Quality by Design Approach for Development and Characterization of Granisetron Hydrochloride-Loaded Orodispersible Films

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Pharmaceut Fronts 2023;5:e297–e309.

Abstract

Granisetron hydrochloride can be used to prevent and treat nausea and vomiting induced by chemotherapy. Its prolonged half-life and reduced dose requirement improve patient acceptance. However, patients undergoing chemotherapy often suffer from dysphagia and drug spitting due to emesis. Hence, the development of a patient-centered formulation of granisetron hydrochloride with simple medication and high compliance is crucial. The current study employed a polymer combination of polyvinylpyrrolidone/polyvinyl alcohol (PVP/PVA) as film-forming materials and Lycoat® RS 780 as a disintegrant to formulate orodispersible films (ODFs) loaded with granisetron hydrochloride. Guided by the concept of quality by design, the quality target product profile and critical quality attributes (CQAs) for the ODF were defined. Through the quality risk assessment, essential factors that have a significant impact on CQAs were identified. The formulation was screened using the Box–Behnken statistical design with three factors and three levels. Our data suggested that all ODF formulations exhibited a disintegration time of less than 60 seconds and complete dissolution within 5 minutes. Furthermore, the formulation displayed appropriate mechanical properties, water residue, and pH values. Thus, the granisetron hydrochloride-loaded ODF is regarded as a patient-friendly formulation that enhances compliance and consequently aids in therapeutic effectiveness.

Keywords
- granisetron hydrochloride
- orodispersible films
- quality by design

Introduction

Chemotherapy is a widely used treatment for malignant tumors; however, patients often experience negative side effects such as nausea and vomiting, impacting their quality of life. Granisetron hydrochloride is a potent 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist, which effectively blocks the 5-HT_3 that arises from chemotherapy drug stimulation. Its affinity for the 5-HT_3 receptor is 4,000 to 40,000 times greater than other receptors, making it a viable antiemetic drug option.[1–3] Compared with ondansetron, another frequently used 5-HT_3 receptor antagonist, granisetron offers benefits such as a prolonged onset time and a decreased drug dosage due to its longer half-life. Additionally, granisetron has a strong performance in terms of drug safety, allowing the application on children over

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received
March 17, 2023
accepted
October 27, 2023
article published online
December 1, 2023

DOI https://doi.org/10.1055/s-0043-1777043.
ISSN 2628-5088.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

2 years old and patients aged 65 years or older.[4–6] Nevertheless, marketed pharmaceutical products still encounter challenges concerning patient compliance. Injections need to be administered by professional medical staff. Long-term sufferers of chronic conditions who require repeated injections may experience decreased compliance with their medication regimen due to the associated discomfort. Patients with difficulty swallowing, children, and elderly individuals, as well as those experiencing nausea or vomiting, may find traditional oral medications such as tablets and capsules to be ineffective.[7–9] Although orally disintegrating tablets do not require water for ingestion, their efficacy may still be compromised due to potential vomiting incidents. Therefore, it is necessary to develop an easy-to-use and patient-friendly granisetron hydrochloride dosage form.

The pharmaceutical film is an innovative dosage form, essentially a thin sheet composed of active pharmaceutical ingredients (APIs), film-forming materials, and other excipients.[10] Recently, with the rapid advancement of films, a multitude of products have received marketing approval. The first official definition of films was recorded in the Chinese Pharmacopoeia in 1990. EP 7.4, USP37-NF S2, and JP 18 supplemented the relevant content for the films in 2012, 2014, and 2021, respectively.

Among different types of films, orodispersible films (ODFs) are of great interest among researchers due to their convenience in use and good patient compliance. Once the ODFs have been moistened and become hydrated, they quickly undergo expansion and disintegration, releasing contents that flow into the gastrointestinal tract along with saliva without the need to drink water. In addition, the ODFs could adhere to the administration site and disintegrate rapidly, therefore preventing the medicine from being spit out, so ODF is suitable for cancer chemotherapy patients experiencing nausea and vomiting symptoms.[4,11]

Quality by design (QbD) is a comprehensive and systematic methodology formulation development, as outlined in the guiding principles of ICHQ8 (R2).[12] Adopting pre-established objectives, this approach prioritizes rigorous process control and in-depth comprehension of the product and process, informed by scientific knowledge and risk assessment. The implementation of QbD mainly takes place in the drug development stage, including the use of accumulated experience and knowledge gained in literature to build the patient-centered quality target product profile (QTPP) and define the corresponding critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs), supplemented by risk assessment to ensure that the final products exhibit consistent desired target characteristics.

Under the guidance of the QbD concept, this study aims to develop a granisetron hydrochloride ODF with appropriate mechanical performance and patient compliance. To save time and cost, the Box–Behnken design (BBD), a statistical experiment optimizer, was utilized.

Material and Methods

Materials

Granisetron hydrochloride was purchased from Sinopharm Chuankang Pharmaceutical Co., Ltd., Chengdu, China. Hypromellose (HPMC) E15 was purchased from Dow Chemicals, Shanghai, China. Polyvinylpyrrolidone (PVP) K30 was purchased from Anhui Shanhe Pharmaceutical excipients Co., Ltd., Huainan, China. Polyvinyl alcohol (PVA) EG-05 was purchased from Mitsubishi Chemical, Tokyo, Japan. Glycerol was purchased from Er Kang Pharmaceutical, Liuyang, China. Lycoat® RS 780 was purchased from Roquette, France. Crospovidone (PVPP) was purchased from Shanghai Chineway Pharmaceutical Tech Co., Ltd., Shanghai, China. Sucralose was purchased from L&P Food Ingredient Co., Ltd, Guangzhou, China. The orange flavor was purchased from Firmenich, Geneva, Switzerland. Titanium dioxide was purchased from Jiangsu Hushen Titanium White Technology Co., Ltd, Tongzhou, China. Potassium dihydrogen phosphate, sodium hydroxide, triethylamine, phosphoric acid, HPLC grade acetonitrile, and 0.45 μm mixed cellulose ester membrane filters were purchased from Sinopharm Chemical Reagent Co., Ltd, Shanghai, China. Hexylamine was purchased from TCI Shanghai, China. The water used in all tests is ultrapure. Marketed orally disintegrating tablets were purchased from Nanchang Hongyi Pharmaceutical Co., Ltd., Nanchang, China.

Analytical Method

A prominence ultrafast liquid chromatograph system (Shimadzu, Kyoto, Japan) was used to develop a reverse-phase chromatography method for determining drug content during formulation development and *in vitro* dissolution study of ODFs of granisetron hydrochloride. The API flowed through XBridge C18 (4.6 mm × 150 mm, 5 μm, Waters, Massachusetts, United States) column maintaining 40°C in an isocratic elution mode along with the mobile phase (0.2% phosphoric acid: acetonitrile = 80:20, % v /v) with additional 0.1% hexylamine adjusted to pH 7.5 with triethylamine at a flow rate of 1.2 mL/min and was detected at 300 nm. All data were collected and analyzed by Shimadzu LabSolutions.

