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FORMULATION AND OPTIMIZATION OF ONDANSETRON HCL FAST-DISSOLVING TABLETS USING RESPONSE SURFACE METHODOLOGY

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Abstract

The aim of the current research work was to prepare and optimise fast-dissolving tablets of ondansetron HCl by the incorporation of different ratios of MCC with lactose. Tablets were prepared by using the direct pressure method in which Ac-Di-Sol and magnesium stearate were incorporated. A two-factor, three-level full factorial design accompanied by response surface methodology (RSM) was used to study the effect of the concentration of MCC and Ac-Di-Sol on the hardness of the tablet and the disintegration time. Optimized formulation was analyzed, which passed all the specifications as desired and showed improved characteristics of tablets, thus providing insight for the formulation of effective fast-dissolving drug delivery systems.

Keywords:*Ondansetron HCl, Fast-Dissolving Tablets (FDT), Formulation Optimization, Response Surface Methodology (RSM), Microcrystalline Cellulose (MCC)*

1. INTRODUCTION

Ondansetron HCl is an extensively used antiemetic for the prevention of nausea and vomiting associated with chemotherapy, radiation therapy, and postoperative surgeries. While it provides several therapeutic advantages, the conventional oral dosage forms of ondansetron, slow onset of action, and difficulty in swallowing, pose a significant challenge in pediatric and geriatric populations. FDTs, in this regard, are being regarded as an alternative. FDTs dissolve or break

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down quickly in the mouth without a need of water. It therefore provides convenience and an improved compliance to a patient, and thereby very useful for the patients who have some problems with swallowing a tablet or capsule.

Preparation of fast-dissolving tablets mainly focuses on an in-depth consideration of excipients choice, drug-excipient interaction, and the production process. Among commonly used excipients in tablet formulation for fast-dissolving attributes are MCC and lactose due to their ability to give the mechanical property associated with a tablet and their ability to help in enhancing the dissolution rate as well. Important disintegrants that have been utilized in ensuring that disintegration occurs quickly and results in the release of the drug have been sodium starch glycolate, also known as Ac-Di-Sol.

The development of FDTs involves the optimization of several formulation parameters simultaneously, which adds further complexities to its development. Traditional methodologies related to optimization by trial and error will take very long periods and often do not provide a near optimal formulation. Advanced statistical techniques such as Response Surface Methodology have thus emerged as significant importance in pharmaceutical formulation. RSM offers an efficacious way for studying the multiple variables and their interactions, allowing for identification of excipient levels that are optimal to provide desired tablet properties.

1.1.Challenges in Conventional Ondansetron HCl Formulations

Ondansetron HCl is a potent antiemetic agent widely prescribed to prevent chemotherapy-, radiation-, and surgery-induced nausea and vomiting. However, oral conventional formulations of ondansetron mainly in tablet and oral solution forms have limitation problems, which hinder a patient's willingness to comply with his or her treatment and creates a limitation in the effectiveness of the therapy. One of the challenges with this product is its delayed onset of action, which can play a pivotal role in managing acute symptoms, such as nausea and vomiting. Traditional oral tablets have to undergo the disintegration and dissolution process within the GI tract, causing a delay in the onset of relief. The delay may be uncomfortable for the patients, especially those receiving chemotherapy or post-surgery, where quick relief of symptoms is crucial.

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One other major issue with traditional formulations of ondansetron is the problem of swallowing that is associated with conventional tablets, especially in pediatric, geriatric, or bedridden patients. Patients in these groups face problems in swallowing large tablets or capsules and therefore discourage compliance with the prescribed treatment. In those cases, liquid preparations are often recommended as alternatives, but they have also their set of problems, including bad taste and dosing errors. Moreover, the need for liquid formulations can require having to have storing and handling precautions that may not always be practical in a domestic setting, especially if used over a protracted period of time.

The conventional tablet formulations of ondansetron are susceptible to variability in bioavailability due to its poor solubility and subsequently impacts on the absorption drug with consistency and reliability. On another hand, ondansetron is known to have low solubility in water, so its absorption might be impact by food intake or variations in gastric pH. Subsequently it would be difficult to maintain plasma levels and ensure therapeutic efficacy. This variability in absorption may lead to the necessity of higher doses, which, in turn, may raise the chances of undesirable side effects. So, there is an urgent requirement for new drug delivery systems that can enhance solubility, improve bioavailability, offer a faster onset of action, and also attend to patient convenience and compliance.

As a result of all these problems, FDTs have now emerged as a second-line formulation strategy. The advantages of FDTs include easy and fast disintegration in the mouth without needing to swallow along with water, thus it facilitates easy intake for patients. Moreover, the dissolution of the FDTs is fast enough for better drug absorption that can lead to a quick onset of therapeutic action. However, the formulation of FDTs with optimal mechanical and dissolution properties requires judicious selection of excipients as well as formulation conditions, where advanced optimization techniques such as Response Surface Methodology is warranted.

