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Development and Characterization of Modified Dosage Forms of Azilsartan Medoxomil for Improved Solubility and Oral Bioavailability

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Abstract

Azolsartan medoxomil solid dispersions based on polyvinylpyrrolidone were developed and analyzed in this study to improve their solubility and dissolution rate in water. The investigation encompasses the utilization of both solvent evaporation and kneading techniques for solid dispersion preparation. Results indicate that solid dispersions produced through the solvent evaporation method exhibit superior enhancements in solubility compared to those prepared via kneading. Notably, among the tested formulations, B3, formulated with a drug-to-carrier ratio of 1:0.5 using solvent evaporation, demonstrates a notable four-fold increase in aqueous solubility. Solid dispersion technology is expected to boost azilsartan medoxomil formulations' bioavailability and therapeutic effectiveness. Further refinement of formulation parameters could yield optimized drug delivery strategies, potentially enhancing treatment outcomes for hypertension and associated conditions.

Keywords: Azilsartan Medoxomil, solid dispersion, polyvinylpyrrolidone, solubility enhancement, dissolution rate, formulation optimization

Introduction:

Azilsartan medoxomil, a potent angiotensin II receptor blocker, is widely used in the management of hypertension. Despite its efficacy, its poor aqueous solubility poses a significant challenge to its oral delivery and bioavailability. This limitation often leads to suboptimal therapeutic outcomes and necessitates the administration of higher doses, which may increase the risk of adverse effects. To overcome this challenge, various strategies have been explored to enhance the solubility and oral bioavailability of azilsartan medoxomil through the development of modified dosage forms. One promising approach to improving the solubility and bioavailability of poorly water-soluble drugs like azilsartan medoxomil is the formulation of modified dosage forms such as nanoparticles, solid dispersions, lipid-based formulations, and cyclodextrin complexes. These formulations aim to increase the dissolution rate and enhance the gastrointestinal absorption of the drug, thereby improving its bioavailability and therapeutic efficacy. Nanoparticle-based formulations offer several advantages, including increased surface area, enhanced drug dissolution, and improved cellular uptake. Various methods such as nanoprecipitation, emulsification, and solvent evaporation have been employed to prepare azilsartan medoxomil nanoparticles with improved solubility and oral bioavailability. In addition, solid dispersion formulations, in which the medicine is dissolved in a hydrophilic polymer matrix, show promise for enhancing the rate of dissolution and gastrointestinal absorption of drugs that dissolve poorly in water. Furthermore, lipid-based formulations such nanostructured lipid carriers and solid lipid nanoparticles provide ways to improve azilsartan medoxomil's solubility and stability, increasing its oral bioavailability. A lot of interest has been shown in cyclodextrins, which are cyclic oligosaccharides with a lipophilic inner cavity and a hydrophilic outside, as complexing agents for improving the aqueous solubility and dissolution rate of pharmaceuticals that are poorly soluble in water. Cyclodextrins have the ability to increase azilsartan medoxomil's solubility and oral bioavailability by forming inclusion complexes with it. Moreover, the selection of appropriate

cyclodextrin derivatives and optimization of formulation parameters can further improve the efficacy of these complexes. In addition to formulation strategies, various techniques such as spray drying, freeze-drying, and hot-melt extrusion have been utilized to prepare modified dosage forms of azilsartan medoxomil with enhanced solubility and oral bioavailability. These techniques offer precise control over the particle size, morphology, and drug-polymer interactions, thereby optimizing the formulation for improved performance. Furthermore, the physicochemical characterization of modified dosage forms is essential to understand their structure-property relationships and predict their in vivo performance. The physical and chemical characteristics of pharmaceutical formulations are routinely examined using techniques including scanning electron microscopy, X-ray diffraction, Fourier-transform infrared spectroscopy, and differential scanning calorimetry. These analytical techniques shed light on the molecular interactions between the drug and excipients, hence providing important insights into the processes underlying azilsartan medoxomil formulations' improved solubility and bioavailability. This work presents new strategies for improving azilsartan medoxomil's oral bioavailability and solubility using altered dose formulations. Our objective is to provide insight into the current state of research and suggest future avenues for investigation by investigating diverse formulation processes and characterisation methodologies. Through the resolution of issues associated with the oral delivery of poorly soluble medications, such azilsartan medoxomil, these novel dosage forms provide opportunities for enhanced therapeutic efficacy and patient compliance in the management of hypertension.

