Development of sustained-release floating tablets of diltiazem hydrochloride

Hung Pham Van, Tung Nguyen Thanh, Nhat Hoang Thi Anh, Hieu Bui Trung, Uyen Dinh Thi Thu, Duyen Nguyen Thi Thanh*

Hanoi University of Pharmacy, 13-15 Le Thanh Tong Street, Cua Nam Ward, Hanoi, Vietnam

Received 13 December 2024; revised 31 December 2024; accepted 4 February 2025

Abstract:

Diltiazem hydrochloride (DTZ), utilised for cardiovascular conditions, possesses a short half-life, necessitating frequent dosing. To enhance compliance, sustained-release (SR) floating tablets were developed using a quality by design (QbD) approach. This study aimed to formulate DTZ 120 mg tablets, conforming to United States Pharmacopeia 2023 dissolution standards, at a batch size of 1000 tablets. Wet granulation was employed with hydrophilic polymers to control drug release, while gas-generating excipients were used to ensure buoyancy. Tablets were evaluated for floating characteristics, *in vitro* dissolution, and drug release mechanisms. Hydroxypropyl methylcellulose K100M controlled release (HPMC K100M CR), $NaHCO_3$, and PVP K30 significantly influenced output variables and were selected for the experimental design. The release rate of DTZ decreased with higher amounts of HPMC and $NaHCO_3$, while PVP had a minimal effect. The optimised formula included HPMC K100M CR (501.5 mg), $NaHCO_3$ (244.8 mg), PVP K30 (32.4 mg), and other excipients. Tablets exhibited a floating lag time of less than 1 minute and a floating duration exceeding 30 hours. Dissolution results met United States Pharmacopeia standards, showing values of 26.99±0.97% at 6 hours, 50.31±0.40% at 12 hours, and 91.46±1.92% at 30 hours. The manufacturing process for 1000 tablets per batch was established, and process parameters were investigated.

Keywords: **diltiazem hydrochloride, floating, quality by design, sustained-release, tablets.**

Classification numbers: **3.3, 3.5, 3.6**

1. Introduction

Diltiazem hydrochloride is a calcium channel blocker used for the treatment and prevention of angina pectoris, as well as for mild to moderate hypertension. The drug has a half-life of approximately 6-8 hours; thus, to maintain therapeutic efficacy when using conventional tablets, patients need to take the medication multiple times a day, which can affect treatment adherence [1]. Compared to conventional formulations, sustained-release forms offer several advantages, such as maintaining therapeutic drug levels in the blood for longer periods, reducing the frequency of dosing, aiding patients in adhering to their treatment schedule, and enhancing the therapeutic efficacy of the drug [2].

A gastric floating system is a system that has the ability to float on the surface of gastric fluids, minimally influenced by the gastric emptying rate. It can be retained in the stomach for a certain period through various mechanisms, releasing the drug substance in a controlled manner. DTZ has good solubility in low pH environments, stability in the gastric acid environment, and is well absorbed in the upper small intestine, making it well-suited for incorporation into a gastric floating system [3-5]. Therefore, this study was conducted with the objective of formulating a sustained-release floating tablet of diltiazem hydrochloride 120 mg on a scale of 1000 tablets that meets the United States Pharmacopeia 2023 dissolution standards.

In this study, the formulation and preparation process of DTZ extended-release floating tablets were conducted based on the quality by design (QbD) approach, following these main steps: pre-formulation studies; screening studies to evaluate the impact of formulation factors on tablet characteristics; application of experimental design in formulation optimisation, including experimental design using response surface methodology, building correlation models between input and output variables using artificial neural networks, and formulation optimisation using the desirability function approach. The preparation process for

*Corresponding author: Email: duyenntt@hup.edu.vn

DTZ 120 mg sustained-release floating tablets at a batch scale of 1000 tablets was developed by investigating several process parameters at the 1000-tablet batch scale.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride (India); HPMC K4M, K15M, K100M CR (Colorcon, USA), lactose monohydrate, Avicel PH-101 (Taiwan, China); sodium bicarbonate, polyvinylpyrrolidone K30 (PVP K30), magnesium stearate, talc, Aerosil 200 (China), and several other excipients and chemicals.

2.2. Methods

2.2.1. Preparation methods

Preparation of sustained-release floating tablets of diltiazem hydrochloride: The DTZ tablets were prepared using the wet granulation method, employing $NaHCO_3$ as a gas-forming agent to generate CO_2, which reduced the density of the system, facilitating buoyancy on the surface of the dissolution medium. Water-soluble polymer excipients (HPMC) were used to retain the generated CO_2 and control the release process of DTZ [6, 7]. Each tablet was planned to contain: DTZ (120 mg), HPMC K4M, K15M, K100M CR, $NaHCO_3$, lactose monohydrate, Avicel PH-101, PVP K30, magnesium stearate, talc, Aerosil 200, and 96% ethanol solvent for preparing the binder solution. During the screening and experimental design phases, each sample was prepared at a scale of 100 tablets per batch.

The steps of tablet preparation: Sieve the drug substance and excipients through an appropriate sieve size. Blend the drug substance and excipients (except for the lubricant excipients and PVP K30) into a homogeneous mixture. Prepare the binder solution: Dissolve PVP K30 in 96% ethanol. Knead the powder mixture with the binder solution to form a wet mass. Pass the wet mass through a 500 micrometre sieve, then dry the granules at 40°C in a drying oven. Dry the granules until the moisture content reaches 2-5% (approximately 2 hours), determined by an Ohaus MB25 moisture analyser, and pass the dry granules through a 500 micrometre sieve. Lubricate the granules with the lubricant excipients. Compress the lubricated granules to form tablets using an 8-station rotary tablet press machine (Shakti), with specific variations in weight and size for each trial (the appropriate tablet weight to accurately contain about 120 mg of DTZ), theoretical tablet weights are: 680 mg for tablets compressed with round cylindrical punches, diameter 12 mm; 750 mg for tablets compressed with caplet-shaped punches, size 19x11 mm; 1000 mg for tablets compressed with oval-shaped punches, size 21.5x10.5 mm; the breaking force of tablets is 5-7 kp, determined by a Pharmatest PTB 511B hardness tester.