1.2.Role of Response Surface Methodology in Formulation Optimization

Pharmaceutical formulation optimisation is greatly aided by Response Surface Methodology (RSM), a potent statistical and mathematical method that is especially important for complicated dose forms such as fast-dissolving tablets (FDTs). RSM makes it possible to systematically explore and optimise several formulation factors at once while developing new

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formulations, which aids in determining the ideal excipient and processing combination to provide the required tablet properties. For instance, important variables like the proportion of microcrystalline cellulose (MCC) and the quantity of sodium starch glycolate (Ac-Di-Sol) in the formulation of ondansetron HCl FDTs can have a major impact on the tablet's hardness, disintegration time, and dissolution profile. RSM assesses the impact of these independent factors and their interactions on the performance of the formulation using experimental designs like factorial and central composite designs. Using RSM, researchers may efficiently determine the ideal circumstances that strike a balance between a number of crucial factors, including the tablet's mechanical strength and quick disintegration in the mouth, both of which are necessary for patient compliance and therapeutic efficacy.

Apart from its capacity to enhance formulation parameters, RSM additionally enables a comprehensive comprehension of the interrelationships among various elements and their collective influence on the ultimate result. This is especially crucial in situations where a number of factors have complicated and non-linear relationships that affect how well FDTs work. RSM offers a thorough understanding of the formulation space by not only assisting in determining the ideal concentrations of each component but also by supplying predictive models to predict the potential effects of changes in one parameter on others. Because RSM is predictive, there is less need for experimental trial-and-error, which saves time and money when optimising. Additionally, RSM may validate the model by comparing the observed and expected responses once an ideal formulation has been found, guaranteeing the accuracy and robustness of the formulation. Because of this, RSM is a vital tool in pharmaceutical research, where careful formulation optimisation can greatly improve the therapeutic efficacy of medications like ondansetron HCl, resulting in better patient outcomes and compliance.

2. LITERATURE REVIEW

Ahuja, R. K. (2015)aimed about different novel advances, including freeze drying, direct compression, shower drying, tablet melding, sublimation, and fast dissolving tablets. Co-processing is the most widely investigated technique for creating directly compressible adjuvants because of its expense viability and in-house capacities.

Chauhan, V. (2017) Fast-dissolving tablets (FDTs) are a revolutionary drug delivery system designed to improve patient compliance and safety by creating an easy-to-administer dose

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form. These tablets dissolve, dissolve, and scatter in saliva in less than 60 seconds without chewing or extra water.

Beena, P. (2021) A review has created oral dissolving tablets of feebly solvent Ondansetron Hydrochloride using different super disintegrants. The European Pharmacopeia introduced the expression "Oro dispersible tablet" to portray tablets that can be inserted in the mouth and rapidly scatter prior to swallowing. These tablets are reasonable for pediatric and older patients and have further developed solubility at a reenacted salivary pH of 6.8.

Namdev, C. (2019) An undertaking was initiated to make and survey ondansetron hydrochloride mouth dissolving pills using a direct compression procedure. Super disintegrants like crospovidone, croscarmellose sodium, and sodium starch glycollate were utilized to make tablets. Pre-compression qualities like mass thickness, tapped thickness, Hausner's proportion, mass thickness, and point of rest were surveyed.

Jain, S. et. al. (2021) intended to make and evaluate an Ondansetron oral fast-dissolving tablet using the Liquisolid Reduced Procedure. Water doesn't break up the counter emetic prescription ondansetron. The tablets were made using the direct compression strategy, and FTIR and UV investigations were utilized to depict them. Ondansetron was made in six formulations (F1-F6), and the tablets were tried for weight varieties, hardness, thickness, friability, disintegration time, and drug content.

3. MATERIALS AND METHODS

3.1.Materials

Ondansetron HCl (pharmaceutical grade), lactose, magnesium stearate, sodium saccharin, Ac-Di-Sol (sodium starch glycolate), and microcrystalline cellulose (MCC) were the ingredients utilised in the manufacture of ondansetron HCl fast-dissolving tablets (FDT). All excipients and chemicals were purchased from commercial vendors and were utilised exactly as supplied, requiring no additional purification.

3.2.Preparation of Tablets

The instant pressure method was used to make Ondansetron HCl fast-dissolving tablets. To achieve even dispersion, the medication and excipients were first carefully combined. A 10-station small press tablet machine was used to compress the powder that resulted from the

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formation of a drug-polymer complex into tablets. To promote smooth tablet creation and to aid in the compression process, magnesium stearate was added as a lubricant. After that, the tablets underwent a number of quality control tests to evaluate their dissolving and mechanical characteristics.

3.3.Optimization of Formulation

Response surface methodology (RSM) was used to improve the formulation. This statistical method was used to investigate how various formulation elements, such as hardness and disintegration time, affected tablet performance. RSM aided in determining the ideal settings to give the required tablet features.

3.4.Statistical Design

The impacts of the independent variables were systematically assessed using a three-level, two-factor full factorial design. The proportion of MCC in the MCC-lactose combination and the concentration of Ac-Di-Sol were the two primary components that were examined. These variables were changed in response to findings from pilot research. The tablets' hardness and disintegration time were selected as the dependent variables for analysis.

3.5.Analysis of Response

To ascertain the importance of each element and their interactions, data from the factorial design were subjected to Analysis of Variance (ANOVA). The model was made simpler and more accurate in predicting the response variables by removing factors that were not significant.

