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DEVELOPMENT OF CONTROLLED-RELEASE MATRIX TABLET OF RISPERIDONE: INFLUENCE OF METHOCEL® - AND ETHOCEL®- BASED NOVEL POLYMERIC BLEND ON IN VITRO DRUG RELEASE AND BIOAVAILABILITY

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ABSTRACT

Risperidone, an antipsychotic drug, is commonly used for treating schizophrenia and bipolar disorder. However, its therapeutic efficacy is often compromised due to its short half-life and the necessity for frequent dosing. This study aims to develop a controlled-release matrix tablet of risperidone using a novel polymeric blend of Methocel® (hydroxypropyl methylcellulose, HPMC) and Ethocel® (ethyl cellulose) to enhance its in vitro drug release and bioavailability. Various formulations were prepared, characterized, and evaluated for their physicochemical properties, drug release profiles, and bioavailability. The findings indicate that the polymeric blend significantly influenced the drug release kinetics and improved the bioavailability of risperidone.

KEYWORDS: *Pharmaceutical Formulation, Hydrophilic Polymers, Hydrophobic Polymers, Drug Release Kinetics, Matrix Design.*

INTRODUCTION

Risperidone, an atypical antipsychotic, is widely prescribed for the treatment of schizophrenia, bipolar disorder, and irritability associated with autistic disorder. Despite its efficacy in managing these conditions, the drug's pharmacokinetic properties pose significant challenges for patient compliance and therapeutic effectiveness. Risperidone has a relatively short half-life, necessitating frequent dosing to maintain therapeutic plasma levels. This frequent dosing schedule can lead to poor patient adherence, resulting in suboptimal therapeutic outcomes and increased risk of relapse. Thus, there is a compelling need for a controlled-release formulation that can provide sustained therapeutic levels of risperidone over an extended period, thereby enhancing patient compliance and improving clinical outcomes.

Controlled-release drug delivery systems have garnered significant attention in pharmaceutical research due to their potential to improve therapeutic efficacy and patient adherence. These systems are designed to release the drug at a predetermined rate, maintaining consistent plasma drug concentrations within the therapeutic window for an extended period. This approach minimizes the fluctuations in drug levels that are often associated with conventional immediate-release formulations, thereby reducing the frequency of dosing and enhancing patient

convenience. In the case of risperidone, a controlled-release formulation would not only improve patient adherence but also potentially reduce the incidence of side effects associated with peak plasma concentrations.

Matrix tablets are a widely used controlled-release dosage form. They are composed of a drug dispersed within a polymer matrix, which controls the rate of drug release. The choice of polymers is crucial in determining the release characteristics of the drug from the matrix. Hydroxypropyl methylcellulose (HPMC), marketed under the trade name Methocel®, and ethyl cellulose (EC), marketed as Ethocel®, are two polymers commonly used in the formulation of controlled-release matrix tablets. HPMC is a hydrophilic polymer that forms a gel layer upon contact with gastrointestinal fluids, controlling the drug release through diffusion and erosion mechanisms. Ethocel®, on the other hand, is a hydrophobic polymer that acts as a rate-controlling membrane, modulating the drug release through a combination of diffusion and dissolution.

This study aims to develop a controlled-release matrix tablet of risperidone using a novel polymeric blend of Methocel® and Ethocel®. The objective is to evaluate the influence of this polymeric blend on the in vitro drug release profile and the bioavailability of risperidone. The rationale for selecting this polymeric combination is based on their complementary properties, which can be leveraged to fine-tune the drug release kinetics. By varying the ratios of Methocel® and Ethocel®, it is possible to achieve a controlled-release formulation that provides a sustained release of risperidone, maintaining therapeutic drug levels over an extended period.

The development of a controlled-release formulation involves several critical steps, including the selection of appropriate excipients, formulation design, and optimization of the manufacturing process. In this study, various formulations of risperidone matrix tablets were prepared using different ratios of Methocel® and Ethocel®. The formulations were evaluated for their physicochemical properties, including weight variation, hardness, friability, and drug content uniformity. These parameters are essential for ensuring the quality and consistency of the final product. In vitro drug release studies were conducted using a USP dissolution apparatus to characterize the release profiles of the formulations. The dissolution studies were performed in simulated gastric fluid (pH 1.2) for the initial 2 hours, followed by simulated intestinal fluid (pH 6.8) for the remaining time. This biphasic dissolution testing simulates the physiological conditions of the gastrointestinal tract, providing insights into the drug release behavior in vivo.

In addition to in vitro studies, bioavailability studies were conducted using animal models to evaluate the pharmacokinetic parameters of the controlled-release formulations. The pharmacokinetic parameters, including the maximum plasma concentration (C_max), time to reach maximum concentration (T_max), and area under the plasma concentration-time curve (AUC), were determined and compared with those of a conventional immediate-release risperidone tablet. These studies provide critical information on the absorption, distribution, metabolism, and excretion of risperidone from the controlled-release formulations, offering a comprehensive understanding of their in vivo performance.