Preliminary Experiment Design

The disintegration time and mechanical properties of various blank formulations composed of PVA, PVP K30, HPMC E15, glycerol, Lycoat® RS 780, and PVPP were evaluated to select the optimal combination for further study preliminarily. All formulations are prepared by a solvent casting method under appropriate process parameters, among which the drying temperature and roller speed were optimized in the range of 70 to 90°C and 0.6 to 1.0 m/min, respectively.

QTPP

The first step in the QbD framework is to define the QTPP. This document offers a prospective summary of the desired properties of the final pharmaceutical product. Besides assuring safety and efficacy, QTPP should also take into account the intended purpose and characteristics of clinical administration.

Fig. 1 Customized coating machine and its operation.

CQAs

After establishing the QTPP, the next step is to identify the factors that have a crucial impact on the target product quality, namely the CQAs generally referring to the physical, chemical, biological, and microbial characteristics of the target product.[13] The selection criteria of these attributes depend on the severity of the potential harm to patients when a particular quality attribute of the target product exceeds or falls short of the threshold.

CMAs and CPPs

CMAs belong to formulation variables, and CPPs are related to the preparation technology and corresponding process procedure. Both are likely to affect the CQAs. Therefore, these essential experimental parameters should be further investigated after determining CQAs.[13]

Quality Risk Assessment Studies

The variables significantly influencing the CQAs need to be assessed for the degree of risks in bringing about changes. These factors ought to be categorized into three levels, "high," "medium," and "low," and thoroughly analyzed based on the probability of risk occurrence and the magnitude of their impacts. To this end, a risk assessment matrix (RAM) is established to evaluate the connections between each influencing factor and CQAs and identify high-risk variables for further research.[14]

BBD

BBD is one of the response surface methodology tools, using statistical strategies and mathematical logic to analyze the relationship between the factors that have major impacts on the experimental procedure and the corresponding responses. Compared with the conventional method of investigating factors, BBD can simultaneously assess multiple variables and levels, reducing the number of experiments.[15,16] Design Expert® software (version 13.0.1.0, Stat-Ease, Minneapolis, United States) was used for the experimental design and model-fitting analysis. The validity and reliability of the fitted model will be verified by the analysis of variance (ANOVA).

Preparation of ODFs

Granisetron hydrochloride (1 mg) and excipients were mixed and ground thoroughly with the appropriate amount of purified water in a mortar. Subsequently, the mixture was degassed under a vacuum to obtain a smooth and homogeneous casting dispersion.

The casting process was conducted on a custom coating machine (►**Fig. 1**), which was created collaboratively by our laboratory and Huanghai Pharmaceutical Inspection Instrument Co., Ltd. in Shanghai, China. The casting dispersion was poured onto the lining layer at a temperature of 90°C and a roller speed of 0.9 m/min. The width specification of the film mold was 10 mm, and the scraper was installed with a planned height of 0.35 to 0.45 mm. The raw films were peeled off from the lining, cut into desired-sized rectangles, and then stored in aluminum foil pouches.

Characterization of ODFs

Digital Microscopy Inspection

The surface inspection on granisetron hydrochloride, blank film, and the optimized film was performed by a VHX 100 digital microscope (Keyence, Osaka, Japan) with 500 magnification times to observe the crystalline form of the drug in the state of unprocessed power and film.

Differential Scanning Calorimetry

The Q2000 differential scanning calorimeter (TA Instruments, New Castle, United States) was used to detect and analyze the crystalline state of granisetron hydrochloride, excipients, physical mixture, blank film, and optimized film. Standard crucible aluminum pans loading 2 to 3 mg samples were heated from 30°C to 360°C with a heating rate of 15°C/min, and the nitrogen gas purge flow was set at a rate of 50 mL/min.

X-Ray Diffraction Analysis

Granisetron hydrochloride, excipients, physical mixture, blank film, and optimized film were scanned by the D8 Advance A25 X-ray diffractometer (Bruker, Karlsruhe, Germany) in the theta-theta mode from 3° to 45° with a

scanning speed of 8.0°/min and 0.02-degree step size. In addition, the Cu X-ray tube was operated at 40 kV and 40 mA.

Thickness and Weight

The micrometer (Shanghai Measuring Tool & Cutting Tool Factory Co., Ltd., China) was used to measure the thickness of the prepared ODFs. The final thickness was calculated by obtaining the average thickness of the center and four corners. Additionally, the BSA224S-CW analytical balance (Sartorius, Goettingen, Germany) was used to determine the weight of every single film in the unit dose specification, and the average weight was calculated. The thickness and weight of films are directly connected with the drug content as indirect indicators of content uniformity.

Disintegration Time

The disintegration time of films was measured using the ZB-1C intelligent disintegrator (Tianjin University Precision Instrument Factory, China) equipped with a basket to hold the clipped films. The basket was immersed in a beaker containing 1000 mL of water heated up to 37°C by a water bath, at the same time, raising and lowering at a constant frequency rate between 30 and 32 cycles per minute, during which the films consistently remained below the liquid surface. The duration required for the complete disintegration of the film was recorded.

Mechanical Properties

The intelligent film tensile testing machine (Jinan Ednor Instrument Co., Ltd., China) was used to measure the tensile strength and elongation at the break of films, which were cut into the shape of a dumbbell and longitudinally placed between two tensile clamps to ensure that the film could break from the middle after being stretched. The length and center width of the measured part between clamps are both 10 mm, which were input into the machine along with the film thickness. The clamps moved at a rate of 100 mm/min, and the complete breakage of the film was considered as the endpoint.

Residual Moisture

Using the automatic Karl Fischer moisture analyzer (Metrohm, Herisau, Switzerland), the residual moisture of films was measured. Samples for titration weighed approximately 0.04 to 0.05 g.

Drug Content

The film of unit dose specification was dissolved in a volumetric flask using 10 mL of mobile phase. The flask was vibrated to get a uniform solution, which was then filtered using a 0.45 μm syringe filter and measured as established in the "Analytical Method" section.

In Vitro Dissolution Studies

The *in vitro* dissolution study was conducted using RCZ-6C3 apparatus (Huanghai Pharmaceutical Inspection Instrument Co., Ltd., Shanghai, China) per the USP2 paddle method at the rotational speed of 50 rpm. The film was settled in a small metal basket to ensure it could be kept at the bottom of the dissolution vessel, which contained 500 mL media of phosphate buffer pH 6.8 maintained at 37 ± 0.5°C. 2 mL of sample was collected at 1, 2, 3, 5, 10, and 15 minutes and filtered through 0.45 μm syringe filter for the measurement using the method established in the "Analytical Method" section. The cumulative release percentage of granisetron hydrochloride at each sampling time point was calculated based on a calibration curve. Corresponding revisions were required for the calculation since the media were not replenished after each sampling.

pH

The films (equivalent to 3 mg granisetron hydrochloride) were placed in a 10 mL glass beaker containing 3 mL pH 6.8 phosphate buffer, covered with parafilm for 5 minutes, and the pH of the buffer solution was determined using a pH meter (Shanghai Weiye Instrument Factory, China).

