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DEVELOPMENT OF PLACKETT–BURMAN DESIGN OF EXPERIMENTAL IN THE OPTIMIZATION OF ONDANSETRON MUCOADHESIVE NASAL SPRAY

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ABSTRACT

The present investigation aimed to design and optimize a mucoadhesive nasal spray formulation of ondansetron hydrochloride to overcome the limitations of oral administration, particularly extensive first-pass metabolism and delayed onset of action. Intranasal delivery was selected as a promising route to achieve rapid absorption, improved bioavailability, and potential direct brain targeting.

A Plackett–Burman experimental design was employed to systematically screen the influence of critical formulation variables, including mucoadhesive polymers, viscosity modifiers, and co-solvents, on key performance attributes. Thirteen randomized trials were conducted to evaluate the effects of these factors on viscosity, pH, drug content uniformity, spray pattern, and mucoadhesive strength. In-vitro diffusion studies using Franz diffusion cells and ex-vivo permeation studies across goat nasal mucosa confirmed efficient drug release and permeation. Statistical analysis (ANOVA) validated the model, identifying significant variables that governed formulation performance.

The optimized nasal spray exhibited desirable physicochemical properties, consistent drug content, and uniform spray delivery. Ex-vivo studies demonstrated successful permeation through nasal mucosa, supporting the feasibility of intranasal administration. Stability testing under ICH accelerated conditions confirmed the robustness of the optimized formulation. Overall, the study establishes that ondansetron hydrochloride nasal spray, optimized using the Plackett–Burman design, offers a viable alternative to oral administration. The formulation provides enhanced bioavailability, rapid onset of therapeutic action, and improved patient compliance, highlighting its potential as an effective dosage form for clinical use. **Keywords:**Plackett–Burman; Mucoadhesive nasal spray; optimization; statistical analysis.

INTRODUCTION

Ondansetron hydrochloride is a selective 5-HT_3 receptor antagonist widely prescribed for the prevention of nausea and vomiting associated with chemotherapy, radiotherapy, and postoperative recovery. Despite its clinical utility, oral administration of ondansetron suffers from extensive first-pass metabolism, resulting in reduced systemic bioavailability and variable therapeutic outcomes. These pharmacokinetic limitations highlight the need for alternative delivery routes that can bypass hepatic clearance and provide rapid onset of action.[1,4]

Intranasal drug delivery has emerged as a promising non-invasive approach, offering advantages such as avoidance of first-pass metabolism, rapid absorption through the highly vascularized nasal mucosa, and potential direct transport to the brain via olfactory and trigeminal pathways. For centrally acting drugs like ondansetron, this route may enhance therapeutic efficacy while improving patient compliance.

Furthermore, incorporation of mucoadhesive polymers into nasal formulations can prolong residence time, enhance mucosal contact, and increase the fraction of drug available for systemic and nose-to-brain absorption.[1,5]

The development of robust nasal formulations requires systematic evaluation of multiple formulation and process variables. Traditional trial-and-error approaches are resource-intensive and often fail to capture complex factor interactions. To address this, statistical experimental designs such as the Plackett–Burman model provide an efficient screening methodology to identify critical factors

influencing key quality attributes. This design enables rapid evaluation of multiple variables with a limited number of experimental runs, thereby guiding subsequent optimization studies.[1,7]

In this context, the present study focuses on the formulation and preliminary optimization of a mucoadhesive ondansetron hydrochloride nasal spray using the Plackett–Burman design. The primary objective is to identify significant formulation variables—such as polymer concentration, viscosity modifiers, and excipient ratios—that influence drug release, viscosity, and spray content uniformity. By systematically screening these factors, the study aims to establish a foundation for developing a stable, patient-acceptable nasal spray capable of enhancing bioavailability, accelerating therapeutic onset, and potentially improving brain targeting of ondansetron.[1,7,9]

MATERIAL AND METHODS

Materials

Ondansetron hydrochloride dehydrate, Polymers: HPMC, HPC, HEC, MCC+Na.CMC. Viscosity modifier: Xanthan gum, SodiumCMC, The pH of the formulations was adjusted to 5.5– 6.5 using suitable buffering agents to match nasal physiological conditions and minimize irritation. Preservatives were added to maintain sterility and stability during storage. Each formulation was prepared under aseptic conditions and filtered through a 0.22 µm membrane filter to remove particulate matter.[12,13]

The final solutions were filled into pre-sterilized, metered-dose nasal spray containers. Each container was sealed and stored at controlled room temperature until further evaluation. The prepared formulations were subjected to physicochemical characterization, including viscosity, pH, drug release, spray pattern, mucoadhesive strength, spray content uniformity, invitro drug release and ex-vivo drug release,to assess the influence of the screened factors on

polycarbophil. Gelling agent: Poloxamer407.

Co solvents: Glycerin, Propylene glycol. Buffer: Citrate buffer (citric acid + trisodium citrate). Preservative: Benzalkonium chloride. Packaging: 100 µL metered dose nasal spray bottles. All the chemicals, excipients used will be of laboratory grade / analytical grade and procured from reliable sources.