Experimental design and formula optimisation: Referring to the dissolution requirements of the DTZ extended-release dosage form in the monograph "Diltiazem Hydrochloride Extended-Release Capsules", United States Pharmacopeia 2023, three output variables (response variables) were selected for this study: the dissolution rate of DTZ extended-release floating tablets at 6 hours (Y1); at 12 hours (Y2); at 30 hours (Y3). Specific information regarding the output variables is presented in Table 1 [8].

Table 1. Selected output variables.

Output variables	Symbol	Unit	Range	Objectives
Amount dissolved at 6 hours	Y1	%	20-40	30
Amount dissolved at 12 hours	Y2	%	35-55	45
Amount dissolved at 30 hours	Y3	%	≥80	90

The input variables significantly influence the output variables, and their corresponding ranges will be selected after screening studies. Experimental design will be conducted using response surface methodology, building correlation models between input and output variables using artificial neural networks. Formulation optimisation will be performed using the desirability function approach. The experimental design and formulation optimisation process will be carried out using SAS JMP Pro 17 software.

Preparation of sustained-release floating tablets of diltiazem hydrochloride 120 mg at a scale of 1000 tablets: Conducting a survey and selecting some process parameters for a batch scale of 1000 tablets, the main preparation stages are similar to the screening scale but are adjusted for some equipment and parameters to suit the scale of 1000 tablets per batch: Sieving drug substance and excipients through appropriate sieves. Mixing powders on a high-speed mixer GHL-10; put the ingredients into the equipment in the specified order: HPMC K100M CR, $NaHCO_3$, DTZ, and Avicel PH-101; impeller speed: 8 Hz, chopper speed: 0 Hz; no use of air blowing. The mixing time varied (4, 8, 12 minutes). Dissolving PVP K30 in 96% ethanol to form a binder solution. Kneading on a high-speed mixer GHL-10, the binder solution will be poured from 2 to 4 times,

with a 5-minute interval between each pouring. After all the binder solution is poured, continue operating the equipment for an additional 5 minutes, impeller speed 6 Hz, chopper speed 10 Hz, with air blowing. Pass the wet mass through a 500 micrometre sieve. Dry the granules in a drying oven (Binder) until the moisture content reaches 2-5%. Pass the dried granules through a 500 micrometre sieve. Lubricate the dried granules with lubricant excipients in a V-mixer (Shakti). Operate the equipment at a speed of 44 rpm, mixing time varied (2, 4, 6 minutes). Compress the lubricated granules on an 8-station rotary tablet press machine (Shakti LP2), with oval-shaped punches, size 21.5x10.5 mm, adjusting the weight and compression force to achieve tablets with a weight of 1000 mg, breaking force of approximately 5-7 kp, investigate tablet compression speed at levels of 6 rpm.

2.2.2. Evaluation methods

Evaluating the interaction between diltiazem hydrochloride and excipients

Observing the color changes of the mixture: Preparing physical mixtures: DTZ and the intended excipients were mixed in equal proportions at a ratio of 1:1 (w/w). The samples were stored in transparent glass vials, tightly sealed with rubber caps, and stored at a temperature of 30±2ºC and a relative humidity of 75±5%. A visual assessment of colour changes in the powder mixtures was conducted after 1 month of storage [9].

Infrared spectroscopy (IR): Preparing physical mixtures: DTZ and the intended excipients were mixed in equal proportions at a ratio of 1:1 (w/w). The samples were stored in sealed aluminium foil bags. After 1 month, infrared spectra of the samples were measured using an FTIR Affinity-1S instrument under the following conditions: sample to potassium bromide ratio=1:5, compression into thin tablets with a pressure of approximately 690 N for 3 minutes, and spectral scanning in the range of wavenumbers 4000-400 cm^{-1} (resolution 4 cm^{-1}). Interaction assessment, if any, was conducted by observing the positions of characteristic signals or the appearance of additional signals in the IR spectra of the physical mixtures compared to the IR spectra of DTZ.

Evaluation of some quality criteria of granules: The moisture content, flowability, and active ingredient content were evaluated before tablet compression.

Evaluation of some quality criteria of sustained-release floating tablets: In vitro dissolution studies: Refer to the dissolution test conditions in the monograph "Diltiazem Hydrochloride Extended-Release Capsules", United States Pharmacopeia 2023 [8], with the main conditions as follows: paddle apparatus, stirring speed of 100 rpm, dissolution medium: 900 ml of HCl solution pH 1.2, temperature: 37±0.5°C, sampling times: 1, 2, 4, 6, 9, 12, 30 hours (the sampling times of 1, 2, 4, and 9 hours are additional conditions compared to the requirements of United States Pharmacopeia 2023). The dissolution requirements at specific times according to United States Pharmacopeia 2023 are summarised in Table 2.

Table 2. The amount dissolved according to United States Pharmacopeia 2023 test-7.

No.	Time (h)	Amount dissolved (%)
1	6	20-40
2	12	35-55
3	30	≥80

Sample processing and calculation results: Put 1 tablet into the dissolution vessel, take a sample at the time specified above, suck exactly 10 ml of the dissolved test solution each time, then add 10 ml of the corresponding environment.

Sample solution: At the time of sampling, suck precisely 5.0 ml of dissolved test fluid into a 50 ml volumetric flask. Dilute with HCl pH 1.2 solution to the volume, shake, and centrifuge at a speed of 6000 rpm for 10 minutes, collecting the upper fluid.

Standard solution: Accurately weigh about 60.0 mg of drug into a 50 ml volumetric flask. Add 30 ml of HCl pH 1.2 solution, sonicate for 10 minutes, add pH 1.2 HCl solution to the volume, and shake well. Pipette exactly 1.0 ml of solution into a 100 ml volumetric flask; add HCl pH 1.2 solution to the volume. Centrifuge the solution at a speed of 6000 rpm for 10 minutes. Collect the clear solution to get a standard sample.

