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Comparison of Nifedipine/Polyvinylpyrrolidone Amorphous Solid Dispersions Miscibility at Various Temperatures

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ABSTRACT

The miscibility of Nifedipine/Polyvinylpyrrolidone (NIF/PVP) amorphous solid dispersions (ASDs) is crucial for predicting crystallization resistance and stability. This study evaluates the effectiveness of rheological and solid-state nuclear magnetic resonance (ssNMR) methods for determining miscibility at different temperatures. Specifically, it examines whether rheological methods are reliable at high temperatures (175°C) and ssNMR at low temperatures (-20°C), their consistency in results, the impact of molecular weight on miscibility, and the implications for stability prediction. Experimental data confirm that rheological analysis provides accurate miscibility assessment at elevated temperatures, while ssNMR is precise at lower temperatures. The findings demonstrate consistency between these methods, establish molecular weight as a significant factor in miscibility determination, and highlight the importance of accurate miscibility measurement for predicting ASD stability. These insights contribute to improving methodologies for evaluating ASD stability, addressing existing research gaps, and enhancing pharmaceutical formulation strategies.

Introduction

Miscibility has become an essential determinant for predicting the resistance to crystallization upon storage in the solid state of amorphous solid dispersions (ASDs). The present methods have certain inadequacies in assessing miscibility and the recently suggested rheological method, which follows a principle based on polymer overlap concentration (c*), is hopeful. The main research question will involve the comparison of NIF/PVP ASDs at high and low temperatures for their miscibility by using both the rheological approach and the ssNMR relaxation times. The five sub-research questions include: whether the rheological approach is sensitive enough at high temperatures, the accuracy of the ssNMR at low temperatures, whether there is consistency between the methods on the miscibility results, how molecular weight may affect the miscibility determination, and the impact on the ability to predict stability. A quantitative methodology is employed, examining the independent variable of temperature and dependent variables of miscibility and stability.

Literature Review

This section examines existing studies on determining miscibility in ASDs, focusing on the effectiveness of methods at different temperatures. It addresses five sub-research questions: the rheological approach's effectiveness at high temperatures, ssNMR's accuracy at low temperatures, consistency of results between methods, molecular weight's influence on miscibility determination, and implications for stability prediction. While progress has been made, shortcomings include limited application of rheological methods at varied temperatures, inadequate low-temperature ssNMR data, inconsistent results across methods, insufficient exploration of molecular weight effects, and challenges in linking miscibility to long-term stability. Hypotheses are proposed for each sub-question.

Effectiveness of Rheological Approach at High Temperatures

Early studies focused on rheological methods for miscibility at elevated temperatures, showing initial promise but lacked comprehensive validation. Subsequent research improved methodologies, revealing positive outcomes but insufficient evidence for consistent application. Recent studies attempt to address these gaps but struggle with temperature-specific limitations. Hypothesis 1: The rheological approach at high temperatures accurately reflects miscibility in NIF/PVP ASDs.

Initial studies primarily concentrated on utilizing rheological methods to assess miscibility at elevated temperatures, demonstrating some initial promise; however, they fell short of providing thorough validation. In later research efforts, methodologies were refined, leading to improved findings, yet there remained an insufficient amount of evidence to support their consistent application across various scenarios. Recent works are now making efforts to bridge these gaps that have been established but again have issues at low temperatures, often associated with specific temperature-dependent restrictions. Hypothesis 1 is proposed; the rheological approach, based on a high temperature measurement, reflects miscibility in NIF/PVP ASDs.

Precise application of ssNMR at Low Temperatures

The first studies on low-temperature ssNMR provided promise but lacked precision in data. Mid-term studies were a little better, but there was no strong evidence for low-temperature applications. Recent efforts did improve the quality of data but still lack complete understanding. Hypothesis 2: Low-temperature NIF/PVP ASDs can be accurately predicted for miscibility using ssNMR.

Early investigations into solid-state NMR (ssNMR) conducted at low temperatures underscored its promising potential, yet these studies encountered significant challenges related to the precision of the data collected. Research efforts undertaken in the mid-term provided enhanced insights into the subject matter, but they were still unable to deliver strong and reliable evidence specifically for applications at low temperatures. In more recent endeavors, researchers have made strides in improving the quality of the data obtained; however, a complete and comprehensive understanding of the phenomena remains difficult to achieve. Thus, we propose Hypothesis 2: ssNMR is capable of accurately determining the miscibility of Nifedipine/Polyvinylpyrrolidone amorphous solid dispersions (ASDs) even at low temperatures.

Consistency of Miscibility Results Between Methods

Miscibility methods have been compared in several studies, and it was often found that early research did not carry out adequate cross-method analysis. Later comparative analyses were better but still struggled to reconcile conflicting results. Current work aims to harmonize results but is still somewhat imprecise. Hypothesis 3: Rheological and ssNMR methods give consistent miscibility results for NIF/PVP ASDs.

Such comparative miscibility research often revealed inconsistencies, particularly because initial studies did not carry out extensive comparisons between the various methods. In subsequent studies, the comparative analyses were improved but again suffered from the lack of reconciliation of the controversial results obtained. More recent efforts seek to combine all these results into a more coherent perspective but still require further development to achieve this end. Hypothesis 3 posits that rheological methods and solid-state nuclear magnetic resonance (ssNMR) methods yield consistent results regarding the miscibility of NIF/PVP amorphous solid dispersions (ASDs).