Preparation of ondansetronnasal spray for nasal delivery

The mucoadhesive nasal spray formulations were prepared according to the experimental design generated by the Plackett–Burman model. Ondansetron hydrochloride was accurately weighed and dissolved in distilled water under continuous stirring to obtain a clear solution. Based on the design matrix, excipients including co-solvent (propylene glycol, glycerin), mucoadhesive polymers and viscosity modifier (hydroxypropyl cellulose, sodium carboxymethyl cellulose, xanthan gum, polycarbophil, hydroxypropyl methylcellulose K15M, microcrystalline cellulose with NaCMC, hydroxypropyl cellulose, polyvinyl alcohol and hydroxyethyl cellulose), and gelling agent (poloxamer 407) were incorporated in varying concentrations as specified in each run.[10,11]

The polymers were dispersed gradually into the drug solution with constant stirring to ensure uniform hydration and viscosity development. product performance.[14,15]

The experimental design was generated and executed using statistical software Design Expert Trial Version. The study type was factorial with a randomized subtype, employing the Plackett–Burman design model focused on main effects. A total of 13 runs were performed, with no blocks incorporated. One center point was included to validate experimental reproducibility. The build time recorded for the design generation was 817

milliseconds, confirming computational efficiency, information for each run was documented, enabling systematic evaluation of factor effects and identification of critical variables for further optimization.

Viscosity

Viscosity of the prepared formulations was determined using a Brookfield viscometer equipped with appropriate spindle at 25 ± 1 °C. Measurements were recorded in triplicate to ensure reproducibility, and values were expressed in centipoise (cP). Viscosity was considered a critical parameter influencing sprayability and mucoadhesive performance.[16]

pH

The pH of each formulation was measured using a calibrated digital pH meter at room temperature. The values were adjusted to fall within the physiological nasal range (5.5–6.5) to minimize irritation and optimize drug absorption.[17]

Drug Content Uniformity

Drug content was assessed by diluting a known volume of formulation with phosphate buffer (pH 6.4) and analyzing spectrophotometrically at the λmax of ondansetron. Results were expressed as percentage of theoretical drug content, with acceptance criteria set at 95–105%.[18]

Spray Pattern

Spray pattern was evaluated by actuating the nasal spray device onto a Whatman filter paper placed at a fixed distance. The distribution of spray was visualized using dye solution and analyzed for uniformity and circularity. Consistency of spray pattern was considered essential for dose reproducibility.[19]

Mucoadhesive Strength

Mucoadhesive strength was determined using a texture analyzer by measuring the detachment force between the formulation and excised nasal mucosa. The force required to separate the mucosa from the formulation was recorded in grams, reflecting the adhesive potential of the polymeric system.[19] **In-Vitro Drug Release**

In-vitro release studies were performed using a Franz diffusion cell with dialysis membrane. The receptor compartment was filled with phosphate buffer (pH 6.4) maintained at 37 ± 0.5 °C and stirred continuously. Aliquots were withdrawn at predetermined intervals and analyzed spectrophotometrically. Cumulative drug release was plotted against time.[17]

Ex-Vivo Drug Release

Ex-vivo permeation studies were conducted using excised goat nasal mucosa mounted on a Franz diffusion cell. The donor compartment contained the formulation, while the receptor compartment was filled with phosphate buffer (pH 5.8). Samples were withdrawn at specific time intervals and analyzed for drug content. Permeation parameters such as flux and permeability coefficient were calculated to assess nasal absorption potential.[17]

Table No 2: Evaluation of Ondansetron Hydrochloride Mucoadhesive nasal spray formulations

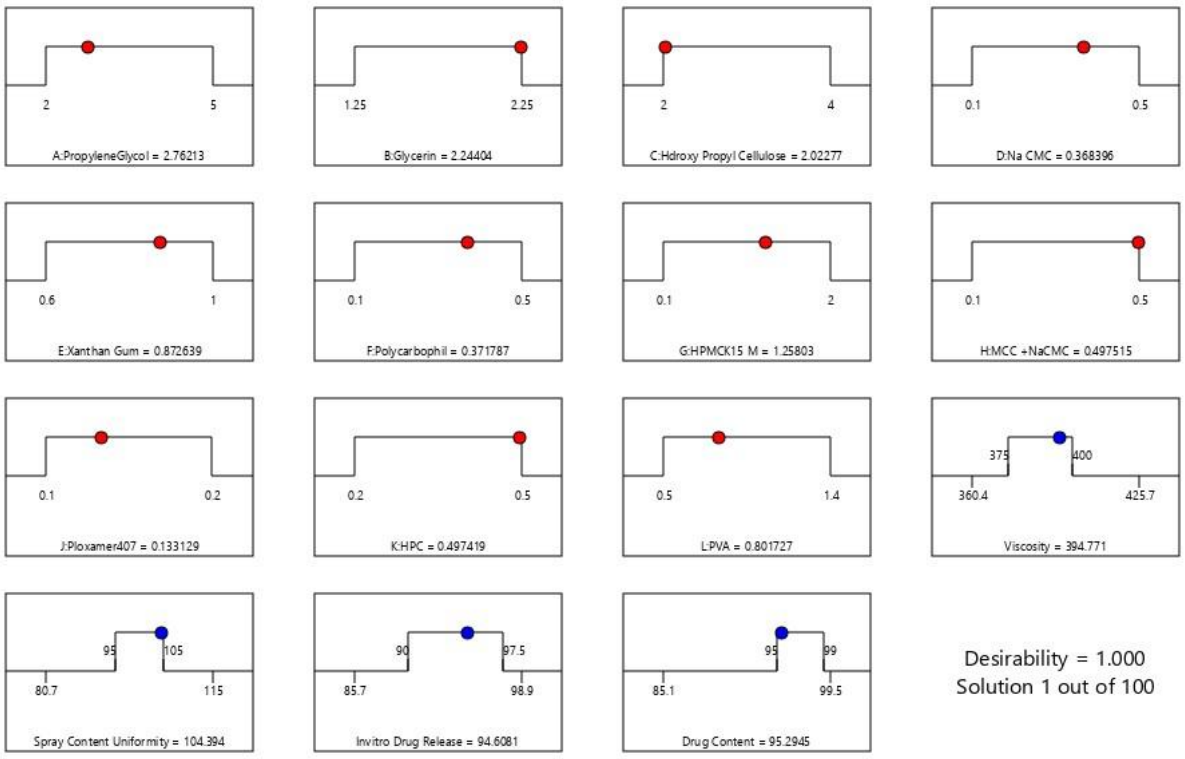
Formulation Code	Viscosity	pH	Spray Content Uniformity	Invitro Drug Release	Drug Content
	cps		%	%	%
1	360.4	6.0	115	98.9	99.5
2	410.6	6.5	81.6	91.2	92.3
3	361.3	6.7	113	97.8	97.7
4	403.5	6.9	111	93.4	94.5
5	413.5	6.7	110	89.9	88.7
6	411.4	6.8	80.7	90.1	90.7
7	400.1	6.7	112	94.5	93.6

