https://doi.org/10.31925/farmacia.2025.1.12 **ORIGINAL ARTICLE**

INFLUENCE OF POLYMER AND BINDER ON EXTENDED-RELEASE ONDANSETRON HCL GRANULES INCORPORATED WITHIN A POLYMER MATRIX

PUTRIANA RACHMAWATI *, LUSY NOVIANI, FRANSISCA NOVI MELIANA

Atma Jaya Catholic University of Indonesia, School of Medicine and Health Sciences, Department of Pharmacy, Jakarta, Indonesia

**corresponding author: putriana.rachmawati@atmajaya.ac.id*

Manuscript received: October 2024

Abstract

Ondansetron, a 5-HT3 receptor antagonist, is widely used to prevent nausea and vomiting in patients undergoing chemotherapy, radiotherapy, and surgery. However, pediatric dose adjustments often require tablet crushing, which alters the release profile. This study aimed to develop extended-release ondansetron HCl granules to maintain controlled drug release while allowing flexible dosing. Optimization involved varying the polymer's molecular weight and concentration, as well as the binder concentration. Encapsulated granules were evaluated for physical properties and dissolution profiles over 24 hours. Increasing hydroxypropylmethylcellulose (HPMC) molecular weight reduced the release rate, prolonging drug release. The optimal formula (F3) contained 50% HPMC K100000 and 5% binder, exhibiting good flowability, uniform particle size (850–425 µm), and acceptable loss on drying (5.79%). Dissolution studies confirmed over 95% drug release within 16 hours in aqueous medium, 8 hours in phosphate buffer (pH 6.8), 4 hours in HCl buffer (pH 1.2), and 12 hours in acetate buffer (pH 4.5). The developed formulation ensures prolonged therapeutic efficacy, making it a promising alternative for managing chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) while allowing dose flexibility.

Rezumat

Ondansetronul, un antagonist al receptorilor 5-HT3, este utilizat pe scară largă pentru a preveni greața și vărsăturile la pacienții supuși chimioterapiei, radioterapiei și intervențiilor chirurgicale. Cu toate acestea, ajustările dozelor pediatrice necesită adesea triturarea comprimatelor, ceea ce modifică profilul de eliberare. Acest studiu a urmărit să formuleze granule de clorhidrat de ondansetron cu eliberare prelungită pentru a menține eliberarea controlată a medicamentului, permițând în același timp o dozare flexibilă. Optimizarea a implicat modificarea greutății moleculare și a concentrației polimerului, precum și a concentrației liantului. Granulele încapsulate au fost evaluate în ceea ce privește proprietățile fizice și profilurile de dizolvare pe parcursul a 24 de ore. Creșterea greutății moleculare a hidroxipropilmetilcelulozei (HPMC) a redus rata de eliberare, prelungind eliberarea medicamentului. Formula optimă (F3) conține 50% HPMC K100000 și 5% liant, prezentând o fluiditate bună, dimensiuni uniforme ale particulelor (850-425 µm) și o pierdere acceptabilă la uscare (5,79%). Studiile de dizolvare au confirmat eliberarea a peste 95% din medicament în 16 ore în mediu apos, 8 ore în tampon fosfat (pH 6,8), 4 ore în tampon HCl (pH 1,2) și 12 ore în tampon acetat (pH 4,5). Formularea dezvoltată asigură o eficacitate terapeutică prelungită, ceea ce o face o alternativă promițătoare în a gestiona greața și vărsăturile postoperatorii sau induse de chimioterapie, permițând în același timp ajustarea dozei..

Keywords: Extended-release granules, polymer matrix, ondansetron HCl, PONV-CINV

Introduction

Ondansetron is a selective serotonin 5-HT3 receptor antagonist used as an antiemetic. Its use is broad and effective in treating nausea and vomiting due to various aetiologies [1]. Ondansetron is FDA-approved for preventing radiation-induced, chemotherapy-induced (CINV), and postoperative (PONV) nausea and vomiting, and is considered a first-line therapy [2, 3, 4]. Chemotherapy-induced nausea and vomiting frequently occur, sometimes even before chemotherapy begins (anticipatory vomiting) or more than 24 h after chemotherapy (delayed emesis). Additionally, there is a risk of the drug being expelled due to vomiting after oral administration [5].

Ondansetron, recognised as an antiemetic drug, is listed among the essential medicines for children by the World Health Organization (WHO). This designation indicates that registered drugs like ondansetron are considered both effective and safe to fulfil the requirements of health systems and patients [6]. Typically, medicinal products available on the market are formulated with dosages intended for adult patients, posing challenges in achieving the correct dosage for paediatric patients [7]. Modifying the dosage form often becomes necessary to administer the appropriate dosage to children. For instance,

tablets can be divided, crushed, and split into the required doses or diluted in various solvents. However, not all tablets are suitable for such modifications. Some tablets may lose their effectiveness, have an unpleasant taste, cause stomach irritation, be designed for sustained release, or even have increased toxicity when manipulated. These factors underscore the complexities involved in adjusting adult dosages for paediatric use and highlight the need for child-specific formulations [8].

