dispersion of azilsartan medoxomil loaded with Beta-Cyclodextrin and evaluate its physicochemical properties and drug release profile.

Material and method

Azilsartan medoxomil was received as a gift sample from Synokem Pharmaceuticals ltd, Haridwar. All the chemicals and polymers used were of analytical grade.

Determination of Azilsartan Medoxomil melting temperature

Melting point of Azilsartan medoxomil was measured according to U.S.P by capillary tube procedure.

Determination of Azilsartan Medoxomil λ_{max}

Azilsartan medoxomil solution was prepared by dissolving 10 mg Azilsartan medoxomil in 5 ml methanol and completed with 0.1N HCl pH 1.2 up to 100 ml. From this stock solution, a dilute (10 µg/ml) solution was prepared and scanned by UV visible from 200 to 400 nm range and the maximum absorption of the drug was determined as its λmax.

Calibration curve of Azilsartan Medoxomil

It was constructed by preparing a serial of dilution of Azilsartan medoxomil with different concentration from stock solution containing 10 mg/100 ml Azilsartan medoxomil in both 0.1N HCl and phosphate buffer pH 6.8. The absorbance was then measured at the λmax of the drug. The measured absorbances were plotted against the respective concentrations.

Solubility determination

Saturation solubility of azilsartan medoxomil was determined in (water, 0.1N HCl pH 1.2 and phosphate buffer (pH 7.4 and 6.8 solution)[16]. Excess amount of azilsartan medoxomil was added to 5 ml of each media and kept in an incubator shaker at 25±1 °C and after 48h, solution was centrifuged at 5000 rpm for 15 min. Supernatants were filtered (0.22 µm pore size) and diluted with the respective solution. Absorbance was measured using (UV) spectrophotometer and solubility was calculated.

Formulation development:

Preparation of Solid dispersion: Solid dispersion is a technique used to enhance the solubility and dissolution rate of poorly soluble drugs. One of the methods used to prepare solid dispersions is the physical admixture method[15]. Physical admixtures of Azilsartan medoxomil with beta-Cyclodextrin were prepared by mixing the required amount of Azilsartan medoxomil and beta-Cyclodextrin in a glass mortar for 30 min at 1:1, 1:2, 1:3,

1:0.5, 1:4, 1:5 (drug: carrier) ratio. The mixtures are then passed through 120 sieves to have uniform size and stored in a desiccator.

Table 1: Formulation ratio of Azilsartan Medoxomil and βCD

Formulation code	Azilsartan Medoxomil:βCD	Formulation Compositions (Azilsartan Medoxomil:βCD)	
AZLC1	1:1	120	120
AZLC2	1:2	120	240
AZLC3	1:3	120	360
AZLC4	1:0.5	120	60
AZLC5	1:4	120	480
AZLC6	1:5	120	600

Characterization of the solid dispersion

Drug content

Solid dispersions equivalent to 20 mg of Azilsartan medoxomil was weighed accurately and dissolved in the 20 mL of ethanol. The solution was filtered, diluted suitably and drug content was analyzed at 248 nm by UV spectrophotometer. The actual drug content was calculated using the following equation as follows:

$$\%\ Drug\ content\ \frac{Absorbance\ of\ test}{Absorbance\ of\ the\ standard\ at\ the\ same\ dilution}x100$$

Fourier transform infrared spectroscopy (FTIR): Fourier transform infrared spectroscopy (FTIR) is a powerful analytical technique used to characterize the chemical composition and structure of materials. It has been widely applied to the study of solid dispersions, which are mixtures of two or more components in a solid state. One common use of FTIR in solid dispersion characterization is to assess the degree of drug-polymer interaction. By analyzing the shifts and changes in peak positions in the FTIR spectra, it is possible to identify changes in the functional groups of the drug and polymer.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is a commonly used technique to characterize solid dispersions. DSC measures the heat flow between a sample and a reference material as a function of temperature. In the case of solid dispersions, DSC can be used to determine the thermal behavior of the drug and the polymer matrix. The DSC thermogram of a solid dispersion typically shows a broad endothermic peak, which corresponds to the melting of the drug and/or the polymer. The peak temperature and the enthalpy of melting can provide information about the degree of drug-polymer interaction and the drug crystallinity.