8	405.2	6.6	88.7	92.3	91.7
9	380.3	6.5	112.5	96.7	95.6
10	392.6	5.9	111.7	95.6	94.4
11	421.5	6.5	83.3	87.9	87.6
12	425.7	6.7	85	85.7	85.2
13	422.3	6.7	84.6	86.7	85.1

Table4: Response of Ondansetron Hydrochloride Mucoadhesive Nasal Spray formulation

Response	Name	Units	Observations	Minimum	Maximum	Mean	SD.	Ratio
R1	Viscosity	cps	13.00	360.4	425.7	400.65	21.58	1.18
R2	Spray Content Uniformity	%	13.00	80.7	115	99.16	14.78	1.43
R3	Invitro Drug Release	%	13.00	85.7	98.9	92.36	4.24	1.15
R4	Drug Content	%	13.00	85.1	99.5	92.05	4.49	1.17

Figure 1: Numerical Optimisation RAMP Model graph of Ondansetron Hydrochloride Mucoadhesive Nasal Spray formulation



Ex-vivo Study: Ex-vivo permeation study wereconducted using franz diffusion cell containing 20ml phosphate buffer(pH-5.8) using excised goat nasal mucosa. The goat head was obtained from local slaughter house and nasal mucosa was removed with the help of veterinary doctor who removed the skin and exposed the septum fully and nasal mucosa was carefully removed using forceps and surgical scissors. Removed mucosal tissue were immediately immersed in phosphate buffer pH-5.8.Freshly excised nasal mucosa was mounted on diffusion cell, 0.2ml formulation containing 4mg ondansetron hydrochloride dihydrate was placed on the membrane and covered with foil so that there is no loss of formulation due to evaporation. Throughout the study phosphate buffer in donar chamber was continuously circulated using magnetic bead at 50 rpm and temperature was maintained at 37°C. At predetermined time interval (0.5hr, 1hr, 2hr,3hr, 4hr), 1ml sample was withdrawn using syringe and replenished with equal amount of phosphate buffer. The sample was diluted appropriately and filtered. Absorbance of sample were measured spectrophotometrically at 310nm using shimadzu UV spectrophotometer.