Extended-release dosage forms are specialised drug delivery systems designed to provide a therapeutic effect by gradually and continuously releasing the drug after a single administration. Release kinetics sustained drug release profiles, indicative of the potential for prolonged therapeutic efficacy [9].

These systems aim to reduce the frequency of dosing, thereby enhancing patient compliance and convenience. Additionally, they seek to increase the drug's effectiveness by localizing its action to the desired site within the body, thereby reducing systemic exposure and potential side effects. The ultimate goal of extended-release formulations is to maintain consistent drug levels in the bloodstream, minimize fluctuations in drug concentration, and improve overall treatment outcomes by ensuring a more uniform and sustained drug delivery [8]. Antiemetic drugs with a sustained release profile provide advantages in treating the side effects of chemotherapy for cancer patients because by administering a single dose, compliance and quality of life for cancer patients can be improved.

Ondansetron dosage forms currently available on the market are oral disintegrating tablets (ODT), injections, oral solutions and tablets. Based on the results of a literature search, ondansetron with a sustained release profile has been developed in the form of bilayer tablets with an osmotic pump system, [1] tablets with a swellable matrix system [4, 10], and parenteral oil suspension [11]. In this research, sustained release granules were developed to provide the benefits of extended-release tablets but can be adjusted in dosage. In the granule dosage form, dose adjustments can be made flexibly by weighing several granules according to the dose calculation results, without changing the drug release system. The granule release profile is designed by incorporating the drug in a polymer matrix and adding a binder whose concentration is varied to obtain granules with the most effective release profile.

Materials and Methods

Formulation of extended-release ondansetron HCl granules

The research method started with the optimization of the sustained release ondansetron HCl granule formulation. The study focused on varying three main components: the concentration of polyvinyl pyrrolidone (PVP) as a binder, ranging from 5% to 10%, and the concentration of hydroxypropyl methylcellulose (HPMC) polymer, ranging from 5% to 50%, utilizing two different molecular weights of HPMC (Table I). Granule formation was carried out using the wet granulation method in a Mixer Granulator Diosna P-1. The binder was dissolved in an aqueous phase and subsequently poured into a dry mix containing ondansetron HCl, polymer, starch, and lactose. The resulting wet granules were then sieved through an 850 µm mesh and dried using heat at 40°C with an air flap set to 10% until the loss on drying (LOD) reached 1 - 5%.

Table I

Variation of formula for extended-release ondansetron HCl granules

Materials	**Function**	**F1**	**F2**	**F3**	**F4**	**F5**
		Concentration (%)				
Ondansetron HCl	Actives	4.4	4.4	4.4	4.4	4.4
HPMC	Polymer as extended-release agent	5 (HPMC) Low	50 (HPMC) High	50 (HPMC*) High	50 (HPMC) High	5 (HPMC) Low
Starch	Disintegrant	25	25	25	25	25
Lactose	Filler	Ad to 100	Ad to 100	Ad to 100	Ad to 100	Ad to 100
Polyvinyl pyrrolidone	Binder	5 - Low	10 - High	5	5 - Low	10 - High

*Molecular weight of HPMC that used in the formula was K100M, the other one was K4M

Physical evaluation of extended-release ondansetron HCl granules

In the evaluation of granules, several key parameters are assessed to determine their quality and suitability for various applications. Firstly, organoleptic properties, which include attributes such as colour, odour, and taste, are examined through sensory analysis to ensure the consistency and acceptability of the granules. This step is crucial for maintaining product standards and consumer satisfaction.

Secondly, the loss on drying (LOD) is measured to determine the moisture content of the granules, a critical factor that can affect their stability and shelf life. LOD is typically assessed using thermogravimetric analysis or a moisture analyser, which provides precise moisture levels expressed as a percentage of the total weight.

Thirdly, flowability is assessed to understand the granules' behaviour during handling and processing. Techniques such as measuring the angle of repose, bulk density, and tapped density are employed to evaluate flow properties. These assessments are crucial for ensuring uniformity and ease of manufacturing, as poor flowability can lead to issues like clogging and uneven dosing.

Lastly, particle size distribution is analysed using methods like laser diffraction or sieving. This parameter is essential for understanding the granules' physical characteristics and their performance in end-use applications. The distribution data is usually represented in terms of mean, median, and mode sizes, offering a comprehensive view of the granule size range and its impact on the product's functionality. Accurate particle size distribution ensures that the granules dissolve at the intended rate and deliver the expected therapeutic effect.

Profile release evaluation of extended-release ondansetron HCl granules

To evaluate the release profile of the active substance, a basket-type dissolution test apparatus was utilised, conducting tests over 24 h in various media. Data collection was automated and analysed using a UV-Vis spectrophotometer, specifically the Shimadzu UV-1900i, at a wavelength of 310 nm.