Results

Analytical Method

Linear equations were successfully established for granisetron hydrochloride in the mobile phase (1–120 μg/mL) and phosphate buffer pH 6.8 (0.4–20 μg/mL). Regression coefficients of 0.9999 and 0.9996 validate the feasibility of this analytical method.

Preliminary Experiment Design

The blank formulations consisting of polymer combinations referring to HPMC E15/PVP K30 and PVA/PVP K30, disintegrants referring to Lycoat® RS 780 and PVPP, and the plasticizer referring to glycerin were evaluated for the preliminary performance. Considering patient acceptance, the ODFs should disperse rapidly, and the mechanical properties were evaluated by examining the condition of the film as it was peeled off the liner and held in hand. The combinations for formulation screening and corresponding results are shown in ►**Table 1**. The film formulated as F16 performed well on mechanical strength and could disintegrate in 31 seconds. Therefore, the formulation comprising PVA, PVP, and Lycoat® RS 780 will be optimized further.

Within the selected range of 70 to 90°C and 0.6 to 1.0 m/min, drying temperature and roller speed had no significant impact on the basic performance of ODFs prepared as the formulation F16. Therefore, a drying temperature of 90°C and a roller speed of 0.9 m/min were selected as the fixed parameters.

Quality Risk Assessment Studies

The objective of this study was to develop a patient-friendly ODF formulation of granisetron hydrochloride for quick and convenient oral administration. Thus, the film should possess appropriate properties such as rapid disintegration and dissolution, as well as enough mechanical strength for handling. Accordingly, the QTPPs of granisetron hydrochloride ODFs are presented in ►**Table 2**.

Table 1 Screening blank formulations

Batches	HPMC (%)	PVA (%)	PVP (%)	Lycoat® RS 780 (%)	PVPP (%)	Glycerol (%)	Disintegration Time (s)	Mechanical Property
F1	90	–	10	–	–	–	49	Good
F2	85	–	15	–	–	–	58	Good
F3	80	–	20	–	–	–	69	Good
F4	60	–	10	30	–	–	53	Good
F5	55	–	10	35	–	–	46	Good
F6	50	–	10	40	–	–	47	Good
F7	65	–	10	–	25	–	30	Brittle
F8	60	–	10	–	30	–	31	Brittle
F9	55	–	10	–	35	–	29	Brittle
F10	60	–	10	–	25	5	48	Brittle
F11	55	–	10	–	25	10	45	Brittle
F12	–	65	35	–	–	–	84	Good
F13	–	60	40	–	–	–	95	Good
F14	–	35	35	30	–	–	47	Good
F15	–	30	35	35	–	–	35	Good
F16	–	25	35	40	–	–	31	Good
F17	–	40	35	–	25	–	59	Brittle
F18	–	35	35	–	30	–	51	Brittle
F19	–	30	35	–	35	–	54	Brittle
F20	–	30	35	–	30	5	48	Sticky
F21	–	25	35	–	30	10	44	Sticky

Abbreviations: HPMC, hypromellose; PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone; PVPP, crospovidone.

Table 2 QTPP of granisetron hydrochloride ODFs

QTPP	Target	Justification
Dosage form	ODFs	It does not require water for ingestion and can adhere to the administration site, preventing drug vomiting and asphyxia, while enhancing drug efficacy
Dosage strength	1 mg/film	The same dosage strength as the marketed oral preparation products
Route of administration	Oral	Patients are capable of self-medication
Dissolution profile	Release more than 85% of the drug within 15 minutes[17]	Refer to the dissolution requirements of immediate-release dosage forms in United States Pharmacopoeia (USP)
Stability	Appropriate residual moisture	Excess water content may result in a sticky surface of films, physical instability of the drug, and facilitate the growth of microorganisms
Patient group	Chemotherapy patients, especially the elderly and children	Patients undergoing chemotherapy have vomiting symptoms, and the elderly and children have difficulty taking medication due to the risk of vomiting and choking. ODFs provide a solution to these problems and achieve enhanced safety
Patient compliance	Good patient acceptability and easy to be taken	Pharmaceutical products should possess appropriate patient acceptability to provide a positive treatment experience, and patient adherence to self-medication is advantageous for the medication to exert its effect

Abbreviations: ODFs, orodispersible films. QTPP, quality target product profile.

Table 3 CQAs and their target and justification of the aimed ODF product

CQA	Target	Justification
In vitro dissolution	Complete dissolution within 15 minutes	The dissolution could influence the release, absorption, and bioavailability of the drug
Disintegration time	ODFs should disperse rapidly	The disintegration time has a significant impact on patient compliance
Mechanical properties	Adequate tensile strength	The ODFs should possess enough strength to withstand cutting, packaging, and handling
Residual moisture	Appropriate residual moisture	The residual moisture could influence the physical properties of ODFs and drug stability
pH	5.8–7.4[18]	The pH in line with the oral physiological conditions can reduce the irritation to oral mucosa and improve the compliance and safety of the medication
Drug content	92–108%[19]	The drug content significantly influences the efficacy and safety of the drug
Drug content uniformity	Comply with USP regulations and perform with good uniformity	The drug content uniformity has a significant influence on the efficacy and safety of the drug

Abbreviations: CQAs, critical quality attributes; ODF, orodispersible film.

Part of the QTPPs may be considered CQAs by nature or through transformation. Hence, based on the QTPPs listed above and the unique properties of the desired product, the CQAs were determined, as shown in ►**Table 3**.

Subsequently, the CMAs and CPPs were identified on the strength of experimental experience and relevant knowledge from the literature. The RAM was established to evaluate their association with CQAs, as shown in ►**Table 4**.

The quality risk assessment study has identified three key factors that could potentially affect disintegration time (R_1), percent cumulative drug release at 1 minute (R_2), and tensile strength (R_3). These factors are the amount of PVP K30 (A), the amount of disintegrant (B), and the wet film thickness (C). To conduct further optimization, a BBD study will be conducted.

BBD

The effects of key variables on CQAs were qualitatively analyzed by BBD with a three-level factor framework. The obtained data were subjected to statistical analysis and model-fitting using Design Expert® software. The experiment design and results are shown in ►**Table 5**.

The results of ANOVA showed that the key variables have significant impacts on the responses of disintegration time (R_1) and tensile strength (R_3) ($p < 0.01$). The values of the coefficient of determination (R^2) represent a good model fit. The model is shown to be valid and accurate as the difference between the predicted R^2 and adjusted R^2 is less than 0.2, the percent coefficient of variance (CV%) is less than 5%, and the value of adeq precision is greater than 4.[20] However, the relationship between the percent cumulative drug release at

Table 4 RAM for risk rating evaluation of the association between CQAs and influencing factors

CQA	CMA/CPP					
	API	Film-forming material	Disintegrant	Wet film thickness	Drying temperature	Roller speed
In vitro dissolution	High	High	High	Medium	Low	Low
Disintegration time	Low	High	High	High	Low	Low
Mechanical properties	High	High	Low	Medium	Medium	Low
Residual moisture	Medium	High	Low	Medium	High	Medium
pH	High	High	Low	Low	Low	Low
Drug content and drug content uniformity	High	High	Low	Low	Low	Low

Abbreviations: API, active pharmaceutical ingredient; CMA, critical material attribute; CPP, critical process parameter; CQAs, critical quality attributes; RAM, risk assessment matrix.