Drug release

The in vitro dissolution study involves the use of a USP II dissolution apparatus. 500mg of the drug product is placed in the dissolution apparatus and immersed in the dissolution medium at a ±37°C temperature. The basket is then set to rotate at a predetermined speed to ensure proper mixing of the drug product and dissolution medium. At 15, 30, 30 and 120

minutes intervals, samples are collected from the dissolution medium through the sampling port and analyzed for drug content using a UV-Vis spectroscopy. The drug release profile is then determined by plotting the cumulative amount of drug released over time.

Result and Discussion

Melting point

The melting point of pure Azilsartan medoxomil was found to be 212-214°C.

Calibration curve of Azilsartan Medoxomil

The Azilsartan Medoxomil content was analyzed using UV-visible spectroscopy at 248 nm. The λ_{max} of Azilsartan Medoxomil are shown in figure 1. The analytical method was validated for specificity, linearity, accuracy, and precision and the results are shown in figure 2.

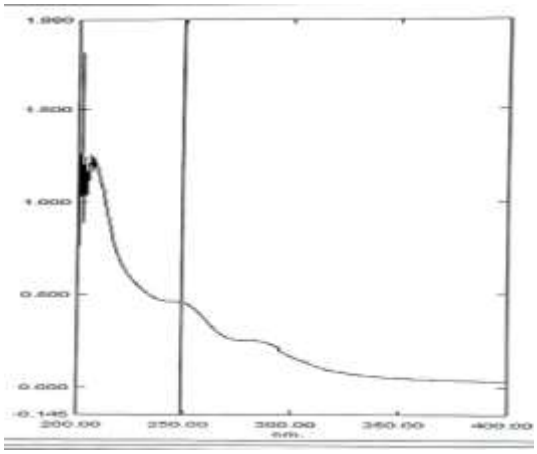

Fig.1: λ_{max} of Azilsartan Medoxomil

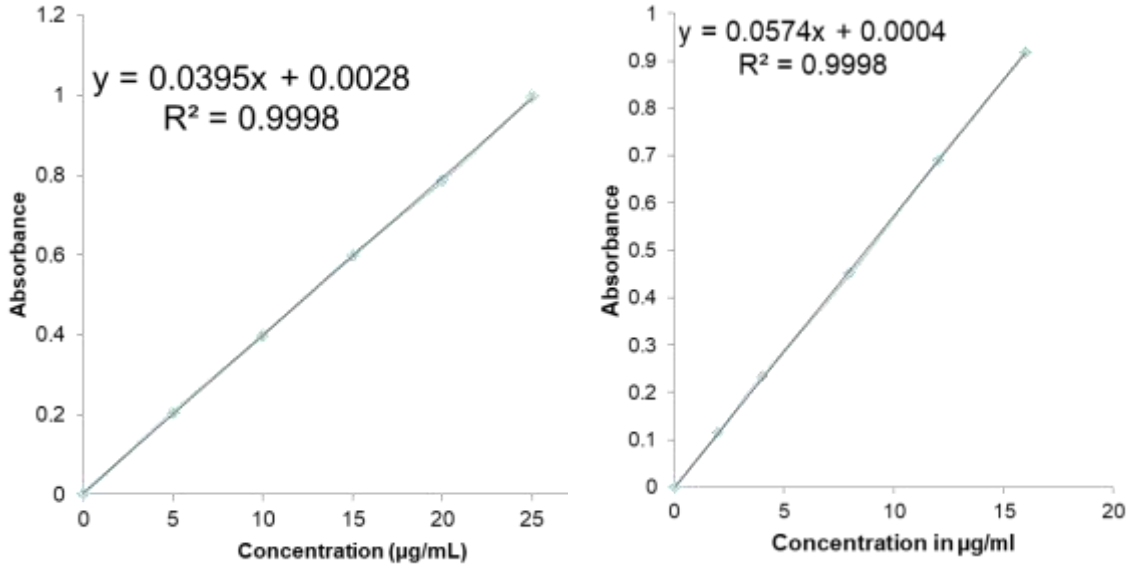

Fig.2: calibration curve of Azilsartan Medoxomil

Solubility Determination