The dissolution media employed included phosphate buffer with a pH of 6.8, acetate buffer with a pH of 4.5, and hydrochloric acid (HCl) buffer with a pH of 1.2. All media were prepared in accordance with the United States Pharmacopeia (USP) 42 standards.

Granules were encapsulated in size 1 capsules, each containing approximately 8.8 mg of Ondansetron HCl, equivalent to 8 mg of the active ingredient. These capsules were then introduced into the vessels of the dissolution apparatus. The study utilised 500 mL of each dissolution medium, maintained at a temperature of 37°C, with a basket apparatus set to a stirring rate of 50 rpm (Agilent 708-DS dissolution apparatus). Samples were collected at specific time intervals: 15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 8 h, 10 h, 12 h, 16 h, 20 h and 24 h.

The samples obtained during the dissolution process were filtered using 0.45 μm Whatman 850-DS 8-channel filters, which were assembled into sampling tubes. For analytical determinations, the absorption intensity of the samples was measured using the UV/Vis spectrophotometer (Shimadzu UV-1900i) at the maximum wavelength of 310 nm.

This comprehensive methodology ensures accurate and reliable evaluation of the release profile of the active substance, providing essential data on the dissolution characteristics of the granules across different pH environments.

Results and Discussion

Physical evaluation of extended-release ondansetron HCl granules

Raw material properties and granule growth should be checked during as intermediate process parameters [12]. Flowability characteristics of granules are of utmost importance in various pharmaceutical and industrial processes. A thorough understanding of flowability is essential for ensuring the efficient and reliable production, transportation, and storage of granular materials. By assessing the flow behaviour of granules, researchers can optimize manufacturing processes, maintain consistent product quality, and minimize the risk of production delays or equipment malfunctions. The direct method, involving parameters such as F1-F5, is commonly employed to evaluate flowability. Granules meeting the flowability requirements outlined by this method indicate favourable flow behaviour (Table II). Additionally, the Hausner ratio, calculated based on the ratio of tapped density to bulk density, serves as a crucial indicator of flowability. A Hausner ratio ranging from about 1.2 for free-flowing powders to 1.6 for cohesive powders signifies acceptable flow properties. These assessments provide valuable insights into the flow characteristics of granules, facilitating informed decision-making and ensuring the smooth operation of pharmaceutical and industrial processes [13].

Loss on Drying (LOD) stands as a pivotal parameter in guaranteeing the quality of drug granules. It denotes the quantity of volatile material, typically moisture, expelled from the granules during a specified drying process. To assess LOD, dried granules underwent testing using the HR73 Halogen moisture analyser (Mettler-Toledo HR 73, Columbus, OH, USA), with the endpoint set at a weight change of less than 1 mg over a runtime of 140 s, at a temperature of 100°C. Granules were subjected to drying at a temperature of 40°C with an air flap set at 10%, meeting the requisite content standards. The study revealed the stability of Ondansetron at elevated temperatures, thus endorsing the suitability of wet granulation techniques for enhancing particle formation. This comprehensive evaluation of LOD underscores its significance in ensuring the integrity and efficacy of drug granules. By meticulously controlling moisture levels, manufacturers can uphold product quality and efficacy, thereby contributing to the safety and effectiveness of pharmaceutical formulations [14]. Maintaining an appropriate loss on drying (LOD) level is crucial for several reasons. Firstly, excessive moisture content can facilitate the growth of mold and bacteria, thereby compromising the sterility and safety of the final drug product. Secondly, high moisture levels can adversely affect the flowability of the granules, thereby hindering efficient processing

during manufacturing. Ensuring proper LOD levels is essential to uphold the quality and safety of pharmaceutical products [15]. The figure of Extended-Release Ondansetron HCl Granules show spherical granules that also confirm the flowability of the granules (Figure 2).

The particle size distribution for each formula predominantly ranged from 250 to 425 µm (Figure 1). Formulas F3 and F4 exhibited a larger quantity of fines compared to the other formulations. These formulas contained a binder quantity that was ten times lower than the others. An inadequate amount of liquid binder or water results in weak, fragile granules with a high percentage of fines, while excess water leads to over-wetting, producing hard, dense granules with uncontrolled growth [16, 17]. Although Formula 1 contains a small amount of binder, the quantity of fines is not as high as in F3 and F4. One contributing factor is the lower quantity of HPMC in Formula 1. The amount of water used in granulation is largely dependent on the properties of the drug and excipients, such as their solubility and water uptake capacity, as well as their composition within the formulation [18]. HPMC tends to absorb moisture from the environment. This reduces the amount of water that should be used to form bridges between granules [19]. Formula 1 contains more lactose compared to Formulas 3 and 4. Lactose monohydrate typically contains approximately 5% w/w water of crystallization, with a normal range of 4.5 - 5.5% w/w water content. Consequently, the water uptake of lactose monohydrate is less compared to HPMC.