Table 5 Box–Behnken design and corresponding responses

RUN	*A* (% w/w)	*B* (% w/w)	*C* (mm)	R_1 (s)	R_2 (%)	R_3 (MPa)
B1	40	30	0.4	30.0	74.20	17.89
B2	30	35	0.45	41.7	65.51	31.68
B3	40	40	0.4	28.7	80.35	27.95
B4	35	30	0.35	23.7	71.20	19.52
B5	30	35	0.35	23.7	62.97	25.93
B6	35	40	0.45	38.0	42.86	33.21
B7	30	30	0.4	33.7	66.03	24.06
B8	35	35	0.4	30.3	75.04	26.12
B9	35	40	0.35	21.7	69.73	28.84
B10	40	35	0.45	40.0	74.41	24.18
B11	30	40	0.4	29.3	64.84	34.23
B12	35	30	0.45	39.7	50.82	25.36
B13	35	35	0.4	29.3	84.92	26.43
B14	35	35	0.4	31.0	57.09	25.89
B15	35	35	0.4	32.0	68.85	26.07
B16	35	35	0.4	30.7	58.39	26.18
B17	40	35	0.35	22.7	70.05	20.46

Note: The symbol *A* represents the amount of PVP K30; *B* is the amount of Lycoat® RS 780; *C* the wet film thickness; R_1 is the disintegration time; R_2 is the percent cumulative drug release at 1 minute; and R_3 is the tensile strength.

Table 6 Fit statistics from ANOVA analysis

Statistics	R_1	R_2	R_3
F-value	179.26	1.30	168.18
p-Value	<0.0001	0.3176	<0.0001
R^2	0.9764	0.2302	0.9954
Adjusted R^2	0.9710	0.0525	0.9895
Predicted R^2	0.9572	-0.3008	0.9335
Adeq precision	37.9087	4.0515	45.3653
CV %	3.38	15.21	1.73

Abbreviations: CV%, percent coefficient of variance; R^2, coefficient of determination.
Note: The symbol R_1 represents the disintegration time; R_2 is the percent cumulative drug release at 1 minute; and R_3 is the tensile strength.

1 minute (R_2) and all variables was not statistically significant. The ANOVA analysis results of all responses are shown in ►**Table 6**.

BBD Data Analysis

Disintegration Time

The disintegration time for all formulations ranged from 21.7 to 41.7 seconds (►**Table 5**). The result of ANOVA showed that the relationship between disintegration time (R_1) and variables conformed to a linear model, and the corresponding Equation (1) is as follows:

$$R_1 = 30.94 - 0.875A - 1.17B + 8.46C \qquad (1)$$

From the coefficient notations of each term, the amount of PVP K30 (*A*) and the amount of disintegrant (*B*) might have a negative effect, while the wet film thickness (*C*) has a positive effect. PVP, a hydrophilic amorphous polymer, causes enhanced water molecule immersion and diffusion, thereby accelerating disintegration. The disintegrant is modified starch, which has hydroxypropyl groups with strong hydrophilic properties. These groups weaken the hydrogen bonds between starch chains allowing for easier swelling. Consequently, a higher percentage of disintegrant leads to enhanced swelling and fragmentation of the film, thereby accelerating disintegration. Wet film thickness is positively correlated with the thickness of the dried film,[11] and its increase would result in a longer path for water molecules to penetrate the film, therefore slowing down disintegration. The three-dimensional (3D) surface plots are depicted in ►**Fig. 2A**.

Cumulative Drug Release Percentage at 1 Minute

The films dissolved rapidly after being placed in the media and became invisible. For all formulations, the films released more than 85% of the drug within 3 minutes, as observed in the dissolution profiles from ►**Fig. 3A**. This correlation is

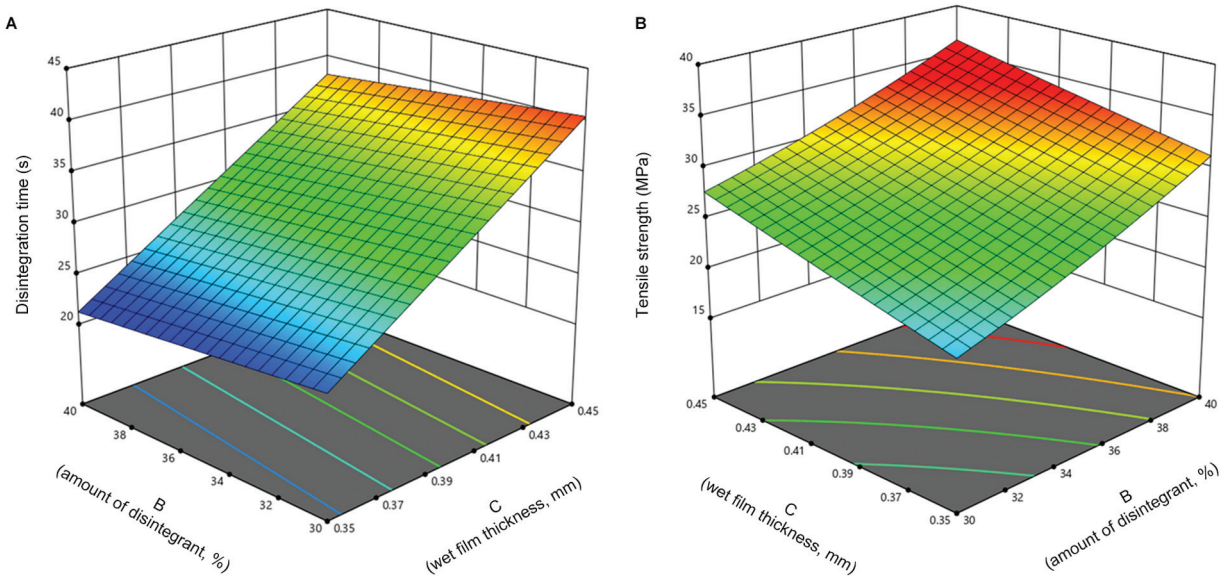

Fig. 2 3D surface graphs demonstrating the impact factors on (**A**) disintegration time and (**B**) tensile strength. 3D, three-dimensional.

linked to the disintegration profiles. The rapid swelling and rupture of films aid in the release of drugs from the formulations, and the high solubility of granisetron hydrochloride also plays a role. Therefore, the overall dissolution performance of the films within the design space was excellent, independent of the polymer ratio and process parameters. The comparison between the optimal film formulation and the marketed reference orally disintegrating tablet is shown in ►**Fig. 3B**.