Blank solution: HCl pH 1.2 solution.

Measure the UV absorbance of the sample solution and standard solution at a wavelength of 236 nm, thereby calculating the percentage of drug released at each time point.

In vitro buoyancy studies: The buoyancy of tablets is evaluated through the floating lag time and floating time, conducted simultaneously during the *in vitro* dissolution test. Floating lag time: determined as the time from putting the tablet in until the tablet floats stably on the surface of the dissolution medium. Floating time is determined as the total time the tablet maintains a stable float on the surface of the dissolution medium. Requirements: floating lag time must not exceed 15 minutes; floating time over 30 hours [7].

Evaluation of similarity of two dissolution profiles: The similarity of two dissolution profiles is assessed using the similarity factor (f_2) according to the following formula [10]:

$$f_2=50.\log\left\{\left[1+\frac{1}{n}.\sum_{i=n}^{n}(R_i-T_i)^2\right]^{-0,5}.100\right\}$$

where n is the number of time points compared, R_i is the average dissolution of the reference product at time point i (%), and T_i is the average dissolution of the test product at time point i (%).

The f_2 value ranges from 0 to 100, with higher values indicating greater similarity between the two dissolution profiles. A value of $f_2 \geq 50$ is generally considered to indicate that the two dissolution profiles are similar.

Evaluation of drug release kinetic models: This study uses two parameters to evaluate the suitability of the models with the experimental drug release process from the dosage form: Akaike's information criterion (AIC) and the adjusted R^2 value (R^2_{adj}) [11, 12].

Akaike information criterion:

$$AIC=n.\ln\left(\frac{SSE}{n}\right)+2k$$

where *SSE* represents the sum of squared errors ($\sum(y_i-y'_i)^2$), n is the sample size, and k is the number of predictors in the model plus one for the intercept, y_i and y_i' are the percentage of drug released at time i according to experiment and model prediction (%). The model with the smallest AIC value is the most suitable model to describe the drug release process from the dosage form.

The R^2_{adj} is determined by:

$$R^2_{adj}=1-\frac{n-1}{p-1}.(1-R^2)$$

with $$R^2=1-\frac{\sum_{i=1}^{n}(C_i'-C_i)^2}{\sum_{i=1}^{n}(C_i-\overline{C})^2}$$

where n is the number of sampling points, p is the number of model parameters, C_i and C_i' are the percentage of drug released at time i according to experiment and model prediction (%), respectively. $\overline{C}$ is the average of the experimental drug release percentage (%). The model with the largest R^2_{adj} value is the most suitable model to describe the drug release process from the dosage form.

The AIC and adjusted R^2 values were calculated using the DDSolver 1.0 tool.

Evaluation of the characteristics of the polymer matrix system during in vitro dissolution testing: Evaluating the ability of water uptake, swelling, and erosion of the tablets. After each period of dissolution testing, the tablet is taken out, using filter paper to absorb all excess water on the surface, and weighed to determine the weight of W_2. The tablets were then dried in an oven for 48 hours, weighing W_1. The initial tablet weight before testing is W_0 [4, 13]. Water uptake (%), matrix swelling, and matrix erosion were calculated from the formulas below:

$$\text{Water uptake (\%)}=\frac{(W_2-W_1)}{W_1}\text{ x 100 (\%)}$$

In addition, DTZ sustained-release floating tablets are also evaluated for a number of criteria, such as appearance, tablet weight uniformity, tablet breaking force, and content.

Methods of analysing and processing data: Research data were processed and analysed using Excel 2016 software, DDSolver 1.0, and SAS JMP Pro 17 software. Differences between groups were evaluated using a one-factor ANOVA analysis. Data are presented as mean and standard deviation (mean±SD).

3. Results and discussion

3.1. Research on the compatibilities of diltiazem hydrochloride with excipients

Conducting infrared spectra scanning of DTZ raw material samples and physical mixture samples of DTZ and excipients. The DTZ sample gives characteristic absorption bands for groups: aromatic C-H group: 3057.3 (cm^{-1}); O-CH3-C-H group: 2839.3 (cm^{-1}); amino hydrochloride group N-H: 2391.8 (cm^{-1}); C=O acetate group: 1741.8 (cm^{-1}); C=O lactam group: 1680.1 (cm^{-1}). Infrared spectra of DTZ samples and physical mixture samples are presented in Fig. 1.