Material and method

The polymers and chemicals used were all of analytical grade.

Method

Solid dispersion preparation: Pharmaceutical compounds that are poorly soluble can be enhanced by solid dispersion preparation, which offers a versatile approach in drug formulation. Among the techniques utilized for its preparation, the physical blending approach emerges as a simple yet effective method (Beneš et al., 2017). This method entails mixing Azilsartan Medoxomil with poloxamer 407 in various proportions, ranging from 1:0.25 to 1:2 (activeingredient: carrier), within a glass mortar for 30 minutes. A hundred sieves are then used to sift the mixtures and to ensure uniform particle size distribution before storage in a desiccator. In this methodology, the selection of a suitable carrier matrix assumes paramount importance, as it profoundly affects the compatibility and enhancement of drug solubility. Frequently employed carrier matrices encompass polymers like polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG). The active ingredient and the chosen carrier matrix are weighed according to the desired ratio, followed by thorough mixing using either a mortar and pestle or a mixer. Careful attention is dedicated to ensuring the homogeneous dispersion of the active ingredient throughout the carrier matrix during the blending process.

Evaluation of the Solid Dispersion

Measuring the Melting Temperature of Azilsartan Medoxomil

The capillary method entails the use of borosilicate glass capillary tubes, which are filled with accurately measured samples of Azilsartan Medoxomil and subsequently sealed. These sealed tubes are placed onto a sample holder within a melting point apparatus, where the temperature is gradually raised. As the temperature increases, the Azilsartan Medoxomil sample enclosed within the capillary tube undergoes melting, and this process is visually observed. The

temperature at which the initial signs of melting become apparent is recorded as the melting temperature of Azilsartan Medoxomil. Before analysis, the melting point apparatus undergoes calibration using known reference standards, and the reliability of the results is confirmed by conducting repeated analyses for consistency. The acquired data on melting temperature are subject to statistical analysis to evaluate precision and reproducibility, ensuring dependable characterization of Azilsartan Medoxomil for quality assurance purposes in pharmaceutical research and development.

Analysis of Azilsartan Medoxomil Absorption Spectrum

For the sample solution preparation, Azilsartan Medoxomil undergoes precise weighing and dissolution in 0.1N hydrochloric acid (HCl) adjusted to pH 1.2, achieving a concentration suitable for optimal absorbance within the spectrophotometer's linear range. Following this, the solution is transferred into a quartz cuvette suitable for UV-Vis spectrophotometry, and its absorbance spectrum is captured across the desired wavelength range of 200 to 400 nm. A blank solution consisting solely of 0.1N HCl at pH 1.2 is employed to correct for any solvent or instrument-related absorbance. Subsequently, the absorption spectrum of Azilsartan Medoxomil in 0.1N HCl at pH 1.2 is scrutinized to pinpoint the wavelength corresponding to maximum absorbance (λmax), signifying the peak absorption point under the given solvent and pH parameters. The absorbance values obtained at λmax are then analyzed to deduce the concentration of Azilsartan Medoxomil in the sample solution, often facilitated by constructing calibration curves using standard solutions.

Establishment of Azilsartan Medoxomil Calibration Curve

To establish the calibration curve for Azilsartan Medoxomil, a range of dilutions is prepared from the stock solution, which contains 10 mg of Azilsartan Medoxomil per 100 ml. These dilutions are made in both 0.1N HCl and phosphate buffer at pH 6.8, resulting in solutions with varying concentrations of the drug. The absorbance of each solution is then measured at the drug's maximum absorbance wavelength (λmax). Plotting the measured absorbance values against their respective concentrations enables the construction of the calibration curve.