Tensile Strength

Tensile strength is an important indicator to evaluate mechanical properties, and for all formulations, it ranged from 17.89 to 34.23 MPa (►**Table 5**). The result of ANOVA showed that the relationship between tensile strength (R_3) and variables conformed to a quadratic model, and the corresponding Equation (2) is as follows:

$$R_3 = 26.14 - 3.18A - 4.68B + 2.46C - 0.0275AB - 0.5075AC - 0.3675BC - 0.6378A^2 + 0.5322B^2 + 0.0623C^2 \quad (2)$$

As shown in the polynomial equation for tensile strength, the amount of PVP K30 (A) has a negative effect, while the amount of disintegrant (B) and wet film thickness (C) have a positive effect. PVP is a highly amorphous polymer with relatively loose intermolecular stacking and weak structural rigidity, resulting in easier stretching of films, and its augmented content would undermine the strength of the film. The molecular weight of Lycoat® RS 780 is much higher than those of the other two polymers (PVP K30, 45–58 kDa, PVA, 20–150 kDa, Lycoat® RS 780, 330 kDa),[21–23] and then the film strength, which could be enhanced by increasing the average molecular weight of the constituent materials, would increase along with the addition of more disintegrant.

The value of tensile strength is calculated by dividing the fracture tensile stress by the cross-sectional area as demonstrated in Equation (3). Equation (2) indicates that the variation tendency of tensile strength parallels the film thickness, which is proportional to the cross-sectional area. This suggests that there is significant growth in the fracture tensile stress. The nonlinear increase of fracture tensile stress is likely due to an increased total material density in the interpenetrating network structure. This structure is formed through the cross-linking of PVA and PVP via hydrogen bonds, enhancing film strength.[24,25] The 3D surface plots are depicted in ►**Fig. 2B**.

$$\text{Tensile strength (MPa)} = \frac{\text{Fracture tensile stress} \times 100}{\text{Cross} - \text{sectional area}} \quad (3)$$

Confirmation of the Optimal Formulation

The goal of the study was to develop a patient-friendly ODF of granisetron hydrochloride with quick disintegration and dissolution, as well as adequate mechanical strength for patient use. During screening for the optimal formulation in the software, the disintegration time decreased while the tensile strength increased. However, as the variables did not significantly affect the dissolution performance, no specific conditions were established for selection. The best formulation with the closest desirability value to 1 was chosen from those calculated by the software, which comprised 30.0% w/w of PVA, 30.0% w/w of PVP K30, and 40.0% w/w of Lycoat® RS 780. The process parameter of the wet film thickness was set to 0.35 mm, showing a desirability value of 0.896. The predicted optimal formulation was examined for reliability, and the predicted values from the software were compared with the observed values, as presented in ►**Table 7**. The deviation rate between the predicted values and observed values was calculated. The percent cumulative drug release at 1 minute was not evaluated due to its independence from the variable level. Both the deviation rates for disintegration time and tensile strength were below 2%, indicating good

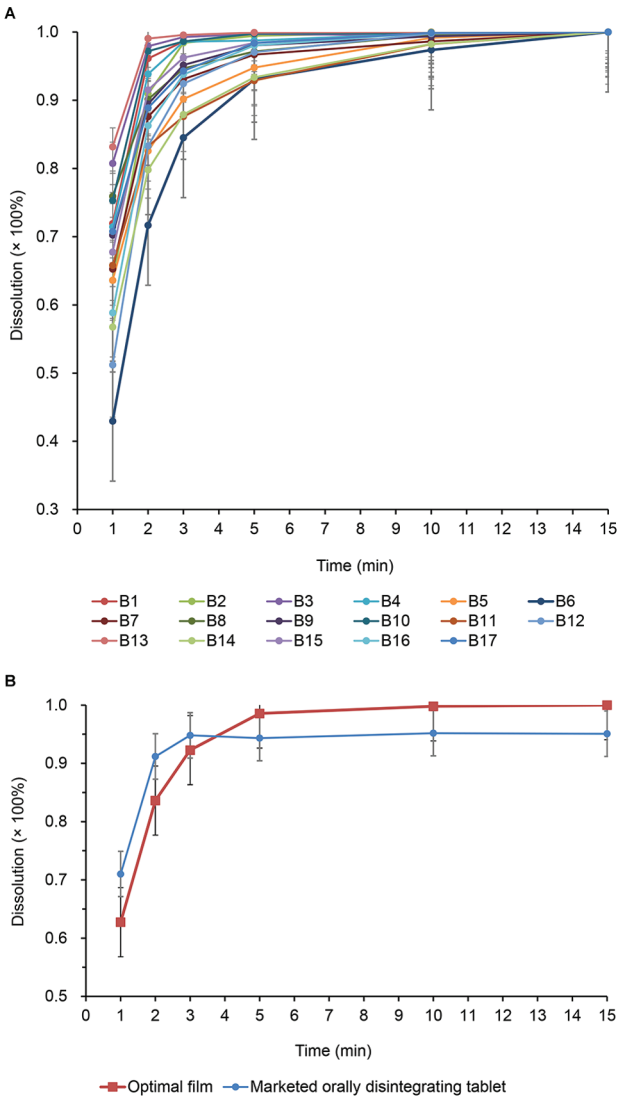

Fig. 3 ODF dissolution profiles for (**A**) all formulations and (**B**) the comparison of the optimal film formulation with marketed orally disintegrating tablet. ODF, orodispersible film.

Table 7 Comparison of predicted and observed values of optimal formulations

Responses	R_1 (s)	R_2 (%)	R_3 (MPa)
Predicted values	22.2	66.43	31.38
Experimental values	22.3	57.40	30.98
Deviation rate (%)	+0.45	−13.59	−1.27

Note: The symbol R_1 represents the disintegration time; R_2 is the percent cumulative drug release at 1 minute; and R_3 is the tensile strength. Each experiment was repeated in triplicate.

reliability of the optimal predicted formulation. Consequently, the predicted formulation was selected as the optimal formula for further research.

Characterization of ODFs

The prepared granisetron hydrochloride ODF was a thin and smooth white sheet without visible particles or bubbles. Physicochemical properties including thickness, weight, elongation at break, residual moisture, drug content, and pH were evaluated and exhibited satisfactory results as shown in ►**Table 8**.

Digital Microscopy Inspection

As shown in ►**Fig. 4**, the unprocessed granisetron hydrochloride is a kind of rectangular crystal, with no sign of crystallization in the images of the blank film and optimized film, suggesting that the drug was evenly dispersed in the films. Meanwhile, a uniform and smooth surface was observed in the images of films without obvious bubbles or cracks.

Differential Scanning Calorimetry

As shown in ►**Fig. 5**, the excipients did not exhibit any significant endothermic peak. The thermogram of the granisetron hydrochloride film revealed a sharp endothermic peak at 303°C, which was also observed in the thermogram of the physical mixture. Although the peak width marginally increased due to the effect of excipients, no endothermic peak was observed at the corresponding position in the thermogram of the blank film and optimized film. These results indicate that the drug was dispersed in an amorphous state in films. The melting of PVA could account for the endothermic peak observed at 244°C in the thermogram of film samples.