Table II

Physical parameters of extended-release ondansetron HCl granules

Parameter	Formula				
	F1	F2	F3	F4	F5
Organoleptic	Spherical, white granules				
Flowability (g/s)	6.1 ± 0.3	5.8 ± 0.4	5.6 ± 0.1	5.5 ± 0.0	6.2 ± 0.2
Hausner Ratio	1.40	1.35	1.29	1.40	1.40
Loss on Drying (%) (2 g, 105°C)	3.48	3.79	3.70	3.65	4.12

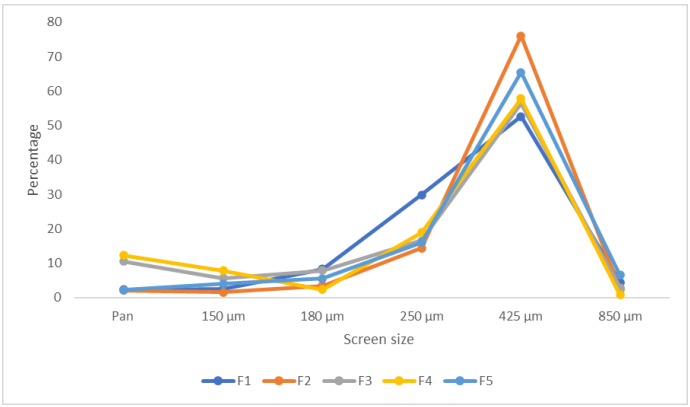

Figure 1.

Particle size distribution of extended-release ondansetron HCl granules

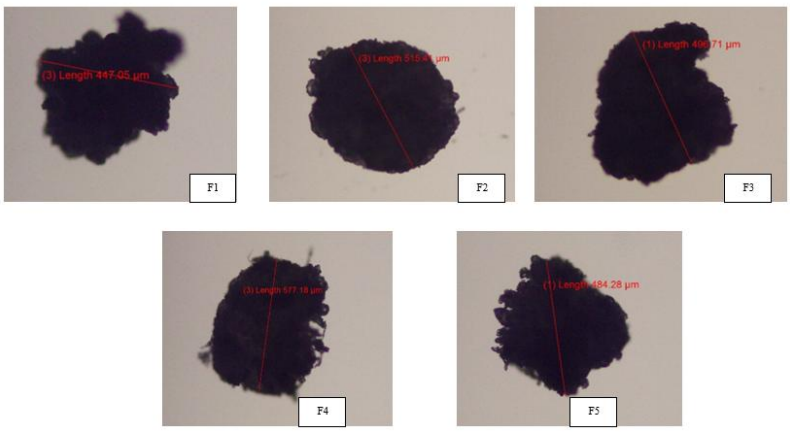

Figure 2.

Appearance of extended-release ondansetron HCl granules

Profile Release Evaluation of Extended-Release Ondansetron HCl Granules

Concentration of HPMC. Based on the dissolution profile, Formula 5 demonstrated the fastest release rate across four different media (Figures 3-6). This rapid release can be attributed to the low concentration of Hydroxypropyl Methylcellulose (HPMC) in the formulation. HPMC is a hydrophilic polymer commonly used as a matrix for drug release with the goal of achieving an extended-release profile. This polymer effectively controls the drug release process because the HPMC matrix can encapsulate drug particles and release them slowly over time. In contrast, the reduced HPMC concentration in Formula 5 resulted in a less controlled and quicker release of the drug [13]. Mechanism of these hydrophilic systems occurs by water absorption, matrix swelling and, finally, drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer [14]. Based on the Noyes-Whitney equation, the dissolution rate of solid in solvent is proportional to, D, diffusion coefficient of the drug in solution. D value is inversely proportional to viscosity. Based on equation, viscosity can reduce the dissolution rate of solid in solvent [15]. The low concentration of HPMC in the formulation significantly impacts the viscosity of the medium surrounding the granules, leading to a lower diffusion coefficient (D value) and consequently a faster dissolution rate. This mechanism also elucidates why Formula 1 exhibits a dissolution profile similar to Formula 5, achieving 100% dissolution within the first hour across all media tested (Table III).

The relationship between viscosity and dissolution profile is further substantiated by the results from Formulas 2 and 4, which contain high concentrations of HPMC K4M. These formulations demonstrated a markedly slower release profile. The higher concentrations of HPMC K4M enhance the viscosity of the surrounding medium, thereby controlling and retarding the drug release process.

This evidence underscores the crucial role of HPMC concentration in modulating drug release rates. Formulations with lower HPMC concentrations facilitate faster drug release due to reduced viscosity, while those with higher HPMC concentrations achieve extended release through increased viscosity, effectively trapping the drug particles and releasing them more slowly. This understanding is essential for optimizing drug formulations to achieve desired therapeutic outcomes.