Assessment of Solubility

By measuring azilsartan medoxomil's saturation solubility in distilled water, 0.1N hydrochloric acid pH 1.2, and phosphate buffers at pH 7.4 and 6.8, a solubility assessment was conducted. The azilsartan medoxomil was agitated for 24 hours in an incubator shaker set at 25°C with 10 ml of each solvent. Post-incubation, the solutions underwent centrifugation at 8000 rpm for 20 minutes to separate any undissolved residues. The resulting supernatants were subsequently filtered using a 0.45 µm pore size filter and then diluted with the corresponding solvent. The solubility of azilsartan medoxomil was determined by measuring the absorbance of the filtered and diluted solutions employing a UV-visible spectrophotometer. The solubility was calculated based on the obtained absorbance readings, providing insights into the compound's solubility profile across different solvents.

Assessment of Drug Content

In the presence of 30 mL of methanol, solid dispersions weighed exactly 10 mg of Azilsartan Medoxomil were dissolved in methanol. Insoluble particles were removed from the filtrate,

and the drug content was determined using a UV spectrophotometer at 248 nm. The following formula was used for determining the actual drug content:

% Drug content = (Actual amount of Azilsartan Medoxomil in solid dispersion powder / Total weight of solid dispersion powder) × 100

This calculation provided the percentage of drug content present in the solid dispersion formulation.

Enhanced Analysis with FTIR spectroscopy

Using Fourier Transform Infrared Spectroscopy (FTIR) enables a thorough examination of material compositions and structures, making it a valuable analytical technique. Its application extends to the investigation of solid dispersions, which involve mixing various components in a solid state to enhance drug solubility and bioavailability. In this context, FTIR plays a pivotal role in evaluating the interactions between drugs and polymers within solid dispersions. By analyzing changes in peak positions and shifts in FTIR spectra, alterations in functional groups of both drug and polymer constituents can be identified. This analysis offers valuable insights into the intricate dynamics of solid dispersions, shedding light on their potential in pharmaceutical formulations to improve drug solubility.

Exploring Thermal Properties with Differential Scanning Calorimetry (DSC)

Various solid dispersions can be analyzed using differential scanning calorimetry (DSC). Furthermore, DSC provides valuable measurements of heat flow between samples and reference materials over a wide temperature range in addition to providing valuable insight into thermal behavior. As a result of DSC, both the drug and the polymer matrix can be determined regarding their thermal properties. This results in a broad endothermic peak, indicating either the drug or the polymer has melted. Drug-polymer interactions and crystallinity can be evaluated through the analysis of parameters like peak temperature and melting enthalpy. This method offers a non-invasive and comprehensive approach to exploring solubility within solid dispersions, providing essential information about their pharmaceutical behavior.

Result and discussion

Table 1: Composition Ratios of Azilsartan Medoxomil and βCD

Batch Code	Drug: βCD Ratio	Azilsartan Medoxomil (mg)	βCD (mg)
B1	1:2.5	120	48
B2	1:1	120	120
B3	1:0.5	120	240

Assessment of Melting point

There was a range of 215°C to 217°C observed for Azilsartan Medoxomil melting point.

