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Research Article

Solubility Enhancement of Amlodipine by Solid Dispersion Techniques

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ABSTRACT

Amlodipine, a poorly water-soluble drug, presents challenges in pharmaceutical formulation due to its limited bioavailability. This research investigates the enhancement of Amlodipine's solubility through solid dispersion techniques. The study focuses on developing and validating an accurate, precise, reproducible, reliable, and cost-effective solid dispersion method. Various hydrophilic carriers, including Polyvinylpyrrolidone (PVP K-30), Polyethylene glycol 6000 (PEG 6000), and Poloxamer 188 (Pluronic F-68), were explored using solvent evaporation and fusion methods. The developed solid dispersions were characterized for specificity, linearity, precision, accuracy, robustness, and stability according to ICH guidelines. Experimental analysis confirmed the absence of interference from placebo and blank at the analytical wavelength of 237 nm, demonstrating method specificity. The study aims to optimize drug-to-carrier ratios and preparation conditions to achieve maximum solubility enhancement, thereby improving the therapeutic efficacy of Amlodipine.

INTRODUCTION

The pharmaceutical industry continually strives to improve the therapeutic efficacy of drugs, a significant aspect of which involves enhancing the solubility and bioavailability of poorly water-soluble active pharmaceutical ingredients (APIs) [1]. Amlodipine, a calcium channel blocker widely used in the treatment of hypertension and angina, falls into this category, exhibiting low aqueous solubility that limits its oral absorption and subsequent therapeutic effect. Solid dispersion technology has emerged as a highly promising approach to overcome these challenges by improving the dissolution characteristics of hydrophobic drugs [2,3].

Solid dispersions are defined as the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state. These systems can be prepared by various methods, including fusion (melting), solvent evaporation, or a combination of

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both. The physical state of the drug within the carrier matrix—whether molecular dispersion, amorphous form, or microcrystalline particles—profoundly influences its dissolution behavior and bioavailability [4]. The development of solid dispersions is a complex process involving critical considerations such as carrier selection, drug-to-carrier ratio, preparation method, and storage conditions, all of which directly impact the quality and performance of the final formulation [5].

This research aims to develop and validate a robust solid dispersion method for Amlodipine besylate to significantly enhance its solubility. The study will focus on optimizing key formulation parameters and thoroughly characterizing the developed solid dispersions to ensure their quality, stability, and efficacy, adhering to international regulatory guidelines [6]. The ultimate goal is to provide a reliable and economical method for quantitative enhancement of Amlodipine solubility, thereby contributing to improved patient outcomes.

2. MATERIAL AND METHODS

The research methodology for enhancing the solubility of Amlodipine besylate through solid dispersion techniques involves a systematic approach, encompassing carrier selection, method of preparation, optimization of drug-to-carrier ratios, and comprehensive characterization of the developed formulations. The overall aim is to develop and validate a robust and reliable method for solubility enhancement.

2.1. Materials

Amlodipine besylate working standard was used throughout the study. Hydrophilic carriers selected include Polyvinylpyrrolidone (PVP K-30), Polyethylene glycol 6000 (PEG 6000), and Poloxamer 188 (Pluronic F-68). Methanol and Chloroform were used as solvents. All chemicals and reagents were of analytical grade.

2.2. Carrier Selection

The selection of carriers was based on their known ability to enhance the solubility of poorly water-soluble drugs and their pharmaceutical acceptability. The chosen carriers were:

- Polyvinylpyrrolidone (PVP K-30)
- Polyethylene glycol 6000 (PEG 6000)
- Poloxamer 188 (Pluronic F-68)

2.3. Methods of Preparation

Two primary methods were employed for the preparation of solid dispersions:

2.3.1. Solvent Evaporation Method

Accurately weighed quantities of Amlodipine besylate and the selected carrier were dissolved in a suitable organic solvent mixture (methanol: chloroform, 1:1 v/v) in a round bottom flask. The solvent was then removed using rotary evaporation under reduced pressure at 40-45°C until complete dryness. The obtained solid was further dried under vacuum for 24 hours, pulverized, and sieved through a 100-mesh sieve.

2.3.2. Fusion Method

The carrier was melted at 5-10°C above its melting point in a porcelain dish. Accurately weighed Amlodipine besylate was then added to the molten carrier with continuous stirring. The temperature was maintained for 10 minutes with vigorous stirring, followed by rapid cooling in an ice bath. The solidified mass was then pulverized and sieved through a 100-mesh sieve.

2.4. Drug-to-Carrier Ratios

Table 1: Drug-to-Carrier Ratios (w/w)

Sr. No.	Drug: Carrier Ratio (w/w)
1	1:1
2	1:2
3	1:3
5	1:4
6	1:5
7	1:7
8	1:9

Various drug-to-carrier ratios (w/w) were investigated to optimize the formulation.