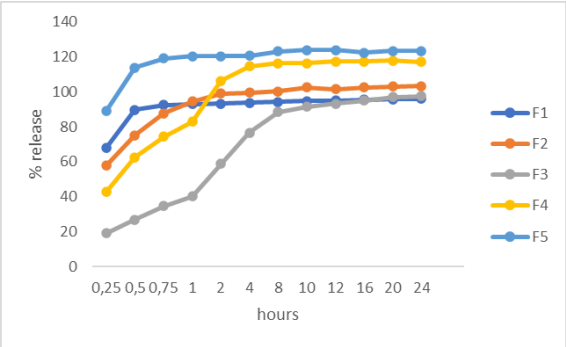

Figure 3.
Release profile of extended-release ondansetron HCl granules in Aquadest

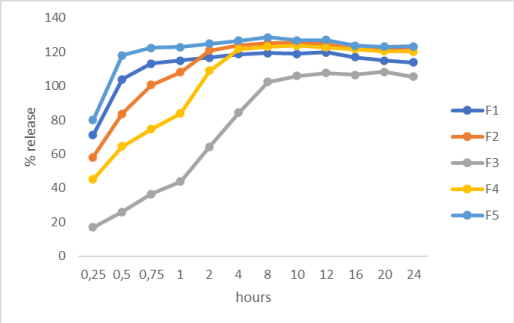

Figure 4.
Release profile of extended-release ondansetron HCl granules in phosphate

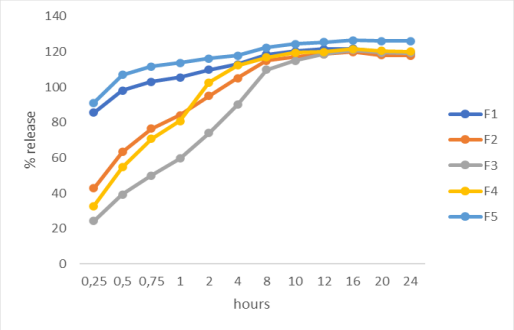

Figure 5.
Release profile of extended-release ondansetron HCl granules in HCl buffer pH 1.2

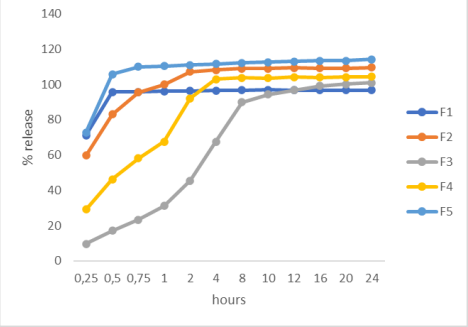

Figure 6.
Release profile of extended-release ondansetron HCl granules acetate buffer pH 4.5

Analysis data of dissolution efficiency to formulation parameters

The dissolution efficiency reported in Tables III, IV was analysed for its p-value with a 95% confidence interval, using linear regression analysis. The results indicate that there is no significant variation in the release profile of the granules with changes in HPMC concentration as a polymer (Table V). This finding aligns with the statement by Ford *et al.*, who noted that the viscosities of hydrated matrices can be identical despite apparent differences in their viscosity grades [20].

Table III

Dissolution efficiency of F1-F5 in medium Aquadest, pH 6.8 phosphate buffer, pH 4.5 acetate buffer and pH 1.2 HCl buffer

Formula	AUC 12 h				AUC 24 h			
	Aquadest	Phosphate buffer pH 6.8	Acetate buffer pH 4.5	HCl buffer pH 1.2	Aquadest	Phosphate buffer pH 6.8	Acetate buffer pH 4.5	HCl buffer pH 1.2
F1	46.210	57.950	47.561	56.595	94.029	116.071	95.965	116.942
F2	48.745	59.723	52.610	52.248	100.118	120.866	107.295	111.634
F3	37.688	42.643	35.773	46.911	85.635	96.229	85.498	106.803
F4	54.150	56.956	47.737	53.770	112.938	117.584	99.823	114.127
F5	60.037	62.142	54.923	59.078	121.639	124.183	111.702	122.156

Table IV

Half dissolution time of F1-F5 in medium Aquadest, pH 6.8 phosphate buffer pH 4.5 acetate buffer and pH 1.2 HCl buffer

Formula	T50			
	Aquadest	Phosphate buffer pH 6.8	Acetate buffer pH 4.5	HCl buffer pH 1.2
F1	0.170	0.165	0.165	0.130
F2	0.205	0.210	0.200	0.315
F3	1.520	1.300	2.380	0.750
F4	0.320	0.290	0.570	0.440
F5	0.130	0.150	0.160	0.125

Table V

p-value (CI 95) of F1-F5 in medium Aquadest, pH 6.8 phosphate buffer, pH 4.5 acetate buffer and pH 1.2 HCl buffer