X-Ray Diffraction Analysis

As shown in ►**Fig. 5**, API presented distinct diffraction peaks in both samples of unprocessed granisetron hydrochloride and physical mixture, ranging from 5° to 36° of 2θ values, and no corresponding peaks were found in either the blank film or optimized film, implying that the drug was dispersed in an amorphous state in the films.

Thickness and Weight

The film thickness ranged from 95.7 to 145.3 µm, while the film weight ranged from 23.2 to 24.3 mg. Both measurements exhibited insignificant standard deviation or relative standard deviation. The slight variations in the thickness and weight reflected the reliability of the preparation process, which guaranteed consistent composition of the ODF.

Disintegration Time

During the early stage of the disintegration process, the film underwent swelling to absorb water, maintaining its morphology intact, and finally broke down into a slurry in the later stage. The disintegration time for all formulations ranged from 21.7 to 41.7 seconds. The addition of Lycoat® RS 780 significantly promoted the disintegration process, thereby improving patient compliance.

Mechanical Properties

The interpenetrating network structure created by PVP and PVA via hydrogen bond cross-linking enhanced the film strength. This effect was intensified further with high-molecular-weight disintegrant. The tensile strength of films

Table 8 ODF characterization for all BBD runs and the optimal formulation

Formulation	Thickness (μm)	Weight (mg)	Elongation at break (%)	Residual moisture (%)	Drug content (%)	pH
B1	113.7 ± 0.51	23.5 ± 0.26	17 ± 2.89	9.64 ± 0.40	103.15 ± 1.32	6.81 ± 0.22
B2	137.0 ± 0.00	23.4 ± 0.25	17 ± 1.73	9.24 ± 0.02	102.98 ± 0.33	6.82 ± 0.08
B3	117.3 ± 0.49	24.3 ± 0.15	13 ± 0.00	8.81 ± 0.61	99.51 ± 0.43	6.80 ± 0.15
B4	99.7 ± 0.58	23.2 ± 0.31	19 ± 2.08	8.91 ± 0.34	99.65 ± 0.75	6.81 ± 0.08
B5	95.7 ± 0.60	23.7 ± 0.15	12 ± 0.58	9.47 ± 0.76	99.00 ± 0.77	6.80 ± 0.08
B6	137.3 ± 0.42	23.7 ± 0.26	15 ± 2.08	9.47 ± 0.12	99.78 ± 0.36	6.81 ± 0.17
B7	114.0 ± 0.00	23.9 ± 0.15	14 ± 1.53	8.88 ± 0.56	101.19 ± 0.77	6.82 ± 0.08
B8	115.3 ± 0.50	23.6 ± 0.21	18 ± 2.08	8.50 ± 0.34	98.83 ± 0.20	6.80 ± 0.15
B9	97.7 ± 0.59	24.1 ± 0.17	15 ± 2.31	8.82 ± 0.43	99.29 ± 0.59	6.81 ± 0.08
B10	145.3 ± 0.40	23.7 ± 0.35	12 ± 0.58	9.09 ± 0.24	98.82 ± 1.12	6.81 ± 0.15
B11	112.3 ± 0.51	23.9 ± 0.15	19 ± 2.00	9.59 ± 0.41	98.57 ± 0.60	6.80 ± 0.17
B12	133.7 ± 0.43	24.0 ± 0.31	14 ± 1.15	9.78 ± 0.16	99.24 ± 0.08	6.80 ± 0.08
B13	113.7 ± 0.51	23.7 ± 0.15	18 ± 2.65	8.72 ± 0.32	102.09 ± 0.78	6.82 ± 0.08
B14	116.0 ± 0.00	23.9 ± 0.25	19 ± 0.58	9.19 ± 0.11	100.61 ± 1.29	6.81 ± 0.17
B15	115.7 ± 0.50	23.6 ± 0.10	19 ± 1.53	9.53 ± 0.12	101.62 ± 0.34	6.81 ± 0.15
B16	118.3 ± 0.49	23.7 ± 0.21	18 ± 1.53	9.19 ± 0.03	99.23 ± 0.37	6.82 ± 0.17
B17	102.7 ± 0.56	24.1 ± 0.25	13 ± 1.15	9.87 ± 0.05	98.99 ± 0.48	6.81 ± 0.08
Optimal	97.7 ± 0.59	24.0 ± 0.36	16 ± 2.08	8.45 ± 0.14	99.05 ± 0.36	6.82 ± 0.08

Abbreviations: BBD, Box–Behnken design; ODFs, orodispersible films.
Note: Results are presented as mean ± standard deviation of three parallels, except the thickness and pH are presented as mean ± relative standard deviation (%) of three parallels.

ranged from 17.89 to 34.23 MPa, and the elongation at break was between 12 and 19%, indicating sufficient mechanical properties to preserve the piece cohesion during cutting, packaging, and usage.

Residual Moisture

The residual moisture ranged from 8.45 to 9.87%. All films had a dry and smooth surface and were easily peeled from the liner without leaving any residue. There was no discernable impact of residual moisture on the selected CQAs related to disintegration time, tensile strength, and dissolution.

Drug Content

The drug content, which is crucial for both the therapeutic effect and safety of the product, fell within the range of 98.57 to 103.15%, meeting the USP limit for granisetron hydrochloride oral dosage form of 92 to 108%.

In Vitro Dissolution Studies

The dissolution process of all films in pH 6.8 phosphate buffer during the first 15 minutes was quantitatively measured and recorded. As shown in ►**Fig. 3A**, the films fully dissolved within 15 minutes, and more than 85% of the drug was released within 3 minutes due to the short disintegration time and good solubility of granisetron hydrochloride.

pH

The pH values of all formulations after dissolving the films in pH 6.8 phosphate buffer ranged from 6.80 to 6.82. This fluctuation margin confirmed the extent of typical measurement errors compared with the pH value of phosphate buffer. Therefore, the buffer's pH value remained almost unchanged after film dissolution, maintaining a normal physiological range of the oral cavity between 5.8 and 7.4 without causing any mucosal irritation.

Discussion

In addition to sufficient mechanical strength ensuring film durability during cutting, packaging, and transportation, this study aims to establish that ODFs must exhibit rapid disintegration to improve compliance and rapid dissolution for prompt drug efficacy. Meeting these attributes would fulfill the patient's clinical requirements. Therefore, disintegration time (R_1), percent cumulative drug release at 1 minute (R_2), and tensile strength (R_3) were selected as the CQAs of granisetron hydrochloride ODF. However, currently, there is no universally accepted criterion for the disintegration time of ODF. A study on the acceptability of patients with ODFs showed that the user experience is considered relatively comfortable when the disintegration time is less than 60 seconds and is independent of other attributes.[26] On all accounts, a short disintegration time is favorable.