Figure 2: Half-Normal Plot of Factors Effects on Viscosity

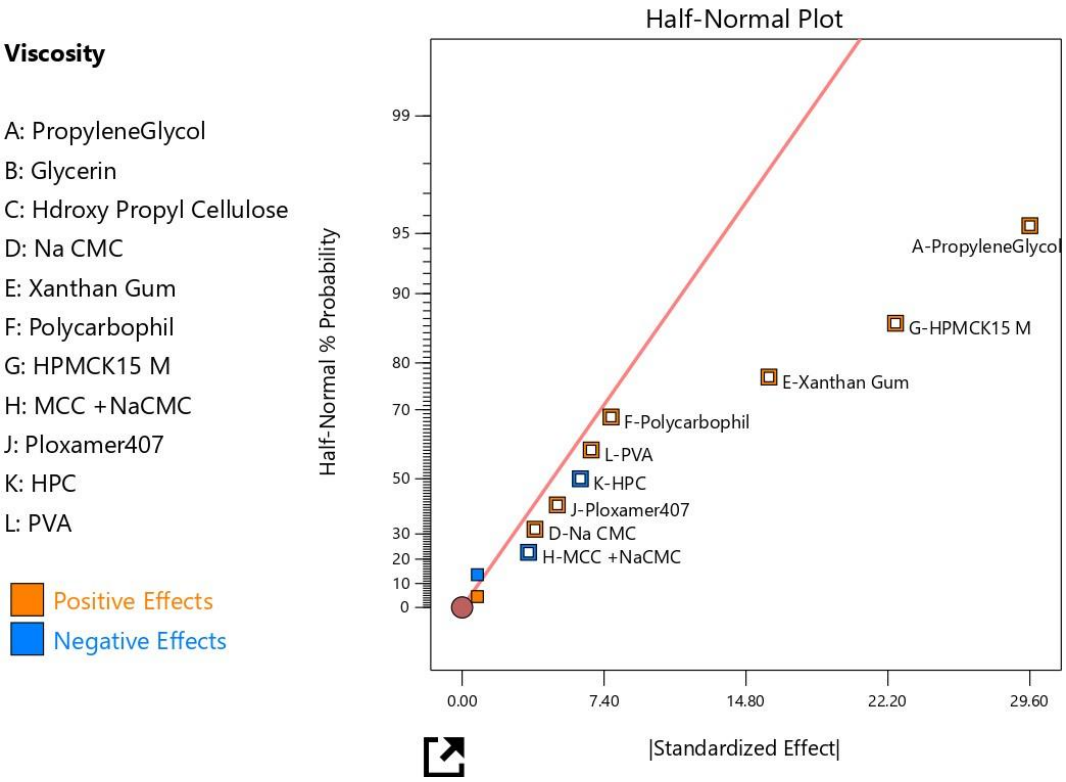


Figure 3: Pareto chart of Factors Effects on Viscosity

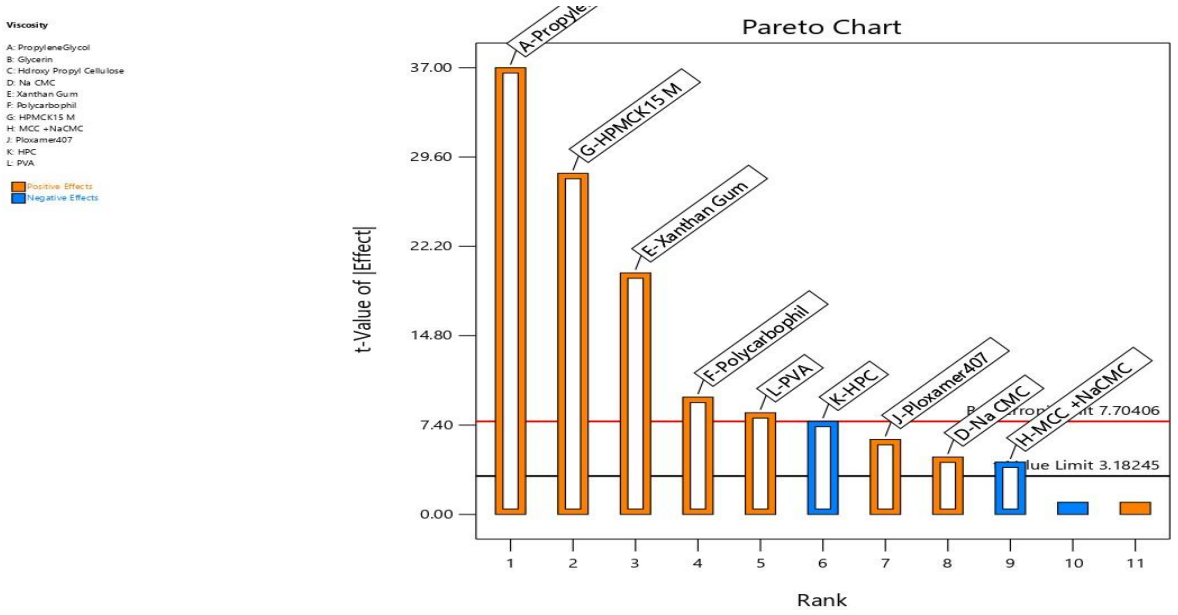


Figure 4: Half-Normal Plot of Factors Effects on Spray content uniformity

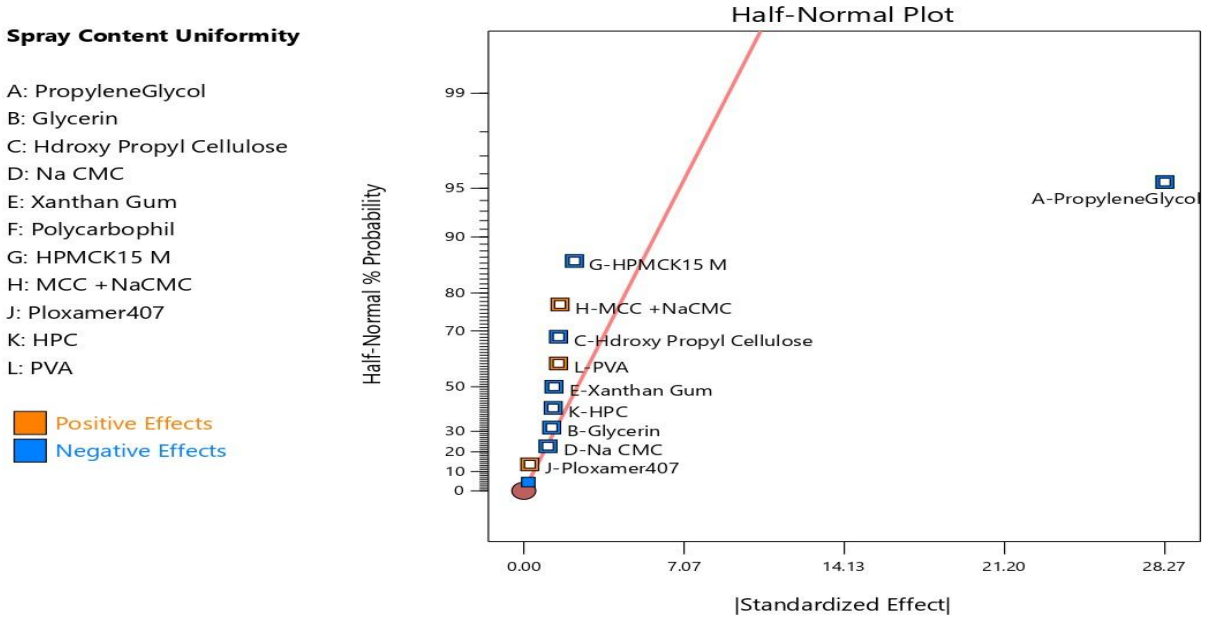


Figure 5: Pareto chart of Factors Effects on Spray content uniformity

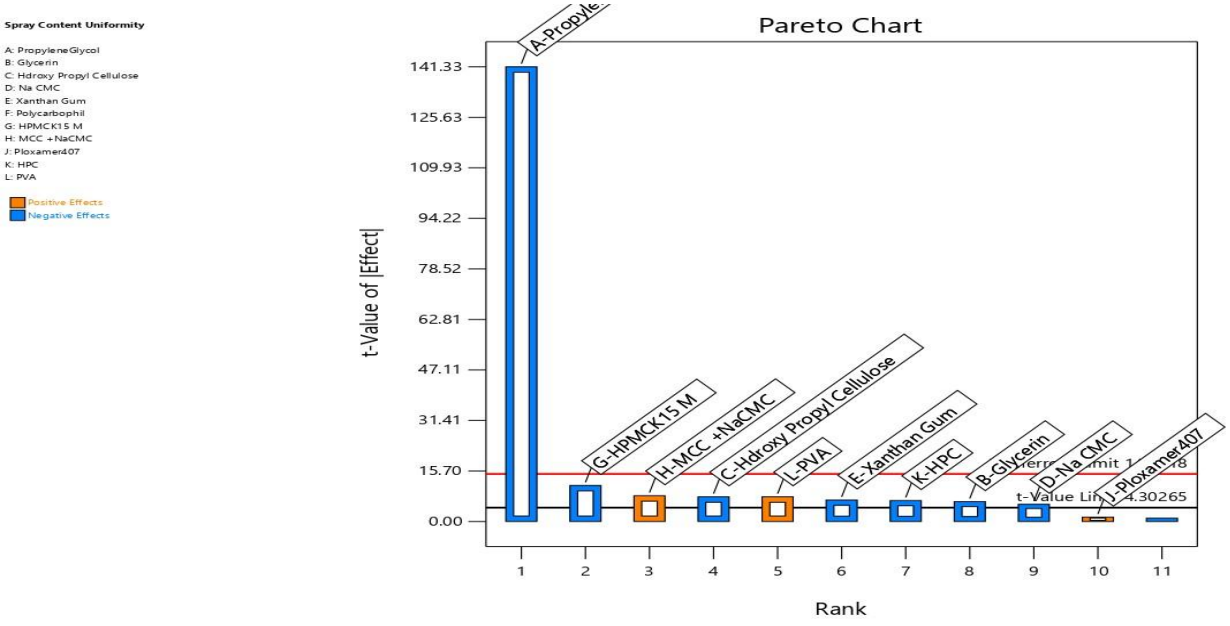


Figure 6: Half-Normal Plot of Factors Effects on Invitro drug release