Formula		% HPMC	MW HPMC	%PVP
AUC 12 h	**Aquadest**	0.890	0.528	0.737
	Phosphate buffer pH 6.8	0.252	**0.043**	0.129
	Acetate buffer pH 4.5	0.548	0.092	0.128
	HCl buffer pH 1.2	0.250	0.270	0.850
AUC 24 h	**Aquadest**	0.959	0.636	0.777
	Phosphate buffer pH 6.8	0.772	0.100	0.255
	Acetate buffer pH 4.5	0.958	0.267	0.218
	HCl buffer pH 1.2	0.334	0.482	0.784
T50	**Aquadest**	0.205	**0.026**	0.287
	Phosphate buffer pH 6.8	0.215	**0.027**	0.382
	Acetate buffer pH 4.5	0.437	**0.080**	0.491
	HCl buffer pH 1.2	0.150	0.146	0.475

This suggests that while HPMC concentration plays a role in controlling drug release, the specific grade of HPMC used may not significantly impact the dissolution profile as much as previously thought. Consequently, factors other than just polymer concentration, such as the overall formulation composition and processing conditions, may also play critical roles in determining the dissolution characteristics of the granules. This insight is vital for optimizing pharmaceutical formulations to achieve consistent and predictable drug release profiles [16]. Campos-Aldrete and Villafuerte-Robles (1997) highlighted the necessity of a high concentration of HPMC, at least 20%, to mitigate the effect of viscosity grade on the Higuchi constant. In the current study design, the low concentration was 5%, and the high concentration was 50%. This substantial gap may have been too wide, preventing a direct one-to-one comparison of the data. Additional data with intermediate HPMC concentrations would be beneficial for a more accurate analysis [21].

Fu *et al.* (2003) reported that while HPMC concentration has little effect on the diffusional

exponent, it significantly influences the kinetic constant in Peppas' equation. Specifically, increasing HPMC concentration decreases the kinetic constant, thereby reducing the drug release rate from HPMC matrices. The effect of HPMC concentration on drug release is also related to the solubility and molecular volume of the drug. Both solubility and molecular volume impact the diffusional exponent: lower solubility and larger molecular volume result in a greater diffusional exponent [20].

Furthermore, the equation derived using a training set of HPMC matrices with varying HPMC concentrations and different drugs has shown good predictive ability when applied to forecast the release of tinidazole from HPMC matrices. This underscores the importance of considering both the HPMC concentration and the specific properties of the drug when designing controlled-release formulations.

The study's findings highlight the complexity of drug release mechanisms and the necessity for a nuanced approach in formulating HPMC matrices. More comprehensive data across a range of HPMC concentrations would enhance our understanding and ability to predict drug release profiles more accurately [17].

Molecular weight of HPMC. Formula 3 exhibited the slowest release profile for ondansetron HCl across all tested media. Complete release of ondansetron HCl was achieved in approximately 8 hours in each medium. Dissolution efficiency data and T50 data reported in Table III were analysed for p-values with a 95% confidence interval using linear regression analysis. The results indicate that the molecular weight of HPMC, as a polymer, significantly impacts the release profile of the granules.

Specifically, tablets formulated with HPMC K100M demonstrated the lowest release rates, corresponding to their higher viscosity grade. This is likely due to the degree of polymer chain entanglement at high molecular weights, which reduces the effective molecular diffusion area. The higher viscosity of HPMC K100M forms a more robust gel matrix that traps the drug particles more effectively, thereby slowing the release rate.

These findings underscore the critical role of HPMC molecular weight in modulating drug release. Higher molecular weight HPMC grades, such as K100M, create a denser and more entangled polymer network, which hinders the diffusion of drug molecules and results in slower release rates. This highlights the importance of selecting appropriate HPMC grades based on the desired release profile and the specific characteristics of the drug being formulated. Further research with intermediate HPMC concentrations and different molecular weights could provide more detailed insights into optimizing drug release profiles [22]. Polymer swelling is an important property in controlling drug release from hydrophilic matrices [19].

Khizer *et al.* (2019) reported that the highest drug release was observed in K4M matrices, whereas the lowest drug release was seen in K100M matrices. The study found that drug release was inversely related to the swelling rate of the matrices. Therefore, K100M matrices, which exhibited the highest swelling rate (Kw), also showed the slowest drug release [23].

The research concluded that polymers with high viscosity led to a higher swelling rate, which in turn results in a slow and extended release of the drug. This is due to the more extensive gel formation and entanglement of polymer chains in high-viscosity matrices, which hinders the diffusion of drug molecules.

Furthermore, it was observed that 3D-printed tablets demonstrated a drug release behaviour similar to that of matrix tablets fabricated using conventional methods. This indicates the potential applicability of 3D printing technologies in the development of hydrophilic matrices for controlled drug release. The use of 3D printing allows for precise control over tablet geometry and internal structure, which can be tailored to achieve desired release profiles comparable to those obtained with traditional fabrication techniques.

These findings emphasize the importance of selecting appropriate polymer grades based on their viscosity and swelling characteristics to achieve targeted drug release profiles. The integration of advanced manufacturing technologies like 3D printing offers promising avenues for optimizing the design and performance of pharmaceutical formulations [18].