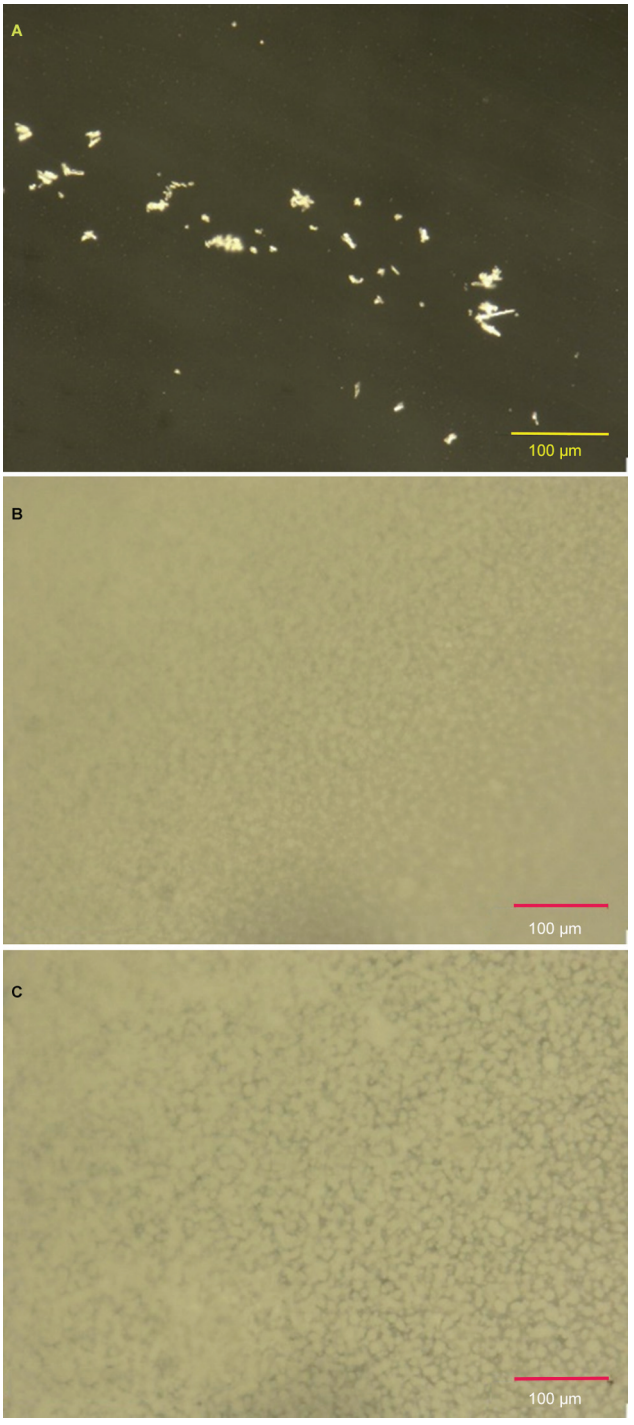

Fig. 4 Digital microscopy images of (**A**) granisetron hydrochloride, (**B**) blank film, and (**C**) optimized film.

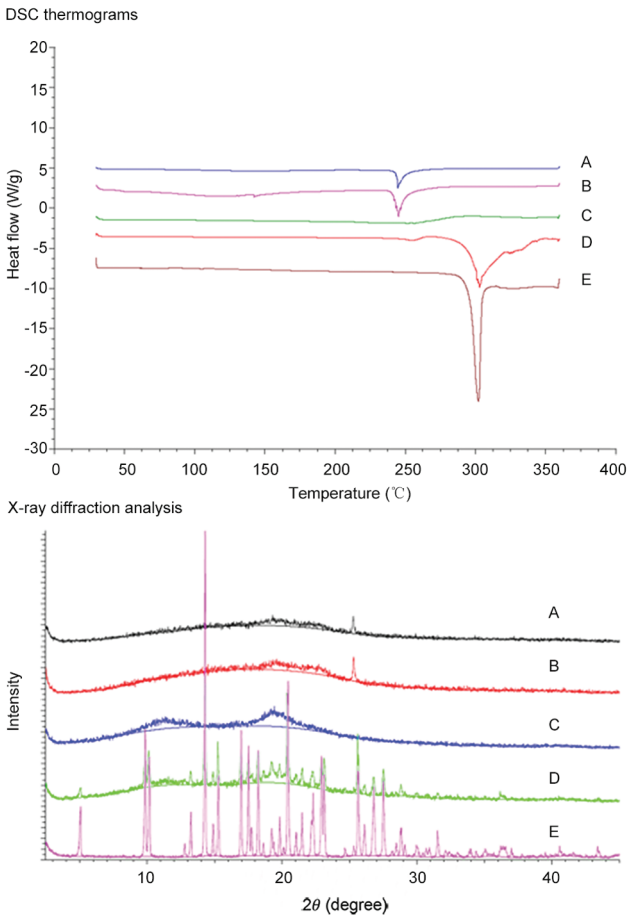

Fig. 5 DSC thermograms and X-ray diffraction analysis of (A) optimized film, (B) blank film, (C) excipients, (D) physical mixture, and (E) granisetron hydrochloride. DSC, differential scanning calorimetry.

Based on the above, a preliminary screening of blank formulations was conducted. PVP K30 is commonly used as a film-forming material known for its property of water absorption, which facilitates the disintegration of films. However, films made solely from PVP K30 did not perform well, and therefore, combinations with other film-forming materials have been tested. HPMC E15 possesses a high molecular weight, and PVA could form a cross-linked network structure with PVP K30 through hydrogen bonding, resulting in the improvement of film performance. Then, Lycoat® RS 780 and PVPP were included as disintegrants to accelerate disintegration. In addition, glycerol was added as the plasticizer due to the poor mechanical properties exhibited by the formulations containing PVPP, and no significant improvement was observed. Consequently, the F16 formulation comprising PVP, PVA, and Lycoat® RS 780 was selected to conduct the BBD experiment.

As demonstrated by the ANOVA results, the hydrophilicity of PVP K30 facilitated the disintegration of films. However, its loose internal structure weakened the tensile strength. The hydroxypropyl groups of Lycoat® RS 780 facilitated water absorption and expansion of films, thus promoting disintegration, and its high molecular weight enhanced the tensile strength. The wet film thickness is positively correlated with the thickness of the dried film, and as it grows, it prevents disintegration by elongating the infiltration path of water molecules. Additionally, the increased thickness accommodates more material per unit area, which enhances the density of the PVA-PVP crosslinking network and ultimately leads to an increase in tensile strength.

The desirability value of the optimal solution provided by the software is 0.896, which falls short of the ideal value of 1. This deviation can be attributed to the conflicting tendency

requirements of the influencing factors along the selected optimization direction of both disintegration time and tensile strength. Reducing the disintegration time necessitated a decrease in film thickness and an increase in PVP K30 content, whereas boosting tensile strength demanded an increase in film thickness and a reduction in PVP K30 content. This conflict was reflected in the desirability value of the optimal solution.