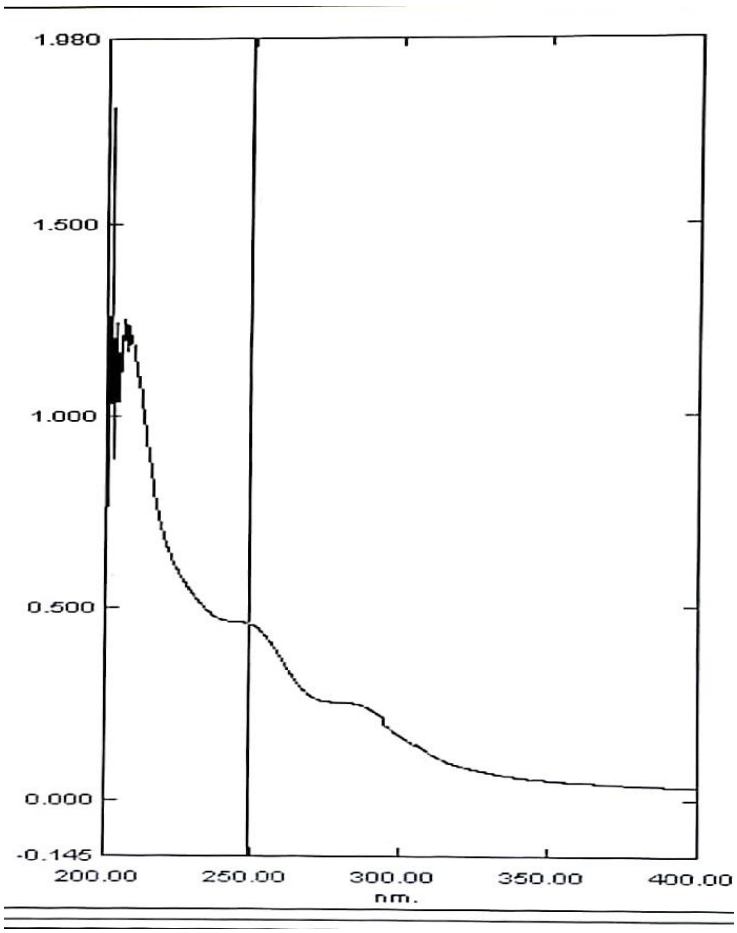

Figure1: Assessment of Melting point of Azilsartan Medoximi

Azilsartan Medoxomil Concentration Calibration Curve

The concentration calibration curve of Azilsartan Medoxomil indicates a peak wavelength (λmax) at 248 nm.