Concentration of binder. Theoretically, a high binder concentration is expected to reduce the drug release speed. This is due to the increased stickiness of the binder surface, caused by high binder viscosity, and the slow dissolution kinetics, which enhance the binder's effectiveness. Consequently, higher binder concentrations can create a more cohesive and robust matrix, thereby slowing the release of the drug.

In conclusion, this study elucidated the critical attributes of binders that significantly impact the granulation process of dicalcium phosphate. It highlighted that binder concentration and viscosity are key factors influencing granule formation and drug release profiles. High binder concentrations not only increase the adhesive properties of the granules but also result in slower dissolution rates, thereby controlling the drug release more effectively.

This comprehensive understanding of binder attributes is essential for optimizing the granulation process in pharmaceutical manufacturing. By

carefully selecting and adjusting binder properties, it is possible to achieve desired drug release profiles, ensuring the efficacy and stability of the final pharmaceutical product [24]. The data indicates a slight difference in drug release profiles at low concentrations of HPMC between Formula 1 (F1) and Formula 5 (F5), which have different binder concentrations. Specifically, F1 exhibits a slightly higher release profile compared to F5. Conversely, at high concentrations of HPMC, such as in Formulas 4 (F4) and 5 (F5), the binder concentration does not provide a clear theoretical comparison.

Dissolution efficiency data and T50 data reported in Table III were analysed for p-value with a 95% confidence interval using linear regression analysis. The results indicate that the molecular weight of HPMC significantly impacts the release profile of the granules. High molecular weight HPMC formulations, such as those using HPMC K100M, show a lower release rate due to increased viscosity and polymer entanglement, which slow down drug diffusion.

This study underscores the importance of considering both HPMC concentration and molecular weight when designing drug release profiles. Low concentrations of HPMC with varied binder concentrations can lead to minor differences in release rates, while at higher concentrations, the molecular weight of HPMC becomes a more critical factor. High molecular weight polymers create a more viscous and entangled matrix, effectively controlling and slowing the release of the drug.

These findings highlight the need for a nuanced approach in pharmaceutical formulation, where both polymer characteristics and binder concentrations are carefully optimised to achieve desired therapeutic outcomes. Further research with intermediate HPMC concentrations and varying binder levels could provide more detailed insights into optimizing drug release profiles.

Since polyvinylpyrrolidone (PVP) is freely soluble in aqueous environments such as gastric fluid, its presence as a binder does not significantly influence the disintegration or dissolution rate of the drug from tablets. Despite this, PVP effectively aids in formulating tablets with good hardness, a property not as readily achieved with other binders like gelatine or hydroxypropyl methylcellulose (HPMC). Kimaro *et al.* (2019) utilised PVP K30 in the formulation of chewable albendazole tablets using a wet granulation method, aiming to enhance the drug's dissolution rate. This approach leverages PVP's solubility to ensure rapid drug release while maintaining tablet integrity and hardness, demonstrating PVP's versatility and efficacy as a binder in pharmaceutical formulations [18].

The study by Kimaro *et al.* underscores the advantages of using PVP K30 as a binder, particularly in enhancing the dissolution rate of poorly soluble drugs like albendazole. This is particularly relevant in the development of chewable tablets, where both rapid dissolution and adequate tablet hardness are critical for patient compliance and therapeutic effectiveness.

Overall, the findings highlight the importance of selecting appropriate binders based on their solubility and mechanical properties to optimize drug release profiles and ensure high-quality tablet formulations. Future research could further explore the comparative effects of different binders on drug dissolution rates and tablet properties to refine formulation strategies for various pharmaceutical applications [25].

Conclusions

The granules were successfully formulated using the wet granulation method, with varying concentrations of polyvinyl pyrrolidone (PVP) as a binder and hydroxypropyl methylcellulose (HPMC) as an extended-release polymer. HPMC and PVP concentration did not significantly influence the drug release profile. On other hand, granules containing higher molecular weight HPMC (*e.g.*, K100M in Formula 3) exhibited the slowest drug release profiles across all tested media. This is attributed to the higher viscosity and more robust gel formation of K100M, which effectively traps drug particles and prolongs their release. Investigate additional HPMC concentrations between the low (5%) and high (50%) extremes to better understand the relationship between polymer concentration and drug release kinetics. By addressing these recommendations, future research can enhance the understanding and application of extended-release formulations, ultimately improving therapeutic outcomes and patient compliance.

Conflict of interest

The authors declare no conflict of interest.

References

1. Gundu R, Pekamwar S, Shelke S, Shep S, Kulkarni D, Sustained release formulation of Ondansetron HCl using osmotic drug delivery approach. *Drug Dev Ind Pharm.*, 2020; 46(3): 343-355.
2. WHO, World Health Organization Model List of Essential Medicines for Children 8th list, 2021.
3. R. Fathi, G. Raday, and G. Goldberg, Ondansetron Extended Release Solid Dosage Forms for Treating Either Nausea, Vomiting, or Diarrhea Symptoms, 2015. US009675588B2
4. Rajan S, Coalco S, Meyyanathan SN, Suresh B, Once-daily sustained-release tablets of ondansetron, a novel anti-emetic. *Am J PharmTech Res.*, 2013; 3: 691.