As the main objective of developing solid dispersion formulations of azilsartan Medoxomil (AZM) is to improve its solubility. The solubility of AZM increased by up to 7.5-fold when formulated with Beta-cyclodextrin as the carrier material. The results (table 2 and figure 3) showed that the solubility of azilsartan medoxomil was significantly enhanced when formulated as a solid dispersion compared to the pure drug.

Table 2: Solubility Determination at different pH of azilsartan medoxomil

Solvent	Solubility(µg/ml) mean±SD of azilsartan medoxomil	Solubility(µg/ml) mean ± SD of azilsartan medoxomil+ Beta-cyclodextrin
pH 1.2	20.30±0.11	25.02±0.13
pH 6.8	374±0.5	432±0.5
pH 7.4	1033±1.2	1066±1.2
Water	16.1±0.1	20.3±0.1

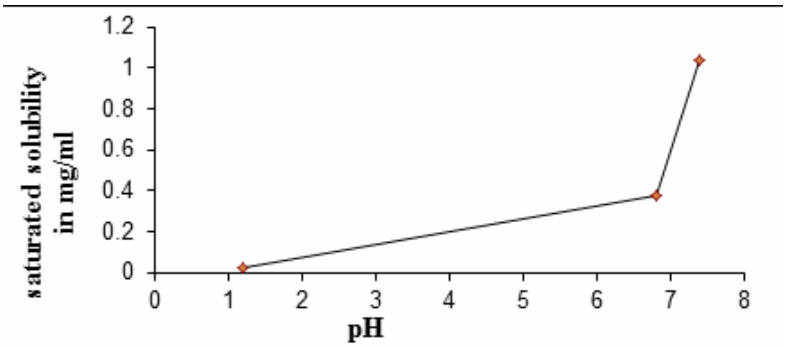

Fig.3: Impact of pH on solubility

Fourier transform infrared spectroscopy (FTIR)

The FT-IR spectra of pure Azilsartan medoxomil solid dispersions, are presented in fig. 4. The spectrum of pure Azilsartan medoxomil showed four absorption peaks at 3398, 3352, 3286 (due to stretching vibration) and 1670 cm^{-1} (due to bending vibration) which are related to the amino group, as well as 1561 and 1322 cm^{-1} which belong to the asymmetric stretching vibration of the carboxyl and sulphonyl groups, respectively. The spectrum of βCD showed important bands at 2954 cm^{-1} due to C-H stretching and 1670 cm^{-1} due to C=O. Lack of any new peaks in the solid dispersions and also no differences in the positions of the absorption bands indicate the absence of significant interactions between Azilsartan medoxomil during solid dispersions preparation and storage.