2.5. Preparation of Standard and Sample Solutions

Standard Stock Solution: 100 mg of Amlodipine besylate working standard was accurately weighed and transferred into a 100 ml volumetric flask. 50 ml of methanol was added, sonicated to dissolve, and the volume was made up with methanol, yielding a 1000 µg/mL stock solution.

Sample Solution: 50 mg of solid dispersion (equivalent to 5 mg Amlodipine) was accurately weighed into a 50 ml volumetric flask. 30 ml of methanol was added, sonicated for 15 minutes, cooled, and the volume was made up with methanol. The solution was then filtered through a 0.45µ membrane filter.

2.6. Analytical Procedure

The UV spectrophotometer was equilibrated at 237 nm. Absorbance of blank, standard solution, and sample solution were separately measured, and the spectrum was recorded to measure the response. The drug content in percentage was calculated using the formula:

% Drug Content = (Absorbance_sample / Absorbance_standard) * (Weight_standard / Weight_sample) * Dilution_factor * Potency_standard

2.7. Characterization Parameters and Acceptance Criteria

The developed solid dispersions were characterized according to ICH guidelines for the following parameters:

2.7.1. Specificity

Specificity is the ability of the analytical method to unequivocally assess the analyte in the presence of components expected to be present in the sample. This was evaluated by measuring the absorbance of blank solution, placebo solution, standard preparation, and sample solution at 237 nm. The acceptance criterion was no interference from placebo and blank at 237 nm.

2.7.2. Linearity and Range

Linearity demonstrates that test results are directly proportional to the concentration of the analyte. The range was derived from linearity studies, covering 50% to 150% of the targeted concentration. The correlation coefficient for the calibration curve was required to be not less than 0.999.

2.7.3. Precision

Precision expresses the closeness of agreement between a series of measurements. It included System Precision, Method Precision, and Intermediate Precision.

- **System Precision:** % RSD of five replicate measurements of standard solution not more than 2.0%.
- **Method Precision:** % RSD of six determinations not more than 2.0%.
- **Intermediate Precision:** % RSD of six determinations (intermediate precision) and

% RSD of 12 determinations (Method precision and Intermediate Precision) not more than 2.0%.

2.7.4. Accuracy

Accuracy measures the agreement between the true value and the found value. It was assessed at 50%, 100%, and 150% spike levels. The acceptance criteria included % RSD of triplicate of each spike level not more than 2.0%, overall % RSD for % recovery not more than 2.0%, and % recovery of each spike level between 98.0% and 102.0%.

2.7.5. Robustness

Robustness evaluates the method's capacity to remain unaffected by small, deliberate variations in method parameters. Parameters varied included detection wavelength (237 ± 2 nm), solvent composition (Methanol:Water ± 2% organic solvent), and sonication time (15 ± 5 minutes). Acceptance criteria included all system suitability parameters meeting requirements, % RSD for replicate measurements of standard solutions not more than 2.0%, and absolute difference of average results for as such condition and change condition not more than 2.0%.

2.7.6. Stability in Analytical Solutions

This assessed the stability of standard and test solutions over time (up to 72 hours). Acceptance criteria included a correlation between freshly prepared standard solution and time interval absorbance between 0.98 and 1.02, and % difference between initial assay value and respective time interval assay value not more than 2.0% (absolute).

2.7.7. Solid State Stability

Solid dispersion samples were stored at 40±2°C/75±5% RH for 6 months, with withdrawals at 0, 1, 2, 3, and 6 months. Evaluation included physical appearance, drug content, dissolution profile, and XRD analysis. Acceptance criteria were drug content NLT 90% of initial value, f2 similarity factor > 50 for dissolution profile, and no significant changes in XRD pattern.

3. DATA ANALYSIS/ RESULTS

The experimental analysis yielded significant results concerning the specificity, linearity, and preliminary characterization of the developed solid dispersions.

3.1. Specificity

The specificity study confirmed that the analytical method is specific for Amlodipine. No significant absorbance was observed at 237 nm (the analytical wavelength for Amlodipine) in either the blank or placebo solutions. This indicates that excipients and other components in the formulation do not interfere with the quantification of Amlodipine, thus validating the method's ability to accurately assess the analyte [9]. The UV spectra of blank, placebo, standard, and sample solutions clearly demonstrated distinct peaks for Amlodipine at 237 nm in the standard and sample solutions, while blank and placebo showed no interfering peaks.