Residual moisture is an essential characteristic of ODF, in addition to mechanical properties, disintegration time, and dissolution. Excessive moisture content may lead to a sticky surface, rendering the films challenging to peel off and use, as well as promoting the growth of microbes, making storage difficult. However, maintaining appropriate moisture content in ODFs is vital for preserving their morphological integrity and basic mechanical properties.[27] Furthermore, films would lose their toughness and become brittle when the moisture content is too low. It is generally considered acceptable to maintain the moisture content below 10%,[28] whereas, this criterion is not as stringent as other characterization items. In this study, the moisture content of granisetron hydrochloride ODF was approximately 10%; however, this did not affect the performance of the films.

Conclusion

This study verified the feasibility of developing granisetron hydrochloride ODF using the QbD concept. The key quality attributes include disintegration time, percent cumulative drug release at 1 minute, and tensile strength. Important high-risk factors are identified as PVP amount, disintegrant amount, and wet film thickness. Additionally, the relationship between CQAs and high-risk variables was explored using the BBD response surface method. As a result, an optimal formulation was successfully developed, and its reliability was confirmed. The optimal formulation contains 30.0% w/w of PVA, 30.0% w/w of PVP K30, and 40.0% w/w of Lycoat® RS 780 with the process parameter of the wet film thickness of 0.35 mm, and the optimal ODF has a disintegration time of 22.3 seconds and a tensile strength of 30.98 MPa. Using the QbD strategy of planned design and quality risk management, we have produced a patient-friendly granisetron hydrochloride ODF that has a good appearance, adequate disintegration, dissolution, and mechanical strength, and meets quality standards.

Conflict of Interest
None declared.

Reference

1 Nguyen TTL, Duong VA, Maeng HJ, Chi SC. Development of an oil suspension containing granisetron hydrochloride as a sustained-release parenteral formulation for enhancement of pharmacokinetic properties. J Drug Deliv Sci Technol 2019;51:643–650
2 Guo Z, Chen P, Liu L, Song H. Compatibility and stability of methylprednisolone sodium succinate and granisetron hydrochloride in 0.9% sodium chloride solution. Medicine (Baltimore) 2022;101(28):e29674
3 Kovac AL. Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. Drug Saf 2003;26(04):227–259
4 Sathanish R, Bengali RV, Kalidass, Amuthan S. Comparative study of ondansetron and granisetron for postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy under general anaesthesia –randomized double blind study. Eur J Mol Clin Med 2022;9(04):2556–2562
5 Guan J, Guo Y, Chang P, et al. Adjunctive granisetron therapy in patients with sepsis or septic shock (GRANTISS): study protocol for a randomized controlled trial. Medicine (Baltimore) 2019;98 (39):e17354
6 Cabanillas Stanchi KM, Ebinger M, Hartmann U, et al. Efficacy, safety and feasibility of antiemetic prophylaxis with fosaprepitant, granisetron and dexamethasone in pediatric patients with hemato-oncological malignancies. Drug Des Devel Ther 2019; 13:3439–3451
7 Singh H, Sharma R, Joshi M, Garg T, Goyal AK, Rath G. Transmucosal delivery of Docetaxel by mucoadhesive polymeric nanofibers. Artif Cells Nanomed Biotechnol 2015;43(04):263–269
8 Singh B, Garg T, Goyal AK, Rath G. Recent advancements in the cardiovascular drug carriers. Artif Cells Nanomed Biotechnol 2016;44(01):216–225
9 Gupta MS, Kumar TP, Gowda DV. Orodispersible thin film: a new patient-centered innovation. J Drug Deliv Sci Technol 2020; 59:101843
10 Özcan Bülbül E, Mesut B, Cevher E, Öztaş E, Özsoy Y. Product transfer from lab-scale to pilot-scale of quetiapine fumarate orodispersible films using quality by design approach. J Drug Deliv Sci Technol 2019;54:101358
11 Mazumder S, Pavurala N, Manda P, Xu X, Cruz CN, Krishnaiah YSR. Quality by design approach for studying the impact of formulation and process variables on product quality of oral disintegrating films. Int J Pharm 2017;527(1–2):151–160
12 Mishra V, Thakur S, Patil A, Shukla A. Quality by design (QbD) approaches in current pharmaceutical set-up. Expert Opin Drug Deliv 2018;15(08):737–758
13 Kovács B, Péterfi O, Kovács-Deák B, et al. Quality-by-design in pharmaceutical development: from current perspectives to practical applications. Acta Pharm 2021;71(04):497–526
14 Silva BMA, Vicente S, Cunha S, et al. Retrospective Quality by Design (rQbD) applied to the optimization of orodispersible films. Int J Pharm 2017;528(1–2):655–663
15 Londhe V, Shirsat R. Formulation and characterization of fast-dissolving sublingual film of iloperidone using Box-Behnken design for enhancement of oral bioavailability. AAPS PharmSciTech 2018;19(03):1392–1400
16 Shen C, Shen B, Xu H, et al. Formulation and optimization of a novel oral fast dissolving film containing drug nanoparticles by Box-Behnken design-response surface methodology. Drug Dev Ind Pharm 2014;40(05):649–656
17 <711> Dissolution. In: U.S. Phramacopeia and National Formulary. Rockville, MD: The United States Pharmacopeial Convention, Inc.; 2021
18 Jain SK, Sahu A, Keservani RK. Oral drug delivery system. In: Keservani RK, Kesharwani RK, Sharma AK. eds. Advances in Novel Formulations for Drug Delivery. Beverly, MA: Scrivener Publishing; 2023:383–400
19 Monograph "Granisetron Hydrochloride Tablets.". In: U.S. Phramacopeia and National Formulary. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2021
20 Sohrabi S, Akhlaghian F. Modeling and optimization of phenol degradation over copper-doped titanium dioxide photocatalyst using response surface methodology. Process Saf Environ Prot 2016;99:120–128
21 Chen A, Miao Y, Pora B, et al. Film-forming compositions for hard capsule shells and hard capsule shells obtained thereof. WIPO Patent WO2018/146165(A1). August, 2018

22 EDQM. Povidone. In: Pharmacopoeia Europea. 10th ed. Strasbourg, France: EDQM Council of Europe
23 EDQM. . Poly(vinyl alcohol). In: Pharmacopoeia Europea. 10th ed. Strasbourg, France: EDQM Council of Europe; 2021
24 Ali FM, Kershi RM, Sayed MA, AbouDeif YM. Evaluation of structural and optical properties of Ce^{3+} ions doped (PVA/PVP) composite films for new organic semiconductors. Physica B 2018; 538:160–166
25 Guo X, Cun D, Wan F, et al. Comparative assessment of in vitro/in vivo performances of orodispersible electrospun and casting films containing rizatriptan benzoate. Eur J Pharm Biopharm 2020; 154:283–289
26 Scarpa M, Paudel A, Kloprogge F, et al. Key acceptability attributes of orodispersible films. Eur J Pharm Biopharm 2018;125:131–140
27 Hoffmann EM, Breitenbach A, Breitkreutz J. Advances in orodispersible films for drug delivery. Expert Opin Drug Deliv 2011;8(03):299–316
28 Drašković M, Turković E, Vasiljević I, et al. Comprehensive evaluation of formulation factors affecting critical quality attributes of casted orally disintegrating films. J Drug Deliv Sci Technol 2020; 56:101614