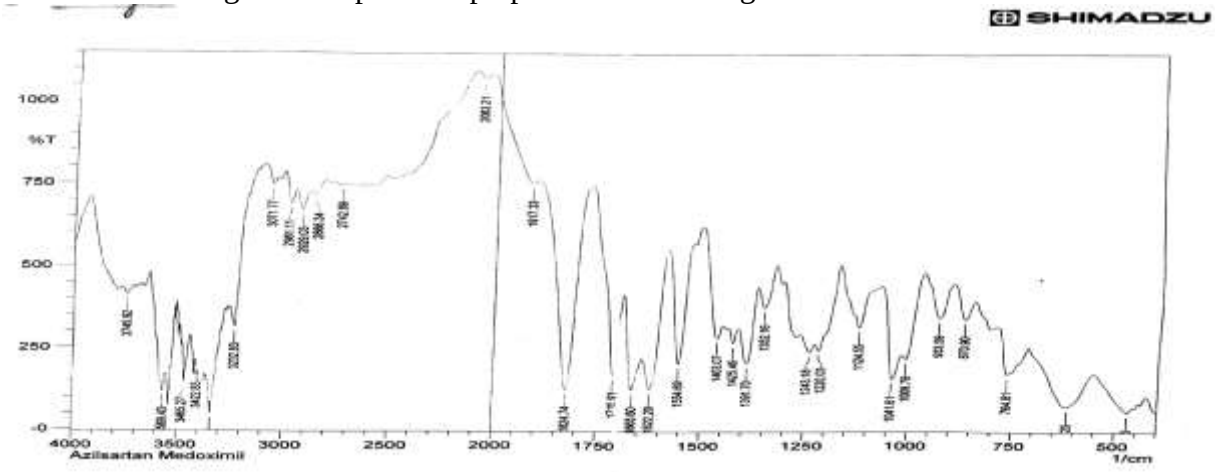

Fig.4: FTIR study of Azilsartan Medoxomil

Differential scanning calorimetry (DSC)

The DSC results showed that there was no significant difference in the thermal behavior between pure drug and solid dispersion, indicating that no interaction between drug and excipient occurred during formulation. The melting point of Azilsartan medoxomil crystals, which is approximately 200-250°C, as determined by differential scanning calorimetry (DSC) analysis are shown in figure 5. The DSC graph of Azilsartan medoxomil with Beta-cyclodextrin exhibits one endothermic peak at 140-148°C, corresponding to its decomposition temperature are shown in figure 6. The melting peaks of Azilsartan medoxomil in ground mixtures (GMs) containing Beta-cyclodextrin were broadened and shifted to a lower temperature as the percentage of Beta-cyclodextrin in the GMs increased. The DSC curves of ground AZM crystals all showed melting peaks at approximately 212-214°C.