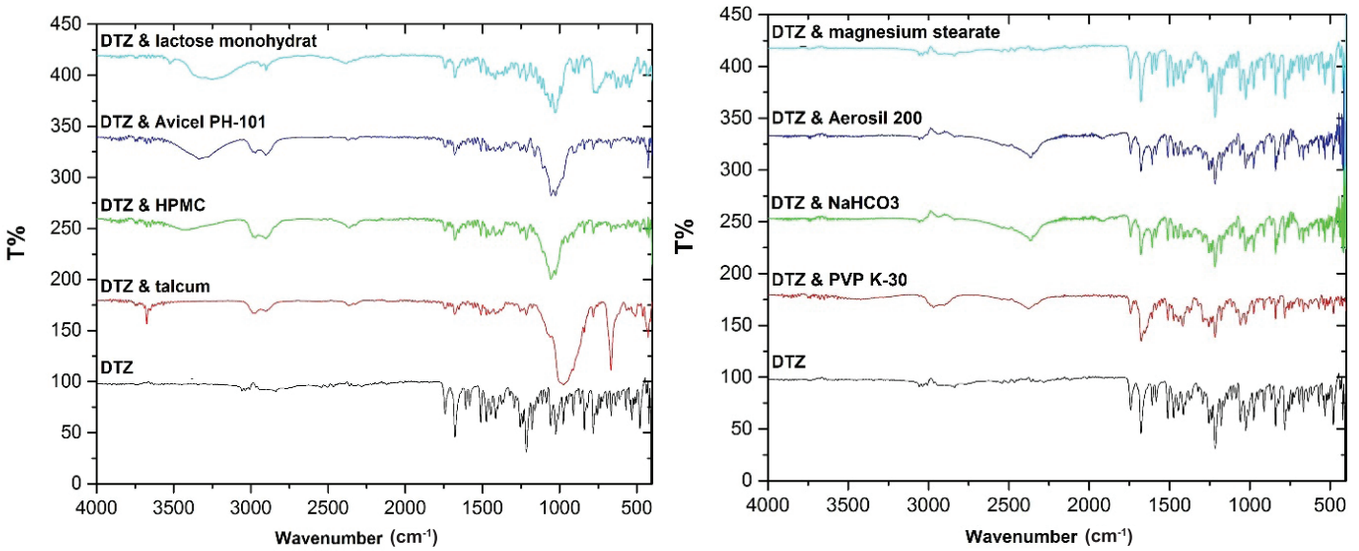

Fig. 1. Infrared spectra of experimental samples. Note: DTZ, DTZ & talcum, DTZ & HPMC, DTZ & Avicel PH-101, DTZ & lactose monohydrat; DTZ & PVP K30, DTZ & $NaHCO_3$, DTZ & Aerosil 200, DTZ & magnesium stearate.

On the IR spectra of the experimental samples, there are signals corresponding to characteristic groups in the DTZ molecule. There are no significant fluctuations in the position or intensity of this signal compared to the IR spectrum of DTZ raw materials.

Evaluation of the appearance of the experimental samples also shows that the samples, after preservation, still retain their original colour without discolouration or other changes in properties.

Thus, incompatibility between DTZ and the excipients selected for use in the study has not been detected, so these excipients can be used to research and develop the formula for DTZ extended-release floating tablets.

3.2. Formulation development of sustained-release floating tablets of diltiazem hydrochloride

Based on a comprehensive literature review and preliminary assessments, it was determined that formulation factors such as the type and amount of water-soluble polymer, the amount of gas-generating excipient, the amount of binder, and the type of filler significantly impact the properties of sustained-release floating tablets, including floating lag time, floating time, and dissolution rate. Therefore, this study focused on evaluating the influence of these formulation variables on the characteristics of the tablets. Specifically, formulations CT1, CT2, and CT3 investigated the effect of the type of release-controlling polymer; formulations CT3, CT4, and CT5 investigated the effect of the amount of release-controlling polymer; formulations CT5, CT6, and CT7 investigated the effect of the amount of $NaHCO_3$; formulations CT7 and CT8 investigated the effect of the type of filler; and formulations CT8, CT9, and CT10 investigated the effect of the amount of PVP K30 on the tablet properties. The screening formulations are presented in Table 3.

The prepared tablet samples were evaluated for their properties, including breaking force, drug content, and weight uniformity. The results showed that all these parameters met the predetermined requirements.

Floating ability: All ten tablet formulations (CT1-CT10) exhibited satisfactory *in vitro* floating ability, with floating lag times of less than 1 minute and floating times of over 30 hours.

Effect of polymer type on drug release: Polymers play a crucial role in controlling drug release in these floating tablets. They also act as a scaffold to retain CO_2 gas generated during the dissolution test, thereby reducing tablet density and maintaining buoyancy. Formulations CT1, CT2, and CT3 were prepared using polymers with different viscosities. The dissolution profiles of these formulations are shown in Fig. 2.

Table 3. Screening formulations investigating the effect of excipients in sustained-release floating tablets of diltiazem hydrochloride.

Composition (mg)	Formulation									
	CT1	*CT2*	*CT3*	*CT4*	*CT5*	*CT6*	*CT7*	*CT8*	*CT9*	*CT10*
DTZ	120	120	120	120	120	120	120	120	120	120
HPMC K4M CR	**300**	0	0	0	0	0	0	0	0	0
HPMC K15M CR	0	**300**	0	0	0	0	0	0	0	0
HPMC K100M CR	0	0	**300**	**325**	**467**	467	467	467	467	467
$NaHCO_3$	150	150	150	150	**200**	**100**	**250**	250	250	250
PVP K30	15	15	15	15	20	20	20	**20**	**40**	**80**
Lactose monohydrate	67	67	67	106	149	248	**98**	0	0	0
Avicel PH-101	0	0	0	0	0	0	0	**98**	58	38
Magnesium stearate	10	10	10	12	16	16	16	16	16	16
Talc	10	10	10	12	16	16	16	16	16	16
Aerosil 200	8	8	8	10	13	13	13	13	13	13
EtOH 96% (ml)	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4
Tablet weight	680	680	680	750	1000	1000	1000	1000	1000	1000

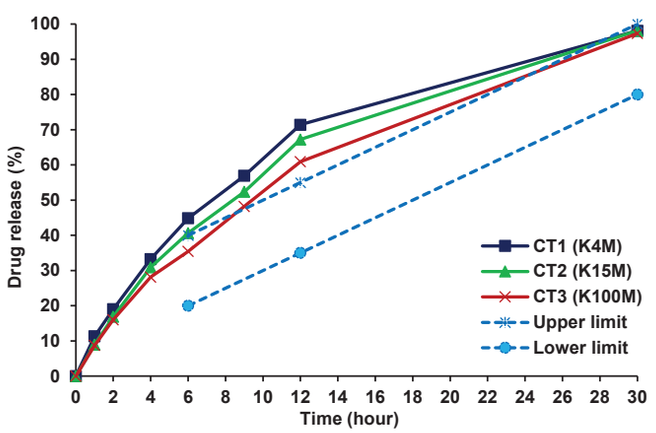

Fig. 2. Dissolution profiles of tablet samples with formulations CT1, CT2, and CT3.