5. Rao KV, Faso A, Chemotherapy-induced nausea and vomiting: optimizing prevention and management. *Am Health Drug Benefits.*, 2012; 5(4): 232-240.
6. Griddine A, Bush JS, Ondansetron, 2023 Feb 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
7. Nunn T, Williams J, Formulation of medicines for children. *Br J Clin Pharmacol.*, 2005; 59(6): 674-676.
8. Adepu S, Ramakrishna S, Controlled Drug Delivery Systems: Current Status and Future Directions. *Molecules*, 2021; 26(19): 5905.
9. Florentina IC, Prisada RM, Anuța V, Popa L, Ghica MV, Fierăscu RC, Trică B, Nicolae CA, Pîrvu CED, A Quality-By-Design approach for optimisation of docetaxel transferosomal formulations. *Farmacia*, 2024; 72(5): 1077-1091.
10. Anilkumar A, Murthy GK, Rani AP, Formulation of ondansetron HCl matrix tablet with microenvironment pH modifier for improved dissolution and bioavailability under hypochlorhydria. *Asian J Pharm.*, 2016; 10(3): 188-197.
11. Nguyen TT, Duong VA, Maeng HJ, Chi SC, Preparation of an oil suspension containing ondansetron hydrochloride as a sustained release parenteral formulation. *Drug Deliv Transl Res.*, 2020; 10(1): 282-295.
12. Mathe R, Casian T, Marina A, Marusca DD, Tomuță I, Multivariate data analysis for tableting performance improvement at industrial scale: a case study focused on understanding and avoiding the occurrence of capping and lamination. *Farmacia*, 2023; 71(4): 798-809.
13. Gad SC, Pharmaceutical manufacturing Handbook: Production and Process, John Wiley &Sons, 2007.
14. Armenian P, Campagne D, Stroh G, Ives Tallman C, Zeng WZD, Lin T, Gerona RR, Hot and Cold Drugs: National Park Service Medication Stability at the Extremes of Temperature. *Prehosp Emerg Care.*, 2017; 21(3): 378-385.
15. Forster SP, Dippold E, Haser A, Emanuele D, Meier R, Integrated Continuous Wet Granulation and Drying: Process Evaluation and Comparison with Batch Processing. *Pharmaceutics*, 2023; 15(9): 2317.
16. Badawy SI, Menning MM, Gorko MA, Gilbert DL, Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer. *Int J Pharm.*, 2000; 198(1): 51-61.
17. Sakr WF, Ibrahim MA, Alanazi FK, Sakr AA, Upgrading wet granulation monitoring from hand squeeze test to mixing torque rheometry. *Saudi Pharm J.*, 2012; 20(1): 9-19.
18. Kimaro E, Tibalinda P, Shedafa R, Temu M, Kaale E, Formulation development of chewable albendazole tablets with improved dissolution rate. *Heliyon*, 2019; 5(12): e02911.
19. Rowe RC, Sheskey PJ, Quinn ME, editors. Handbook of pharmaceutical excipients. 6th ed. London: Pharmaceutical Press; 2009; 506-509.
20. Ford JL, Rubinstein MH, Hogan JE, Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl-methylcellulose matrices. *Int J Pharm.*, 1985; 24: 327-338.
21. Campos-Aldrete ME, Villafuerte-Robles L, Influence of the viscosity grade and the particle size of HPMC on metronidazole release from matrix tablets. *Eur J Pharm Biopharm.*, 1997; 43: 173-178.
22. Kristensen J, Schaefer T, Kleinebudde P, Direct pelletization in a rotary processor controlled by torque measurements. II: effects of changes in the content of microcrystalline cellulose. *AAPS PharmSci.*, 2000; 2(3): E24.
23. Khizer Z, Akram MR, Sarfraz RM, Nirwan JS, Farhaj S, Yousaf M, Hussain T, Lou S, Timmins P, Conway BR, Ghori MU, Plasticiser-Free 3D Printed Hydrophilic Matrices: Quantitative 3D Surface Texture, Mechanical, Swelling, Erosion, Drug Release and Pharmacokinetic Studies. *Polymers (Basel)*, 2019; 11(7): 1095.
24. Contreras L, Melgoza LM, Aguilar-de-Leyva A, Caraballo I, Collaboration between HPMC and NaCMC in order to reach the polymer critical point in theophylline hydrophilic matrices. *Sci World J.*, 2012; 2012: 171292.
25. Colombo P, Bettini R, Santi P, De Asentiis A, Peppas N, Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. *J Control Release.*, 1996; 39(2-3): 231-242.