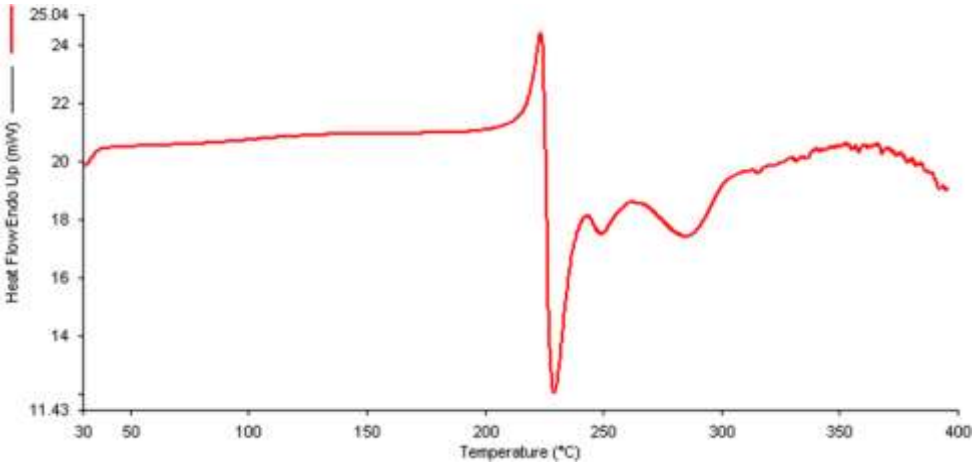

Fig.5: Differential scanning calorimetry of Azilsartan medoxomil

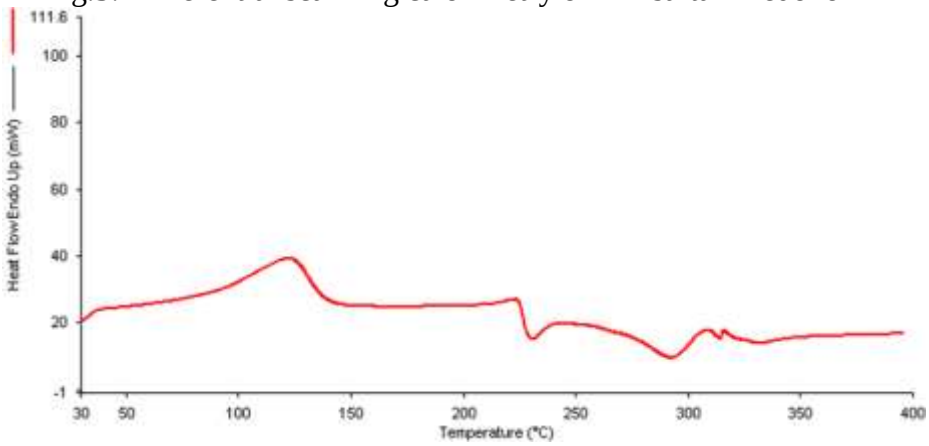

Fig.6: Differential scanning calorimetry of Azilsartan Medoxomil + Betacyclodextrin

Drug Content

Drug content for all the formulations were in the range of 94.05%–99.03%, which is acceptable value as per the official monograph.

***In Vitro* dissolution studies**

The dissolution efficiency (DE) of azilsartan medoxomil with Beta-cyclodextrin was evaluated using the dissolution curve up to a certain time expressed as a percentage of the area of the rectangle dissolution at the same time. The results of these studies show that solid dispersion formulations can significantly improve the dissolution rate of AZM compared to the pure drug. For instance, a study has reported that the dissolution rate of AZM increased by up to 85% when formulated with Beta-cyclodextrin as the carrier material. The in vitro

dissolution studies showed that the dissolution rate of azilsartan medoxomil was significantly enhanced when formulated as a solid dispersion compared to that of pure drug, indicating that it was successfully formulated as a highly soluble system.

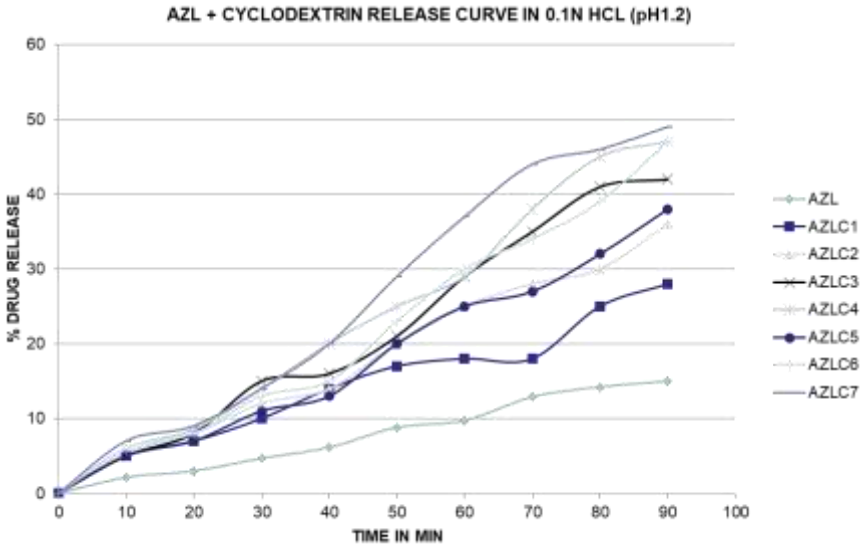

Fig.7: *In vitro* drug release profile.

CONCLUSION

This study showed that solid dispersions of azilsartan medoxomil with Beta-cyclodextrin in different ratios successfully enhanced the aqueous solubility and dissolution rate of azilsartan Medoxomil. The results obtained from this study indicate that azilsartan medoxomil formulated as a solid dispersion can be used to modify existing dosage forms with improved solubility and dissolution rate. The dissolution rate of azilsartan medoxomil was enhanced by increasing the grinding duration and partly transforming it into an amorphous phase. Solid dispersions prepared by the physical mixture method showed more improvement in the solubility and out of the six prepared formulations AZLC2 (1:2 drug: carrier ratio prepared by physical mixture method) showed a four-fold increase in the aqueous solubility.

Conflict of interest

None

Funding

None

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