The results demonstrated that the drug release control ability increased in the order of CT1, CT2, and CT3, corresponding to the use of polymers with increasing viscosity. HPMC is an excipient that can control drug release through a gel diffusion or gel erosion mechanism. As the viscosity of HPMC increases, the formed gel layer becomes more stable, reducing the erosion rate of the matrix, the permeation rate of the dissolution medium into the tablet structure, and the diffusion rate of the drug solution out of the tablet. Formulation CT3 (using HPMC K100M CR) exhibited the best drug release control ability, and therefore HPMC K100M CR was selected as the main release control excipient for further studies.

Effect of tablet weight on drug release: Formulations CT4 and CT5 were prepared with excipients similar to those of CT3, using increasing amounts of excipients in the formulation and a corresponding increase in tablet weight. The dissolution profiles of these formulations are shown in Fig. 3.

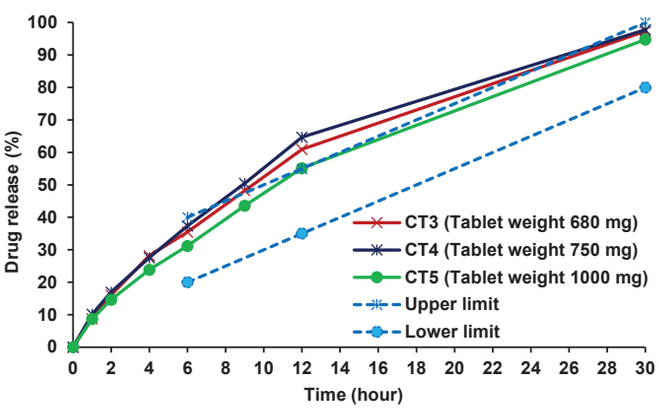

Fig. 3. Dissolution profiles of tablet samples with formulations CT3, CT4, and CT5.

The results showed that formulations CT3 and CT4 have similar drug release profiles. Formulation CT5 exhibited the best drug release control, nearly meeting the dissolution requirements. Due to the use of similar excipients in the formulation, CT5 was prepared with the highest excipient weight (and also the highest tablet weight), resulting in the largest release control matrix mass. Additionally, the DTZ ratio in the CT5 tablet sample is also the smallest, which increased the diffusion path length for the dissolution medium to reach and dissolve DTZ within the tablet structure and for the DTZ solution to diffuse out of the system. Consequently, this formulation exhibited the slowest DTZ release rate. Based on these findings, a DTZ tablet with a mass of 1000 mg was designed for further studies. The tablet had an oval shape and dimensions of 21.5x10.5 mm.

Effect of gas-generating excipient amount on drug release: Formulations CT5, CT6, and CT7 were prepared with varying amounts of $NaHCO_3$, and their dissolution profiles are shown in Fig. 4.

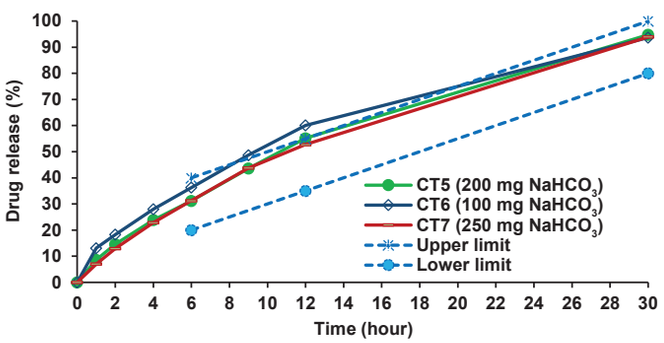

Fig. 4. Dissolution profiles of tablet samples with formulations CT5, CT6, and CT7.

Formulations CT5 and CT7 demonstrated superior control over drug release, exhibiting nearly identical release profiles at all time points. CT6, which contained the least amount of $NaHCO_3$, showed a release rate that exceeded the upper limit and was higher than those of CT5 and CT7. This may be attributed to the dual mechanism of $NaHCO_3$ in controlling drug release: (i) pH-dependent solubility: $NaHCO_3$ is an alkaline excipient that forms an alkaline solution around drug particles upon dissolution, thereby reducing the dissolution rate of DTZ (due to DTZ's decreased solubility at higher pH); (ii) Gas barrier effect: $NaHCO_3$ reacts to generate CO_2 gas in the dissolution medium, and the CO_2 layer acts as a gas barrier, slowing down the diffusion and release of the drug.

For these reasons, formulations with a higher $NaHCO_3$ content are expected to have better release control. Based on these results, formulation CT7 was selected for further investigation of formulation factors affecting DTZ tablets.

Effect of filler type on drug release: Formulation CT8 was prepared with excipients similar to CT7, but using Avicel PH-101 as the filler. The dissolution profiles of CT7 and CT8 are shown in Fig. 5.

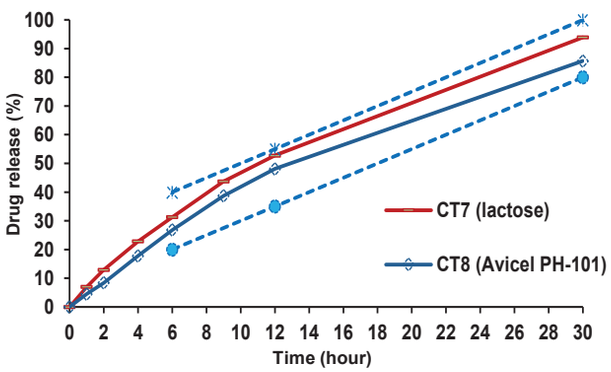

Fig. 5. Dissolution profiles of tablet samples with formulations CT7, and CT8.

Formulation CT7, which used lactose monohydrate as a filler, exhibited a higher release rate compared to CT8 (which used Avicel PH-101). Lactose monohydrate is a water-soluble filler that can create channels within the tablet structure, facilitating the penetration of the dissolution medium into the tablet structure to dissolve DTZ and the diffusion of the DTZ solution out of the system. In contrast, Avicel PH-101 is a cellulose derivative with good compression properties. Upon exposure to the dissolution medium, Avicel PH-101 swells but does not dissolve, and it is retained within the polymer core, reinforcing the tablet matrix structure. Based on these analyses, Avicel PH-101 was selected as the filler due to its superior release control compared to the other formulations.