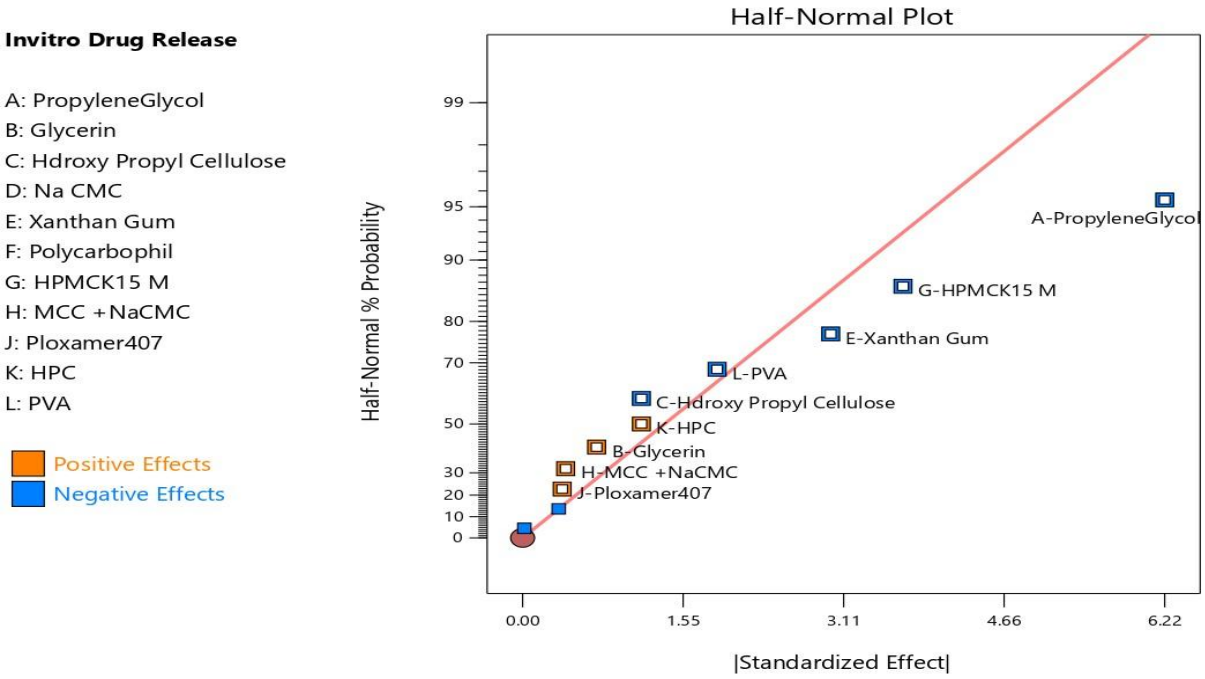


Figure 7: Pareto chart of Factors Effects on Invitro drug release

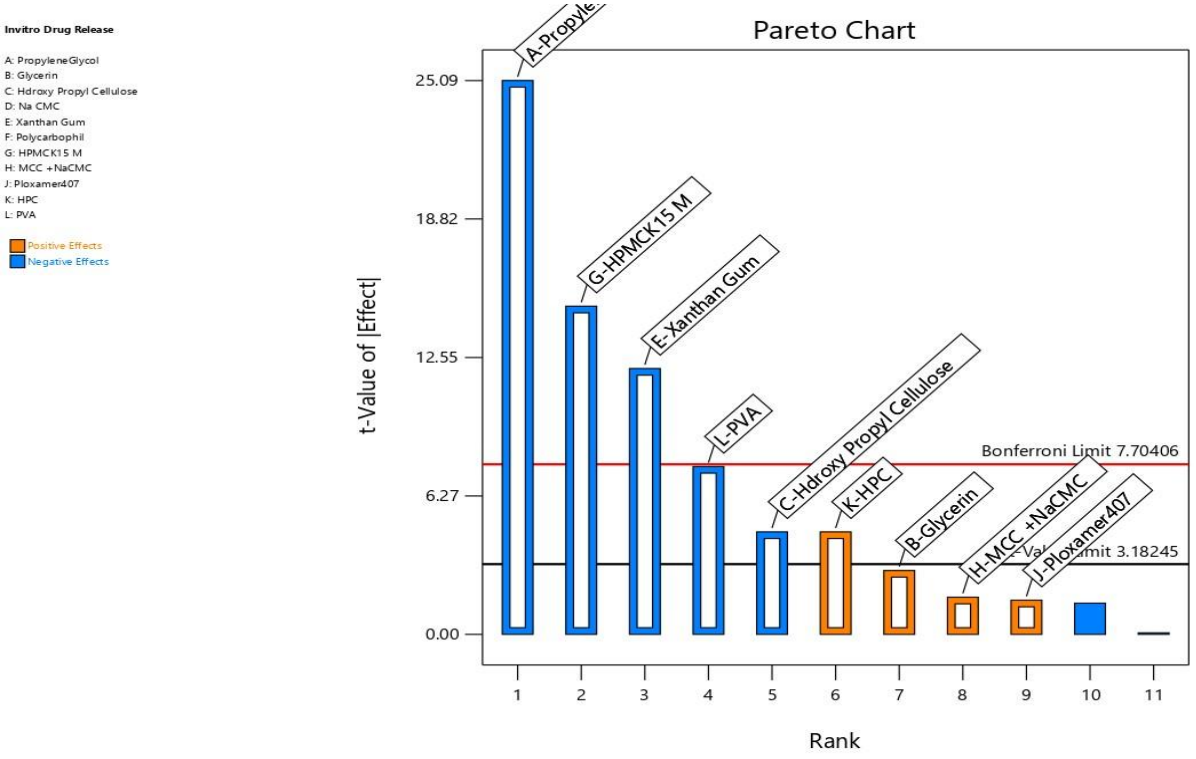


Figure 8: Half-Normal Plot of Factors Effects on Drug Content

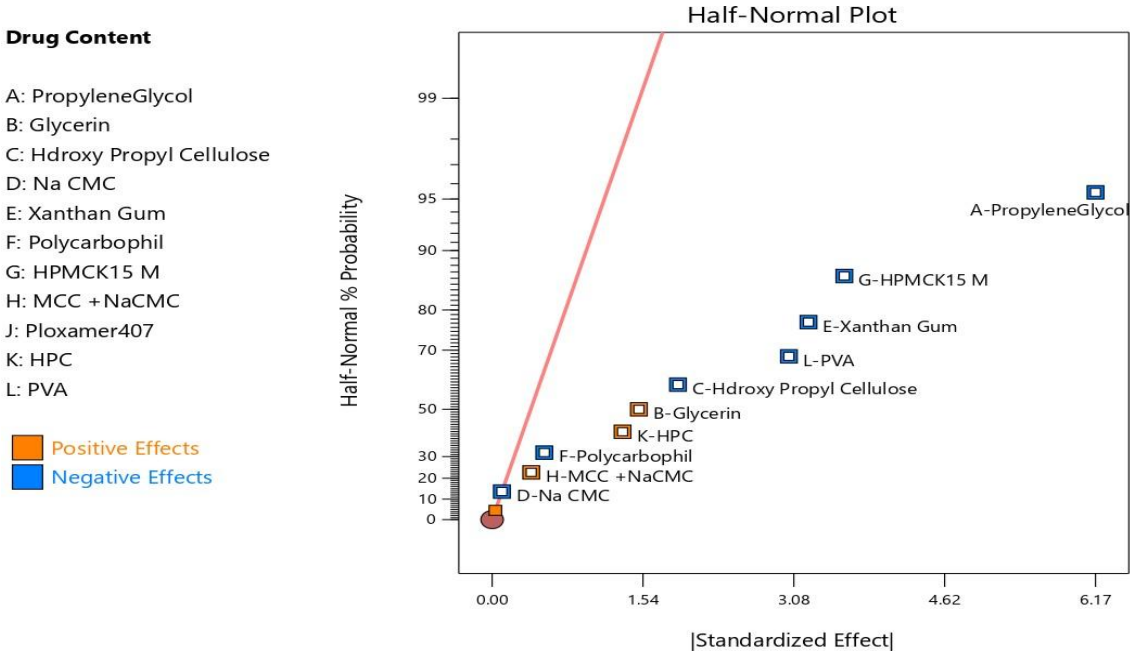


Figure 9: Pareto chart of Factors Effects on Drug Content

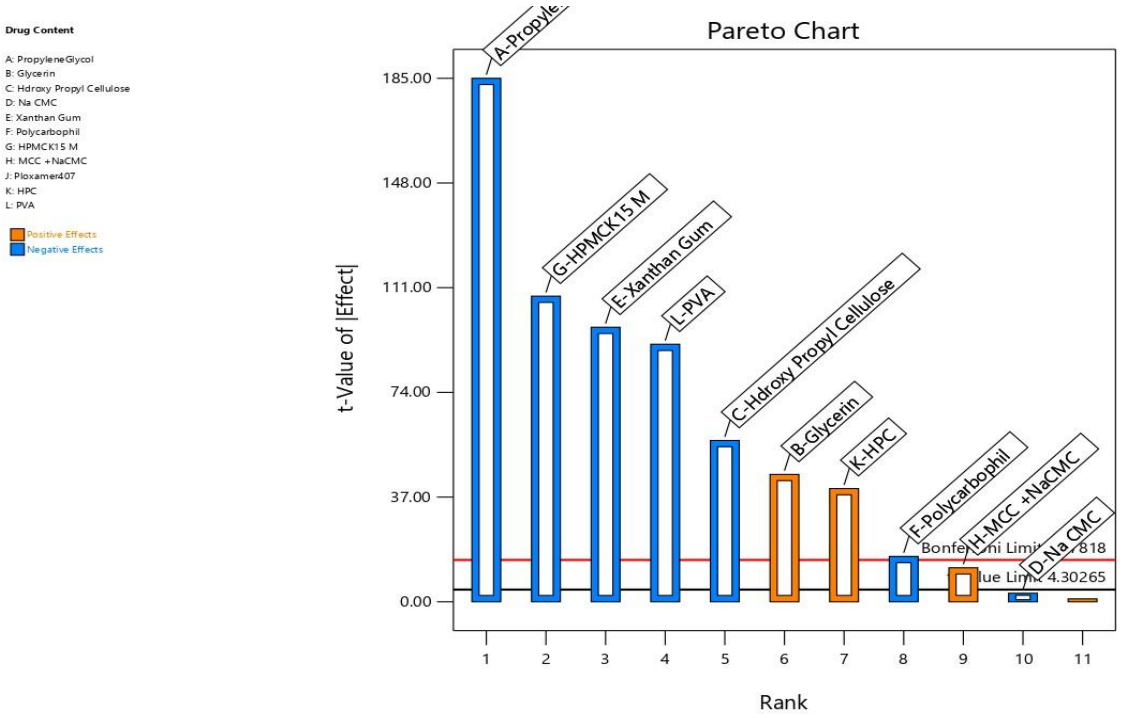


Figure 10: *Ex-Vivo* experimental setup

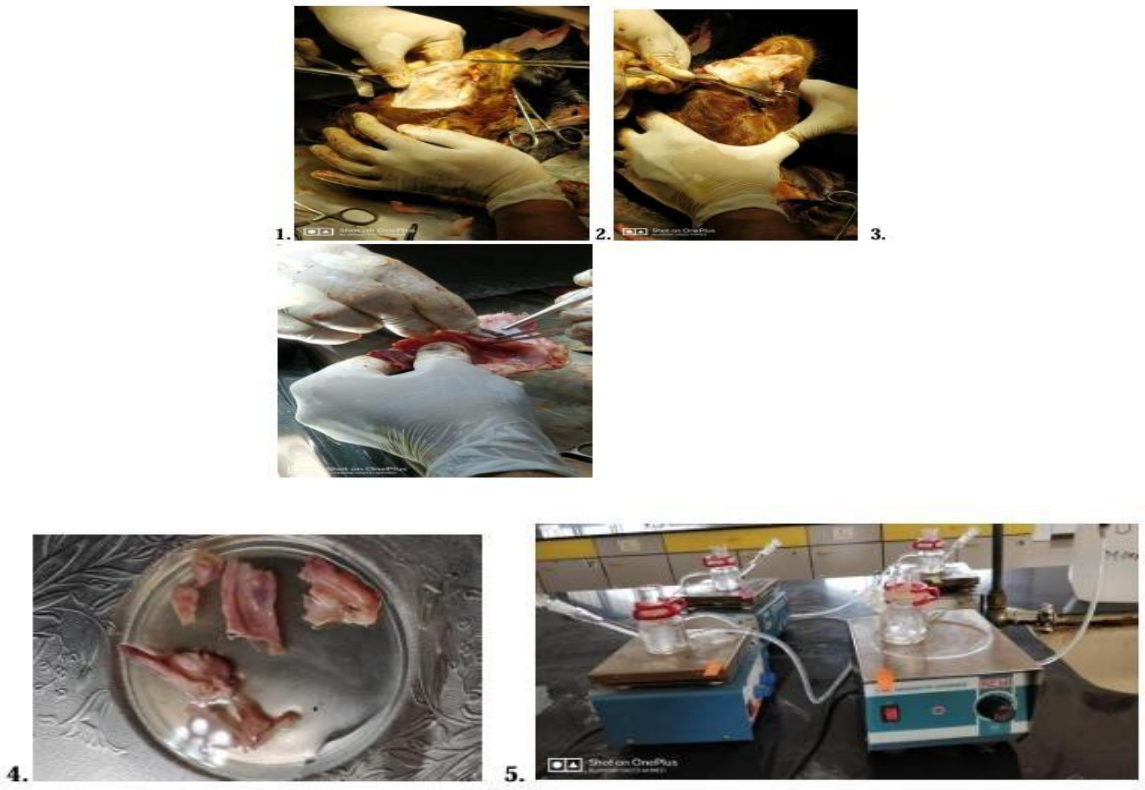


Table 5: Evaluation table of Ex-vivo study

Parameter	Observation/Response	Remarks
Tissue Source	Fresh goat nasal mucosa from slaughterhouse	Ethical and practical source, handled by vet
Membrane Preparation	Carefully excised and preserved in buffer	Maintains tissue integrity
Diffusion Cell Setup	Franz cell with 20 ml phosphate buffer (pH 5.8)	Standardized and physiologically relevant
Formulation Applied	0.2 ml containing 4 mg ondansetron Hcl	Adequate dose for permeation study
Evaporation Control	Covered with foil	Prevents formulation loss
Agitation & Temperature	50 rpm, 37°C maintained	Mimics in vivo nasal environment
Sampling Intervals	0.5, 1, 2, 3, 4 hours	Provides kinetic profile
Sample Handling	Diluted, filtered, analyzed at 310 nm	Ensures accuracy and reproducibility
Analytical Method	UV spectrophotometry (Shimadzu)	Reliable and validated technique
Overall Outcome	Successful permeation observed	Supports intranasal delivery potential