3.6.Validation of the Statistical Model

After the model was created, experimental batches with the ideal factor levels were created in order to verify the predicted results. The model's correctness and the applicability of the optimised formulation were confirmed by comparing the observed responses—such as hardness and disintegration time—with the expected values.

3.7.Preparation of Optimized Batch

The statistical model's recommendations were followed in the preparation of the optimised batch of fast-dissolving tablets. The medication and excipients were precisely weighed,

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combined, and compressed into tablets to provide the ideal formulation. Following preparation, the tablets' hardness and disintegration time were assessed to make sure they fulfilled the requirements for the formulation of the fast-dissolving tablet.

4. RESULT AND DISCUSSION

4.1. Design And Optimization of FDT Of Ondansetron HCL Using Different Ratio Of MCC And Lactose

- **Preparation of tablet**

Ondansetron HCl fast-dissolving tablets were created using the immediate pressure method, combining crude ingredients with a drug polymer complex. The powder was squashed using a 10-station mini press tablet machine, lubricated with magnesium stearate.

Table 1: Composition of fast dissolving tablet

Ingredient	Value (%)
DPC	24
Ac-Di-Sol	2-6
MCC	0-70
Lactose	100-30
Magnesium Stearate	1.5
Saccharine Sodium	0.6

- **Optimization of formulation**

Response surface methodology-based optimization strategy was used. Response surface approach is a statistical technique that determines and concurrently solves multivariate equations using quantitative data from relevant studies. It represents the reaction that is close to the optimum and is often used to identify the best set of parameters that provide the desired result. In the current research, this technique was used to improve the factors influencing the formulation.

- **Statistical design**

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A two-factor, randomized, three-level full factorial design was used to systematically study the formulation of ondansetron HCl fast-dissolving tablets (FDT). Twelve trial runs by and large, each with three focus points, were done in each possible arrangement. The independent factors were picked in light of trials led during the pilot clumps. Hardness and disintegration time were picked as the reliant factors. Table records the numerous factors used in the total factorial plan. Table shows the grid plan for the overwhelming majority preliminary attempts.

- **Analysis of response**

After analyzing the responses using Analysis of Variance (ANOVA), the non-essential components were eliminated from the full model, resulting in a simplified model.

Table 2: Factors in a three-level full factorial study

Factor	**Levels (%)**	**Low (-1)**	**Middle (0)**	**High (+1)**
X1: MCC in MCC-Lactose combination	30	50	70	
X2: Ac-Di-Sol Concentration	2	4	6	

Table 3: Layout of full factorial design

Batch	**X1: % MCC in Lactose/MCC combination (%)**	**X2: Ac-Di-Sol (%)**
OH 1	1	-1
OH 2	0	0
OH 3	-1	0
OH 4	0	0
OH 5	0	-1
OH 6	-1	-1
OH 7	0	0
OH 8	1	1
OH 9	-1	1
OH 10	1	0
OH 11	0	0
OH 12	0	1

- **Validation of statistical model**

Different levels of factors were chosen, and the results that the statistical models predicted were computed. These levels were used to create the tablets, and practical measurements were made

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of the responses. The degree of agreement between the expected and observed responses was assessed by comparing them.

- **Plots of response surfaces**

For each reaction, reaction surface plots were made to examine the impact of these parameters on the response. Tablets were made in light of the affirmation report (Two-sided, Certainty = 95%, n = 1) as displayed in Table, after different constraints were forced.

Table 4: Constraints

Name	Goal	Lower Limit	Upper Limit
X1: MCC in Lactose/MCC Combination	In range	-1	1
X2: Ac-Di-Sol	In range	-1	1
DT: Disintegration Time	Target = 25	22	38
Hardness	Target = 4.5	4	4.5

Table 5: Report of Confirmation (Bi-Partite, 95% Confidence, n = 1)

Factor Name	Level	Low Level	High Level	Std. Dev.	Coding
X1: MCC in Lactose/MCC Combination	Actual	30	70	0.000	Actual
X2: Ac-Di-Sol	Actual	2	6	0.000	Actual

- **Preparation of optimized batch (OFDT1)**

The optimized batch was made using the previously mentioned procedure. The improved batch formula (DFDT2) is shown in Table.

Table 6: Composition of optimized Batch

Ingredient	Quantity (%)	Quantity (mg)
DPC	24	60
Ac-Di-Sol	4.9	11
MCC	66:34	114.4:58.9
Magnesium Stearate	1.5	3.75
Saccharine Sodium	1	0.6

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5. CONCLUSION

In conclusion, the response surface methodology-guided optimisation of ondansetron HCl fast-dissolving tablets utilizing a combination of lactose and MCC successfully enhanced important tablet characteristics like hardness and disintegration time. The investigation showed that a formulation that satisfied the required standards for quick dissolution and mechanical strength could be achieved by making the necessary modifications to the concentrations of MCC and Ac-Di-Sol. This method offers a useful framework for creating high-performing, quickly dissolving drug delivery devices that improve patient compliance and therapeutic efficacy.

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