Effect of binder amount on drug release: PVP K30 serves as a binder in the tablet and, in many cases, can also act as a pore-forming agent to enhance drug release. Conversely, PVP K30 can also strengthen the tablet structure, slowing down drug release. Formulations CT9 and CT10 were prepared with excipients similar to CT8 but with increasing amounts of PVP K30. The dissolution profiles of CT8, CT9, and CT10 are shown in Fig. 6.

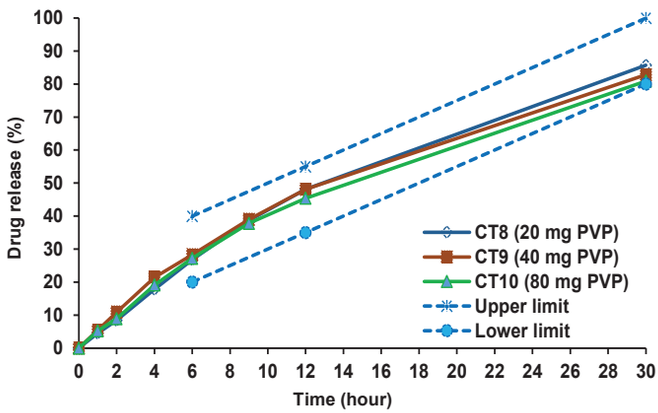

Fig. 6. Dissolution profiles of tablet samples with formulations CT8, CT9, and CT10.

All tested formulations exhibited drug release profiles that met the desired requirements. Formulations CT8 and CT9, with PVP K30 amounts of 20 and 40 mg, respectively, showed similar drug release profiles. Formulation CT10, with a PVP K30 amount of 80 mg, exhibited a slower release rate. This is likely due to the higher binder content (8% of tablet weight), which resulted in a denser, more tightly bound granulate that eroded more slowly and maintained its matrix shape better during dissolution testing. However, using a high amount of binder made it difficult to prepare the binder solution, wet mixing, and subsequent granulation. Therefore, a PVP K30 amount of 20 mg (as per CT8) was selected for the tablet formulation.

Based on the evaluation of formulation factors, formulation CT8 met the requirements for buoyancy and dissolution. Composition of formulation CT8: DTZ 120 mg, HPMC K100M CR 467 mg, $NaHCO_3$ 250 mg, Avicel PH-101 98 mg, PVP K30 20 mg, magnesium stearate 16 mg, talc 16 mg, Aerosil 200 13 mg, and the tablet weight was 1000 mg.

3.3. Experimental design and optimisation of sustained-release floating tablet formulation

3.3.1. Selection of input variables and experimental design

Based on the results of the screening study, three input variables were selected for experimental design and formulation optimisation: HPMC K100M CR amount (X1), $NaHCO_3$ amount (X2), and PVP K30 amount (X3). Specific information about the input variables is presented in Table 4.

Table 4. Input variables.

Input variables	Type	Unit	Abbreviation	Lower limit	Upper limit
HPMC K100M CR	Continuous	mg/tablet	X1	367	517
$NaHCO_3$	Continuous	mg/tablet	X2	100	250
PVP K30	Continuous	mg/tablet	X3	20	80

*: All formulations included the following additional components: DTZ 120 mg, magnesium stearate 16 mg, talc 16 mg, Aerosil-200 13 mg, Avicel PH-101 filler to a final tablet weight of 1000 mg.

A 16-experiment design was created using response surface analysis, the input variable compositions and corresponding output variable results for these 16 experiments are summarised in Table 5.

Table 5. Design values of input variables and obtained values of output variables.

Experiment	Input variables			Output variables		
	X1	*X2*	*X3*	*Y1*	*Y2*	*Y3*
1	367	100	20	33.64	54.96	86.48
2	367	100	80	29.46	48.63	80.94
3	367	175	50	36.84	63.33	95.55
4	367	250	20	31.47	53.45	92.64
5	367	250	80	30.2	53.95	91.72
6	442	100	50	34.8	54.78	89.64
7	442	175	20	34.18	52.01	88.61
8	442	175	50	30.38	54.72	89.16
9	442	175	50	31.11	53.96	89.69
10	442	175	80	29.9	54.23	88.17
11	442	250	50	27.27	51.71	87.7
12	517	100	20	31.15	49.57	81.75
13	517	100	80	32.25	50.68	85.55
14	517	175	50	34.37	50.99	86.49
15	517	250	20	27.58	47.68	87.31
16	517	250	80	31.93	54.74	90.15

Relationship between input and output variables: Artificial neural networks (ANNs) were constructed to model the relationship between each output variable and the input variables. The network structure consisted of 1 output variable, 3 input variables, and 2 hidden neurons in 1 layer. Both hidden neurons used the Gaussian activation function (Fig. 7). The networks were trained using the K-fold method, divided into 5 subgroups, with a learning rate of 0.1 and 1000 training tours.