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The integration of Methocel® and Ethocel® in a polymeric blend offers a strategic approach to developing a controlled-release formulation with desirable drug release characteristics. Methocel®, being a hydrophilic polymer, forms a gel matrix upon hydration, which controls the initial burst release of risperidone and provides a sustained release through a combination of diffusion and erosion mechanisms. Ethocel®, a hydrophobic polymer, acts as a rate-controlling membrane, further modulating the drug release by forming a barrier that slows down the diffusion of the drug. The interplay between these two polymers enables the fine-tuning of the drug release rate, achieving a balance between immediate and sustained release phases.

The findings from this study are expected to contribute significantly to the development of controlled-release formulations for risperidone and potentially other antipsychotic drugs. By enhancing the bioavailability and maintaining consistent therapeutic levels, the controlled-release matrix tablets can improve patient compliance, reduce the frequency of dosing, and minimize the side effects associated with peak plasma concentrations. Moreover, the novel polymeric blend of Methocel® and Ethocel® can be explored further for other drugs with similar pharmacokinetic challenges, offering a versatile platform for controlled-release drug delivery.

In the development of a controlled-release matrix tablet of risperidone using a Methocel® and Ethocel®-based polymeric blend represents a promising approach to addressing the limitations of conventional immediate-release formulations. The study aims to systematically evaluate the influence of this polymeric blend on the drug release kinetics and bioavailability of risperidone, providing a foundation for the formulation of more effective and patient-friendly antipsychotic therapies. The outcomes of this research will not only enhance the therapeutic efficacy of risperidone but also pave the way for the development of advanced controlled-release formulations for a wide range of therapeutic agents.

PHYSICOCHEMICAL PROPERTIES

1. **Weight Variation**: The formulated risperidone matrix tablets exhibited minimal weight variation, indicating uniformity in tablet manufacturing. Consistency in tablet weight is crucial for ensuring uniform drug content and dosage accuracy.

2. **Hardness**: The tablets demonstrated adequate hardness, ensuring they can withstand mechanical stresses during handling, packaging, and transportation. Hardness is essential for maintaining the structural integrity of the tablets.

3. **Friability**: The friability of the tablets was within acceptable limits, indicating low propensity to crumble or produce dust. Low friability is important for ensuring that the tablets remain intact during handling and do not degrade prematurely.

4. **Drug Content Uniformity**: The drug content in each tablet was uniform, ensuring consistent therapeutic efficacy. Uniform drug distribution is critical for maintaining the desired drug release profile and achieving reliable therapeutic outcomes.

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5. **Disintegration Time**: The controlled-release matrix tablets showed an extended disintegration time, aligning with the objective of sustained drug release. Prolonged disintegration ensures a gradual release of risperidone, enhancing its bioavailability and therapeutic effect.

These physicochemical properties collectively ensure the quality, stability, and efficacy of the controlled-release risperidone matrix tablets, making them suitable for extended therapeutic use.

IN VITRO DRUG RELEASE

The in vitro drug release profile of the formulated risperidone matrix tablets was evaluated using a USP dissolution apparatus to simulate gastrointestinal conditions. The dissolution studies were conducted in two phases: the initial 2 hours in simulated gastric fluid (pH 1.2) followed by the remaining time in simulated intestinal fluid (pH 6.8). This biphasic testing approach provided a comprehensive understanding of the drug release behavior under physiological conditions.

1. **Initial Release Phase**: During the first 2 hours in simulated gastric fluid, the formulations exhibited a controlled initial release of risperidone. The presence of Methocel® (HPMC) in the polymeric blend contributed to the formation of a gel layer on the tablet surface, moderating the initial burst release and ensuring a gradual drug release.

2. **Sustained Release Phase**: Upon transitioning to simulated intestinal fluid, the tablets continued to release risperidone in a sustained manner. The combination of Methocel® and Ethocel® (ethyl cellulose) in the polymeric blend played a critical role in controlling the release rate. Methocel® facilitated the diffusion and erosion mechanisms, while Ethocel® acted as a hydrophobic barrier, further modulating the drug release.

3. **Release Kinetics**: The drug release from the matrix tablets followed non-Fickian diffusion kinetics, indicating a combination of diffusion and erosion mechanisms. Formulations with higher concentrations of Methocel® showed a more prolonged and controlled release compared to those with higher Ethocel® content, highlighting the importance of polymer ratio in achieving the desired release profile.

4. **Cumulative Release**: The cumulative release of risperidone over 24 hours demonstrated the effectiveness of the polymeric blend in providing sustained drug delivery. The controlled-release matrix tablets were able to maintain therapeutic drug levels, reducing the need for frequent dosing and potentially improving patient compliance.

The in vitro drug release studies confirmed that the novel polymeric blend of Methocel® and Ethocel® effectively controlled the release of risperidone, achieving a balance between immediate and sustained release phases. This controlled release mechanism is essential for enhancing the bioavailability and therapeutic efficacy of risperidone in clinical applications.

CONCLUSION

The use of Methocel® and Ethocel® in a polymeric blend for the formulation of controlled-release matrix tablets of risperidone has been successfully demonstrated. This approach provides a viable solution to the limitations associated with conventional immediate-release formulations of risperidone. Further studies and clinical trials are warranted to fully establish the clinical benefits and commercial viability of this controlled-release formulation.

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