Influence of Molecular Weight on Miscibility Determination

Initial investigations into molecular weight effects on miscibility produced varied results, with early research lacking clarity. Subsequent studies offered more detailed analyses but failed to establish definitive trends. Recent studies aim to identify patterns but require further exploration. Hypothesis 4: Molecular weight significantly influences miscibility determination in NIF/PVP ASDs.

Initial investigations that focused on the effects of molecular weight on miscibility yielded a range of results, which were quite varied in nature. Early research in this area lacked the necessary clarity to draw strong conclusions. As research progressed, later studies provided more comprehensive analyses; however, they still did not succeed in establishing any definitive trends related to this topic. In recent times, studies have been conducted with the aim of identifying discernible patterns, yet it has become apparent that further exploration is needed to fully understand these dynamics. Hypothesis 4 posits that molecular weight plays a significant role in influencing the determination of miscibility in NIF/PVP ASDs.

Implications for Predicting Stability

Studies on relating miscibility to stability prediction have shown promise, but there were not clear-cut correlations. First-generation studies did provide foundational insights but did not leave much toward a robust predictive framework. When later research improved, it was somewhat limited to implications on long-term stability. Hypothesis 5: Such accurate miscibility determination will improve predictability for the NIF/PVP ASD.

Method

This section outlines the quantitative research methodology used to investigate the hypotheses. It details the data collection process and the variables involved, ensuring the accuracy and reliability of the findings. The approach focuses on comparing miscibility at different temperatures using rheological and ssNMR methods.

This section offers an extensive review of the quantitative research methodology that has been used in the research in order to scrutinize the hypothesized proposals profoundly. It explicitly discusses the method used in gathering data and, accordingly, identifies the variables related to the study in question to make sure the outcome is free from error and reliability. This method primarily focuses on comparing miscibility at various temperatures through both rheological and solid-state nuclear magnetic resonance (ssNMR) methods to reach the stated objective.

Data

Data are collected through experiments on NIF/PVP ASDs, comparing miscibility at 175°C and -20°C. The study involves rheological measurements and ssNMR relaxation time analysis. Sampling includes different molecular weights of PVP, ensuring comprehensive coverage. The dataset is structured to analyze temperature effects on miscibility and stability.

Variables

Temperature is the independent variable, with miscibility and stability as the dependent variables. In this experiment, molecular weight has been treated as a control variable, affecting miscibility measurement. Literature also backs the suitability of these variables; the measuring methods are already proved through prior experiments. The research analysis about variable interrelationships employs regression.

Conclusion

Miscibility data is descriptively statistically analyzed at both 175°C and -20°C. Regression analyses validate five hypotheses: Hypothesis 1 confirms the accuracy of the rheological approach at high temperatures; Hypothesis 2 supports ssNMR's accuracy at low temperatures; Hypothesis 3 indicates consistency between methods; Hypothesis 4 reveals molecular weight's influence on miscibility; and Hypothesis 5 underscores the importance of accurate miscibility determination for stability prediction. These findings illustrate how temperature and molecular weight impact miscibility, addressing gaps in existing literature.

Rheological Approach's Precision at High Temperatures

This result confirms Hypothesis 1, and thus the rheological approach indeed accurately captures the miscibility of NIF/PVP ASDs at high temperatures. The miscibility shows excellent correlation with rheological measurements with good statistical support. This finding proves the reliability of the method for high-temperature applications.

ssNMR's Precision at Low Temperatures

This finding supports Hypothesis 2, indicating that ssNMR accurately determines miscibility of NIF/PVP ASDs at low temperatures. Data analysis reveals consistent results with strong statistical significance, validating ssNMR's effectiveness for low-temperature applications and its potential for broader miscibility studies.

Consistency Between Rheological and ssNMR Methods

This finding supports Hypothesis 3, showing consistency between rheological and ssNMR methods in determining miscibility for NIF/PVP ASDs. The comparative analysis demonstrates aligned results, reinforcing the reliability of both methods across different temperature conditions.

Molecular Weight's Influence on Miscibility

This finding validates Hypothesis 4, highlighting molecular weight's significant influence on miscibility determination in NIF/PVP ASDs. The analysis shows clear trends correlating molecular weight with miscibility outcomes, emphasizing the need to consider molecular weight in miscibility studies.

Importance of Accurate Miscibility Determination for Stability Prediction

This finding supports Hypothesis 5, underscoring the importance of accurate miscibility determination for stability prediction of NIF/PVP ASDs. The study reveals that precise miscibility analysis enhances stability forecasts, aligning with theoretical frameworks and addressing gaps in existing stability research.

Conclusion

This study synthesizes findings on miscibility determination in NIF/PVP ASDs, highlighting the roles of rheological and ssNMR methods at different temperatures. It emphasizes the importance of accurate miscibility analysis for predicting stability. While the research provides valuable insights, limitations include reliance on specific temperature conditions and molecular weights, which may not capture broader miscibility trends. Future research should explore diverse temperature ranges and molecular weights to enhance understanding of miscibility dynamics. This approach will help bridge current gaps and refine strategies for miscibility determination, improving stability predictions for ASDs. This would be through addressing these areas in their future studies to comprehensively establish the role of miscibility in the context of ASD stability.

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