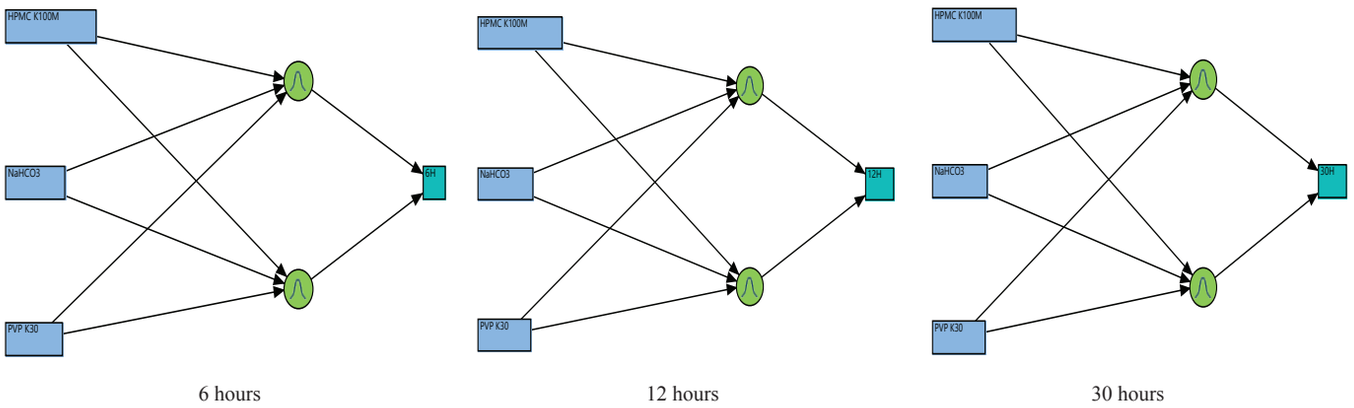

Fig. 7. Artificial neural network structure modelling the relationship between each output variable and the input variables.

Evaluation results of the constructed artificial neural networks are summarised in Table 6.

Table 6. Evaluation results of the constructed artificial neural networks.

Parameters	Y1		Y2		Y3	
	Training	*Validation*	*Training*	*Validation*	*Training*	*Validation*
R^2	0.992	0.952	0.979	0.851	0.907	0.997

The constructed ANNs all had R^2 values greater than 0.8, indicating that the ANNs with the constructed structure could well describe the correlation between input and output variables. The relationship between input and output variables is further illustrated in Fig. 8, based on the constructed ANNs.

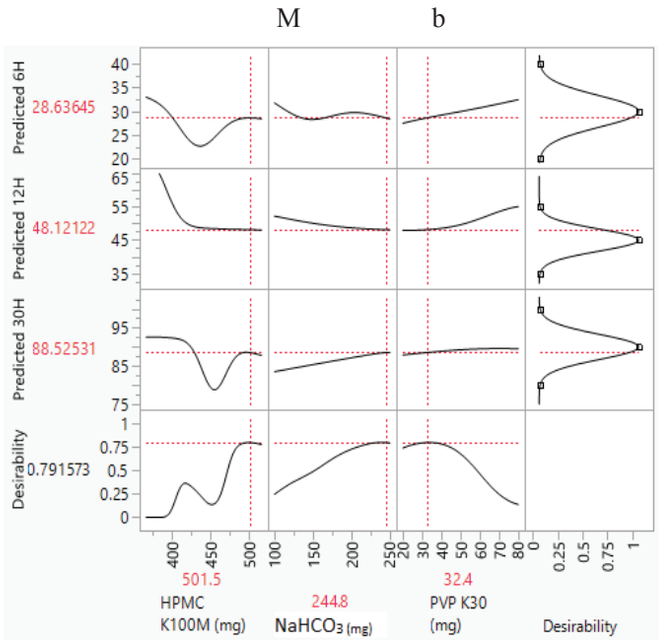

Fig. 8. Effect of input variables on output variables.

Effect of X1 (HPMC K100M CR) on output values: Holding X2 ($NaHCO_3$) constant at 244.8 mg and X3 (PVP K30) constant at 32.4 mg, the dissolution at 6, 12, and 30 hours all showed a decreasing trend as X1 increased from about 367 to 450 mg. Further increasing X1 from 450 to 517 mg, the dissolution at 6 and 30 hours showed an increasing trend, while the dissolution at 12 hours remained relatively unchanged.

Effect of X2 ($NaHCO_3$) on output values: Holding X1 (HPMC K100M CR) constant at 501.5 mg and X3 (PVP K30) constant at 32.4 mg, the dissolution at 6 hours was less affected as X2 increased, with the dissolution value fluctuating slightly around 30%. The dissolution at 12 hours showed a slight decreasing trend, and the dissolution at 30 hours showed a slight increasing trend.

Effect of X3 (PVP K30) on output values: Holding X1 (HPMC K100M CR) constant at 501.5 mg and X2 ($NaHCO_3$) constant at 244.8 mg, the dissolution at 6 hours, 12 hours, and 30 hours all showed a general trend of little or slight increase as X3 increased.

3.3.2. Design space

Based on the constructed ANNs, the design space was determined as shown in Fig. 9.

Figure 9A shows the design space when the PVP K30 variable is fixed at 32.4 mg. Fig. 9B shows the design space when the $NaHCO_3$ variable is fixed at 244.8 mg. The white space is the experimental design space. When the input variables take different values within this space, the output variables will achieve the set target.

