Simultaneous Determination of Antiemetics Ondansetron and Domperidone Using RPHPLC: An in Vitro Investigation of Drug-Drug Interactions

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ABSTRACT

Background: Cancer, characterized by abnormal cell growth, is a life-threatening cause globally and usually treated via chemotherapy regimens or radiation. Despite advancements in targeted therapies, side effects remain a significant issue, particularly chemotherapy-induced nausea and vomiting (CINV), which is the most prevalent and distressing. If left neglected, it can severely impact the overall treatment efficacy, adherence to chemotherapy protocols, and the patient's quality of life. CINV can be managed with antiemetics and prokinetic agents like Ondansetron (OND) and Domperidone (DOM), which are commonly used in clinical practice.

Existing literature suggested that there is a no sufficient data available regarding the interactions between OND and DOM, when these are co-administered. There is a significant lack of insight into their compatibility profile. Alone methods for both drugs are available but their use in combination has not been rigorously investigated, even though both drugs are well established in managing CINV as an individual therapy, but potential drug-drug interactions between OND and DOM remain undiscovered. This gap highlights the importance of investigating their simultaneous administration to ensure safety, optimize efficacy, and propose a well-tolerated combined formulation for the improved patient outcomes.

An innovative approach of developing a combination dosage form that contains both drugs OND and DOM has been uncovered to fulfill the identified gap, that will lead to more efficient management of CINV. This approach will potentially be enhancing therapeutic efficacy and reducing pill burden, which will encourage patient compliance. However, it is also very essential to establish the compatibility of both drugs to prevent adverse interactions that may affect safety and efficacy,

Objectives: The aim of this proposed study is to establish a reliable, rapid and cost-effective reverse-phase HPLC method for the simultaneous determination of OND and DOM to propose a combined dosage form for the improved CINV management and also to investigate their compatibility through drug-drug interaction studies.

Methodology: A reverse-phase HPLC method that was simple, precise, rapid, and accurate, developed using a C18 column and a mobile phase of methanol: distilled water: acetonitrile (8:1.5:0.5), at a flow rate of 1 ml/min. Detection was carried out at 217 nm. The proposed method was validated against all parameters provided by ICH guidelines, for linearity, accuracy, precision, robustness, and ruggedness. Detection limits and quantification limits were established for both drugs. In-vitro interaction studies were performed at 37°C across four simulated body environments: gastric pH (empty and full), blood and intestinal pH with pH values of 1.2, 4.2, 7.4, and 9 respectively. A statistical paired sample t-test was performed to analyze precision.

Key Findings: The validated method showed excellent linearity (r^2>0.998 for OND and 0.9995 for DOM) across the ranges 2.5-30 µg/ml and 0.625-20 µg/ml, respectively. The accuracy of both drugs ranges from 100.01% -100.83%, with precision for DOM between 0.001% and 0.08%, and for OND between 0.003% and 0.08%. Additionally, the methods demonstrate robustness and ruggedness. Detection limits were 0.1 µg/ml for OND and 0.2 µg/ml for DOM, and quantification limits were 0.4 µg/ml for OND and 0.7 µg/ml for DOM. A paired sample t-test was employed to confirm the precision of the analysis.

In vitro interaction studies were conducted in four simulated body environments. Both drugs were almost stable across all pH levels, with only slight interactions observed in the 3rd hour.

Conclusion: In vitro data suggest co-administration does not trigger significant in vivo interactions, though further research is needed. These results indicate that OND and DOM can be used together to improve CINV management. Pharmaceutical companies might consider developing a combined dosage form to enhance patient adherence and cost-effectiveness.

Keywords: CINV, Ondansetron, Domperidone, HPLC, Drug Compatibility, Drug Interaction.

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