Table No 1: Formulations table of Ondansetron Hydrochloride Mucoadhesive Nasal Spray

Formulation code	Ondansetron Hcl	A:PropyleneGlycol	B:Glycerin	C:Hdroxy Propyl Cellulose	D:Na CMC	E:Xanthan Gum	F:Polycarbophil	G:HPMCK15 M	H:MCC +NaCMC	J:Ploxamer407	K:HPC	L:PVA	Citrate buffer	Benzalkoniumchloride	Distilled water in ml
	mg	%	%	%	%	%	%	%	%	%	%	%	pH	%	Q.S
1	2	2	1.25	2	0.1	0.6	0.1	0.1	0.1	0.1	0.2	0.5	4	0.12	100
2	2	5	2.25	2	0.5	1	0.5	0.1	0.1	0.1	0.5	0.5	4	0.12	100
3	2	2	2.25	4	0.5	0.6	0.1	0.1	0.5	0.1	0.5	1.4	4	0.12	100
4	2	2	2.25	2	0.5	1	0.1	2	0.5	0.2	0.2	0.5	4	0.12	100
5	2	2	2.25	4	0.1	1	0.5	2	0.1	0.1	0.2	1.4	4	0.12	100
6	2	5	2.25	4	0.1	0.6	0.1	2	0.1	0.2	0.5	0.5	4	0.12	100
7	2	2	1.25	2	0.5	0.6	0.5	2	0.1	0.2	0.5	1.4	4	0.12	100
8	2	5	2.25	2	0.1	0.6	0.5	0.1	0.5	0.2	0.2	1.4	4	0.12	100
9	2	2	1.25	4	0.1	1	0.5	0.1	0.5	0.2	0.5	0.5	4	0.12	100
10	2	3.5	1.75	3	0.3	0.8	0.3	1.05	0.3	0.15	0.35	0.95	4	0.12	100

11	2	5	1.25	4	0.5	0.6	0.5	2	0.5	0.1	0.2	0.5	4	0.12	100
12	2	5	1.25	2	0.1	1	0.1	2	0.5	0.1	0.5	1.4	4	0.12	100
13	2	5	1.25	4	0.5	1	0.1	0.1	0.1	0.2	0.2	1.4	4	0.12	100

The study was well-structured, scientifically sound, and yielded promising results for nasal drug delivery of ondansetron hydrochloride.

Stability studies

Mucoadhesive nasal spray were formulated, evaluated and packaged were subjected to stability study. Batches selected for stability study are optimised formulations and all these batches were subjected to various temperature condition as per ICH guideline for accelerated stability study (4°±2°C,40°±2°C/75%±5%RH,25°C±2°C/60%± 5%RH) for Accelerated stability conditions. Study time intervals monthly for six months.
Parameter were analysed with pH, clarity, sprayability, spray content uniformity, spray weight uniformity, assay, viscosity, priming.

DISCUSSION

The experimental design employed in this study provided valuable insights into the interplay of formulation variables and their collective impact on nasal spray performance. The Plackett–Burman model proved effective in identifying critical factors, allowing systematic screening rather than relying on trial-and-error approaches. The observed variations in viscosity, spray content uniformity, and drug release profiles highlight the sensitivity of nasal formulations to polymer concentration and co-solvent ratios.

The ex-vivo permeation studies further emphasized the importance of mucoadhesive strength in prolonging nasal residence time, which directly influenced drug absorption. The findings suggest that the nasal mucosa can serve as a

reliable route for ondansetron delivery, provided the formulation maintains physiological compatibility in terms of pH and osmolarity. Moreover, the statistical analysis confirmed that not all excipients contributed equally; certain polymers had a disproportionately strong effect on drug release and spray performance, underscoring the need for careful excipient selection.[14,15]

Stability testing under accelerated conditions demonstrated that the optimized formulation retained its integrity, which is crucial for ensuring consistent therapeutic outcomes during storage and distribution. These results collectively support the feasibility of intranasal ondansetron delivery as a practical alternative to conventional oral administration.[16,17]

CONCLUSION

The application of Plackett–Burman experimental design in this study has demonstrated its effectiveness as a statistical tool for identifying and prioritizing critical formulation variables in the development of a mucoadhesive nasal spray of ondansetron hydrochloride. By systematically screening multiple excipients and process parameters, the design enabled efficient recognition of those factors exerting the most significant influence on viscosity, spray content uniformity, drug release, and mucoadhesive strength. This approach reduced experimental workload while ensuring scientific rigor in formulation optimization.

The optimized nasal spray exhibited favorable physicochemical characteristics, maintained compatibility with nasal physiology, and showed consistent drug content and spray performance. Ex-vivo permeation studies confirmed successful drug transport across nasal mucosa, supporting the potential of intranasal delivery to bypass hepatic metabolism and achieve rapid therapeutic onset. Stability testing under accelerated conditions further validated the robustness of the formulation, ensuring its suitability for long-term storage and clinical application.

Overall, the findings establish intranasal ondansetron delivery as a promising alternative to conventional oral administration, offering improved bioavailability, faster onset of action, and enhanced patient compliance. Beyond the specific case of ondansetron, this work highlights the broader utility of Plackett–Burman design in pharmaceutical development, where efficient screening of variables can streamline formulation research and accelerate the path toward clinically viable dosage forms. Future studies should extend these findings through pharmacokinetic and clinical evaluations to confirm therapeutic benefits and patient acceptability in real-world settings.

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