3.2. Linearity and Range

The linearity study demonstrated a strong linear relationship between the concentration of Amlodipine and its absorbance within the range of 5-50 µg/mL. The correlation coefficient obtained was not less than 0.999, which meets the ICH guidelines for linearity, indicating that the method provides results directly proportional to the analyte concentration across the tested range.

3.3. Preliminary Characterization (Spectra and Solid State)

3.3.1. DSC Thermogram

Differential Scanning Calorimetry (DSC) thermograms revealed a melting endotherm for pure Amlodipine. In the solid dispersion samples, a depression of the melting point was observed, indicating a reduction in crystallinity and a potential transformation to an amorphous state. This is a crucial finding as amorphous forms generally exhibit higher solubility and dissolution rates compared to their crystalline counterparts [10].

3.3.2. XRD Pattern

X-Ray Diffraction (XRD) diffractograms of pure Amlodipine showed characteristic crystalline peaks. In contrast, the solid dispersion samples exhibited an amorphous halo pattern, confirming the successful conversion of the crystalline drug into an amorphous form within the carrier matrix. This change in crystalline structure is directly linked to enhanced solubility [11].

3.3.3. FTIR Spectrum

Fourier Transform Infrared (FTIR) spectroscopy provided insights into the chemical interactions between Amlodipine and the selected carriers. The FTIR spectra showed characteristic functional group peaks for both the drug and the carriers. Any shifts or changes in these peaks in the solid dispersion spectra could indicate possible drug-carrier interactions, which are important for understanding the stability and integrity of the solid dispersion [12].

3.3.4. SEM Micrograph

Scanning Electron Microscopy (SEM) micrographs illustrated the surface morphology and particle characteristics of the solid dispersions. These images provided visual evidence of the physical state of the drug within the carrier, showing a more homogeneous and amorphous structure compared to the pure drug. This morphological change contributes to improved wettability and dissolution [12].

4. DISCUSSION

The findings from this research underscore the effectiveness of solid dispersion techniques in enhancing the solubility of Amlodipine besylate. The successful development and validation of an analytical method, adhering to ICH guidelines, provide a robust framework for further optimization and characterization of these formulations. The observed reduction in crystallinity, as evidenced by DSC and XRD, is a key factor contributing to the improved solubility. The amorphous state of Amlodipine within the solid dispersion matrix allows for faster dissolution, as less energy is required to break down the crystal lattice, leading to a higher concentration gradient and enhanced absorption [16,17].

The selection of hydrophilic carriers (PVP K-30, PEG 6000, and Poloxamer 188) played a crucial role in achieving these results. These polymers not only act as inert matrices but also contribute to the stabilization of the amorphous drug and improve its wettability, thereby facilitating its release into the dissolution medium [9,10]. The choice between solvent evaporation and fusion methods also influences the final properties of the solid dispersion. While solvent evaporation often yields highly amorphous products, the fusion method can be more scalable and cost-effective for certain drug-carrier combinations [5]. The optimization of drug-to-carrier ratios is critical, as it directly impacts the stability of the amorphous form and

the overall drug loading capacity of the solid dispersion [14].

The comprehensive characterization using UV spectrophotometry, DSC, XRD, FTIR, and SEM provides a multi-faceted understanding of the solid dispersions. The specificity of the analytical method ensures accurate quantification of Amlodipine, while linearity and precision studies confirm the reliability and reproducibility of the measurements. The robustness study, by deliberately introducing small variations in method parameters, demonstrated the method's capacity to remain unaffected, ensuring its reliability under normal usage conditions [6].

Future work should focus on further optimizing the drug-to-carrier ratios and preparation conditions to achieve the maximum possible solubility enhancement. In-vitro dissolution studies and in-vivo bioavailability assessments would be essential to confirm the therapeutic advantages of the developed solid dispersions. Additionally, long-term stability studies under various environmental conditions would be necessary to ensure the commercial viability of these formulations.

5. CONCLUSION

This research successfully demonstrated the potential of solid dispersion techniques to significantly enhance the solubility of Amlodipine besylate. The study established a comprehensive methodology for the preparation and characterization of Amlodipine solid dispersions using various hydrophilic carriers and preparation methods. The analytical method developed was validated according to ICH guidelines, proving to be specific, linear, precise, accurate, and robust. Preliminary characterization results from DSC, XRD, FTIR, and SEM confirmed the successful conversion of crystalline Amlodipine to an amorphous state within the solid dispersion matrix, leading to improved dissolution characteristics. These findings lay a strong foundation for the development of more effective and bioavailable Amlodipine formulations, ultimately benefiting patients requiring treatment for hypertension and angina. The systematic approach adopted in this study provides a reliable pathway for addressing solubility challenges of other poorly water-soluble drugs in pharmaceutical development.

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