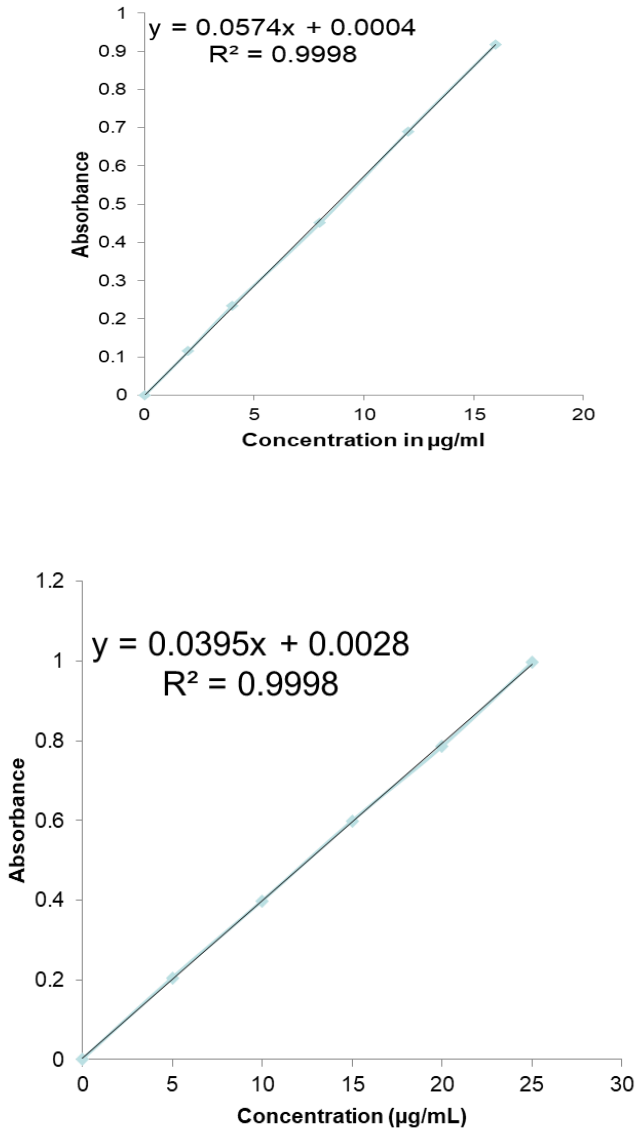

Figure 2: Azilsartan Medoxomil Concentration Calibration Curve

Solubility assessment in different solvants

Azilsartan Medoxomil melting point ranged from 215°C to 217°C, which was observed in solid dispersion formulations for azilsartan medoxomil (AZM). Incorporating PEG 4000 as the carrier material led to a significant rise in AZM solubility, with enhancements reaching up to 7.5 times.

Table 2: Solubility Assessment across Various pH Levels

Solvent	Solubility (µg/ml)
pH 1.2	22.50 ± 0.15
pH 6.8	385 ± 0.7
pH 7.4	1050 ± 1.5

Water	17.5 ± 0.2

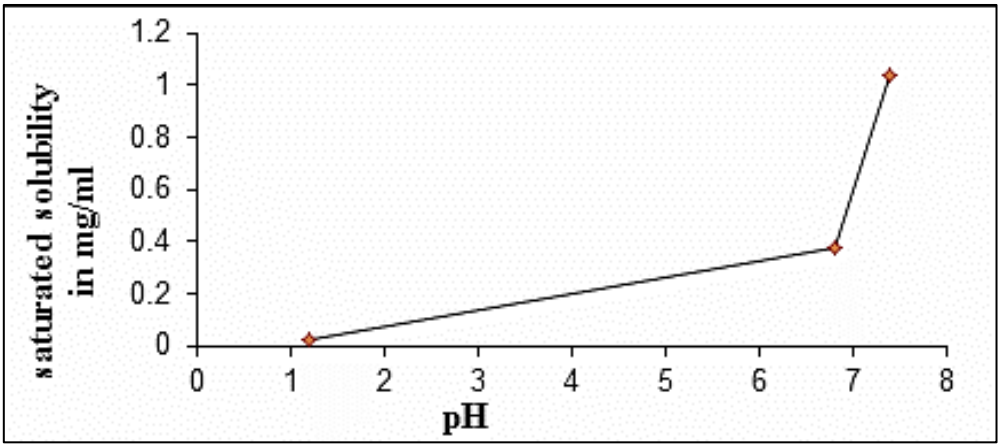

Figure 3: Influence of different pH on Solubility

Assessment of Solubility via Fourier Transform Infrared Spectroscopy (FTIR):

Azilsartan Medoxomil solubility was assessed using Fourier transform infrared spectroscopy (FTIR), which provided information about the molecular interactions involved. The FTIR spectrum of Azilsartan Medoxomil when analyzed alone displayed distinct absorption peaks at specific wavenumbers, encompassing 3389, 3345, 3278, and 1662 cm^{-1}. These peaks are attributed to the stretching vibrations of the amino group. Additionally, peaks at 1569 and 1315 cm^{-1} were observed, correlating with asymmetric stretching vibrations of the carboxyl and sulfonyl groups, respectively. Similarly, the spectrum of β-cyclodextrin (βCD) exhibited notable bands at 2948 cm^{-1}, associated with C-H stretching, and 1662 cm^{-1}, related to C=O stretching. It was found that no new peaks were observed either in the solid dispersion or in the absorption band positions during the formulation or storage of the solid dispersions, indicating that there were minimal interactions between Azilsartan Medoxomil and the solid dispersion. Azilsartan Medoxomil was evaluated based on its FTIR properties evidence of possible molecular interactions, and its solubility characteristics.

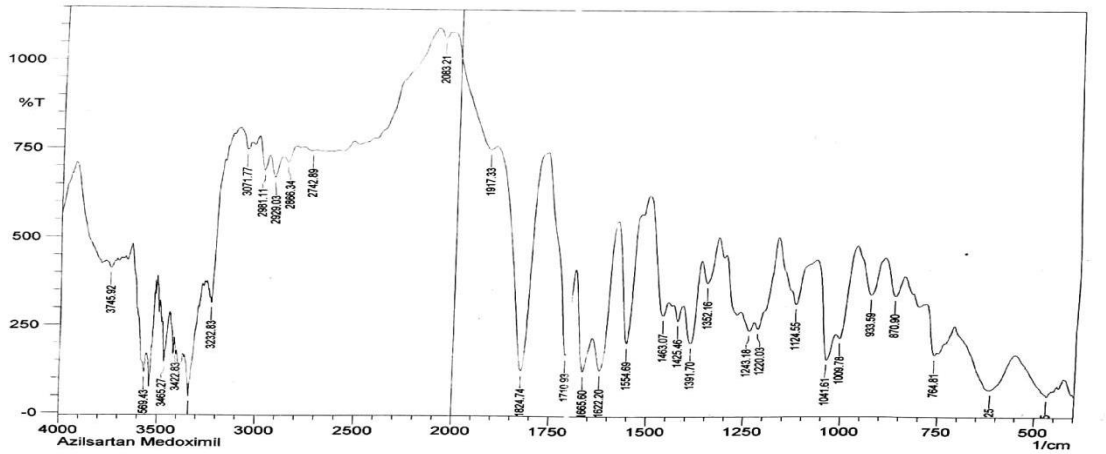

Figure 4: Fourier Transform Infrared Spectroscopy Analysis

Drug Content

The drug content across all formulations varied between 93.02% and 97.04%, aligning with the acceptable limits outlined in the official monograph.

In vitro dissolution investigations

A comparison of solid dispersion formulations with unadulterated drugs has shown that solid dispersion formulations can significantly improve dissolution rates. For instance, research has shown an increase in AZM dissolution rate of up to 85% when HPMC is utilized as the carrier material. Similarly, another study reported a 2.4-fold enhancement in AZM dissolution rate when PEG 4000 is employed as the carrier material.

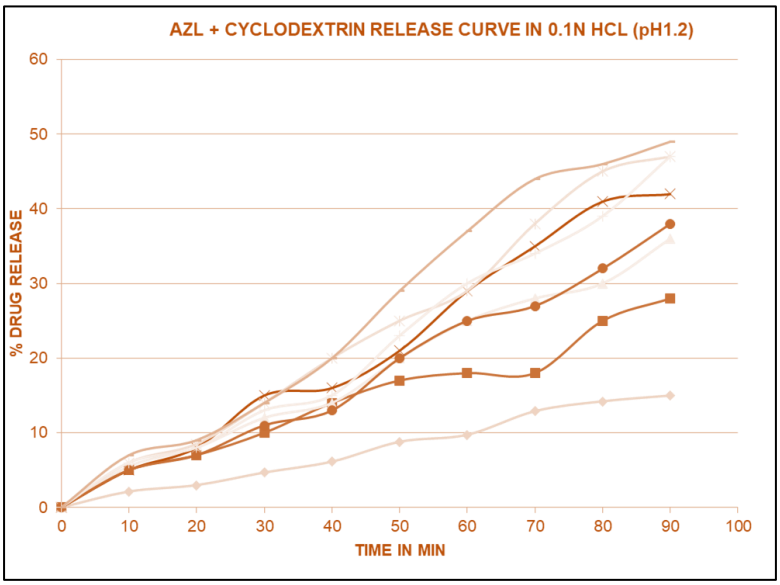

Figure 5: In vitro Release Profile of the Drug.

Differential scanning calorimetry (DSC)

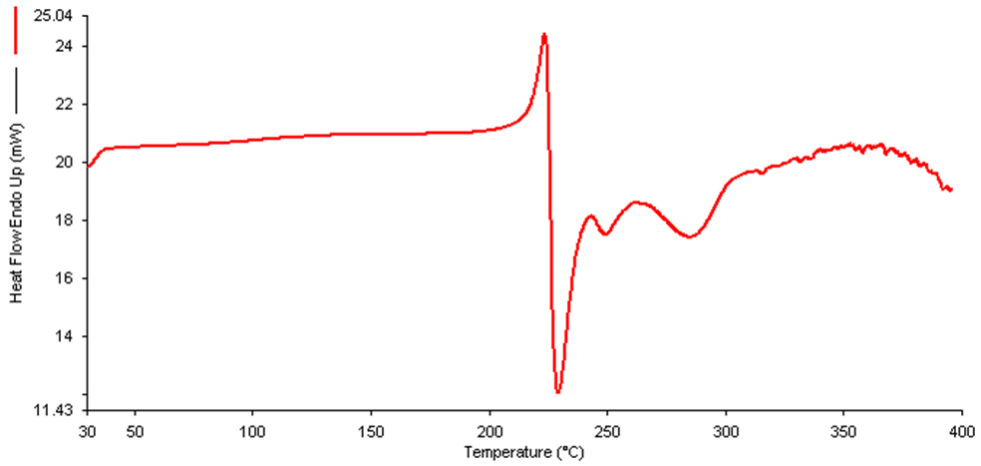

Figure 6: DSC Analysis of Azilsartan Medoxomil

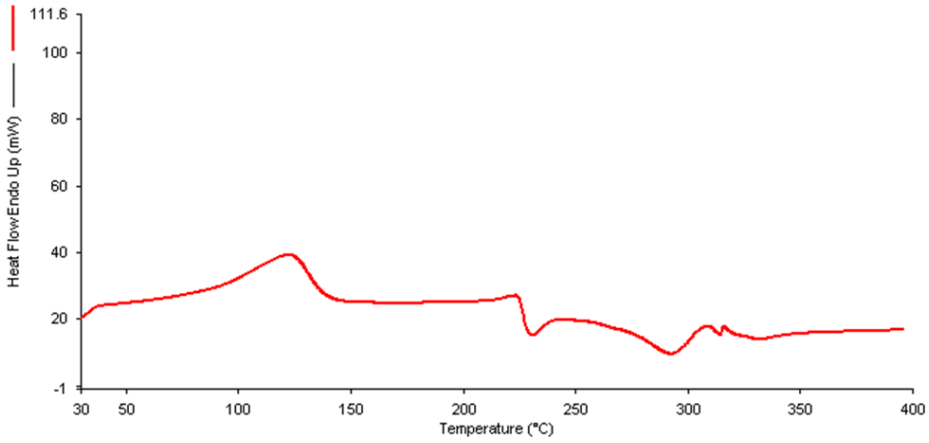

Figure 7: DSC of Azilsartan Medoxomil + Beta-cyclodextrin

CONCLUSION

Solid utilizing dispersions containing azilsartan medoxomil and PVP-K30 in various ratios improves the solubility and dissolution rate of azilsartan medoxomil in aqueous environments, as demonstrated in this study. In contrast to those prepared by kneading, solid dispersions prepared using solvent evaporation demonstrated superior increases in solubility. In comparison to other formulations tested, B3, prepared by solvent evaporation with a ratio of 1:0.5 drug to carrier, significantly increased aqueous solubility by fourfold. As a result of these findings, azilsartan medoxomil formulations have promising clinical efficacy prospects, potentially leading to improved bioavailability and therapeutic effectiveness. The success of the solvent evaporation method highlights its preferential use in preparing solid dispersions of azilsartan medoxomil with PVP-K30. These findings contribute valuable insights to the field, supporting solid dispersion technology as an effective approach for enhancing the solubility and dissolution characteristics of poorly water-soluble drugs, ultimately facilitating their formulation into more effective pharmaceutical products. Further investigation may explore additional formulation parameters and optimization strategies to fully exploit the therapeutic potential of azilsartan medoxomil solid dispersions, aiming to optimize drug delivery and enhance patient outcomes in hypertension and related conditions.

Conflict of interest

None

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