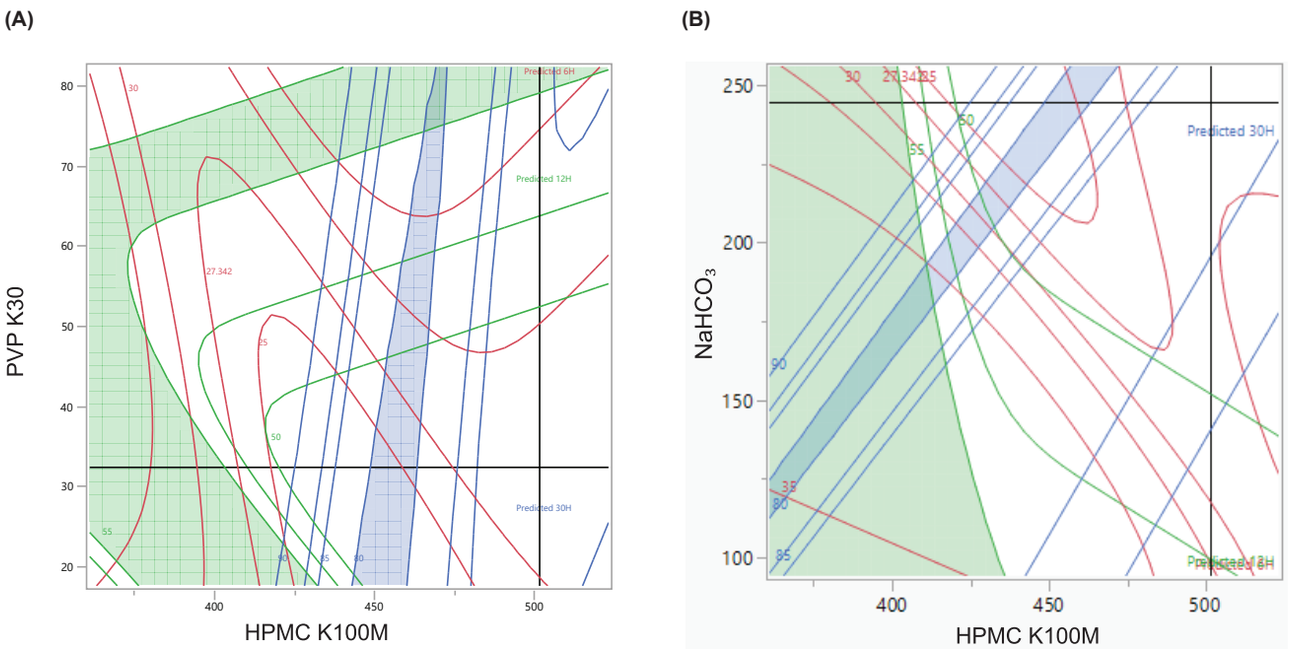

Fig. 9. Design space of formulation variables. (A) Design space with PVP K30 fixed at 32.4 mg; **(B)** Design space with $NaHCO_3$ fixed at 244.8 mg.

3.3.3. Formulation optimisation

The method of optimisation using the desirability function was applied. The specific desirability function for the dissolution value at 6 hours (D1), 12 hours (D2), and 30 hours (D3) is as follows:

$$D_1 = \begin{cases} 0 \text{ if } Y1=20 \\ 1 \text{ if } Y1=30 \\ 0 \text{ if } Y1=40 \end{cases}$$

$$D_2 = \begin{cases} 0 \text{ if } Y2=35 \\ 1 \text{ if } Y2=45 \\ 0 \text{ if } Y2=55 \end{cases}$$

$$D_3 = \begin{cases} 0 \text{ if } Y3=80 \\ 1 \text{ if } Y3=90 \\ 0 \text{ if } Y3=100 \end{cases}$$

The overall desirability function is calculated as:

$$D = D_1^{1/3} . D_2^{1/3} . D_3^{1/3}$$

The goal is to find the values of the input variables (HPMC K100M CR, $NaHCO_3$, and PVP K30) that maximise the overall desirability function (D) while maintaining the buoyancy within the acceptable range. The optimal values of the input variables and the predicted values of the output variables are presented in Table 7. The maximum achievable value of D is approximately 80%.

Table 7. Optimal values of input variables and predicted values of output variables.

Optimal values of input variables		Predicted values of output variables	
HPMC K100M (X1, mg)	501.5	Dissolution value at 6 hours (Y1)	28.64
$NaHCO_3$ (X2, mg)	244.8	Dissolution value at 12 hours (Y2)	48.12
PVP K30 (X3, mg)	32.4	Dissolution value at 30 hours (Y3)	88.53

Optimised formulation for sustained-release floating DTZ tablets: DTZ: 120 mg, HPMC K100M CR: 501.5 mg, $NaHCO_3$: 244.8 mg, PVP K30: 32.4 mg, Avicel PH-101: 56.3 mg, magnesium stearate: 16 mg, Talc: 16 mg, Aerosil-200: 13 mg, Ethanol 96%: 0.4 ml, and the tablet weight was 1000 mg.

3.3.4. Preparation and evaluation of the optimised formulation

Buoyancy and in vitro drug release: Three batches of DTZ tablets were prepared according to the optimised formulation, each batch containing 100 tablets. All tablets from the three batches exhibited floating lag times of less than one minute and remained buoyant throughout the 30-hour *in vitro* dissolution test. The average dissolution data of the three optimal tablet batches are as follows: 1 hour:

6.26±1.12%; 2 hours: 9.69±0.97%; 4 hours: 17.82±0.95%; 6 hours: 26.99±0.97%, 9 hours: 39.79±1.60%; 12 hours: 50.31±0.40%, 24 hours: 79.67±2.71%; and 30 hours: 91.46±1.92%. The dissolution of the three batches of tablets prepared according to the optimised formulation met the requirements (Fig. 10). The *in vitro* drug release profiles were similar to the predicted release profiles generated by the software (f2≥70%).

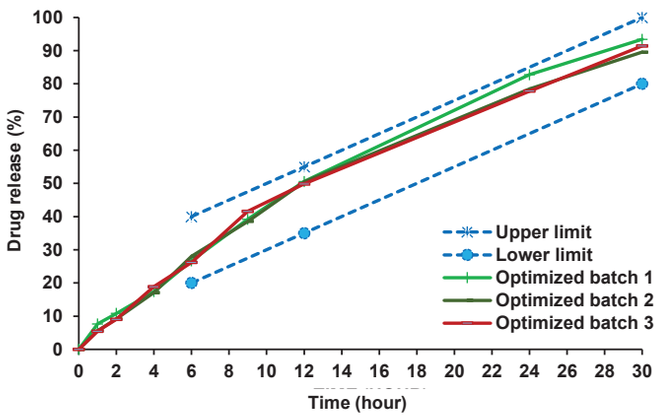

Fig. 10. Dissolution profiles of three batches of tablets prepared according to the optimised formula.

Effect of different in vitro dissolution medium: The pH of the empty stomach is typically in the range of 1-2. However, under the influence of meals or when taking certain antacids, the gastric pH can range from 3.3 to 5.3 [14]. This experiment aimed to evaluate the buoyancy and drug release of the sustained-release floating tablets in different pH environments. The tablets remained buoyant in pH 4.5 medium with a floating lag time of less than one minute and a floating time of over 30 hours. The dissolution of the optimised formulation tablets in pH 1.2 and 4.5 mediums is shown in Fig. 11.

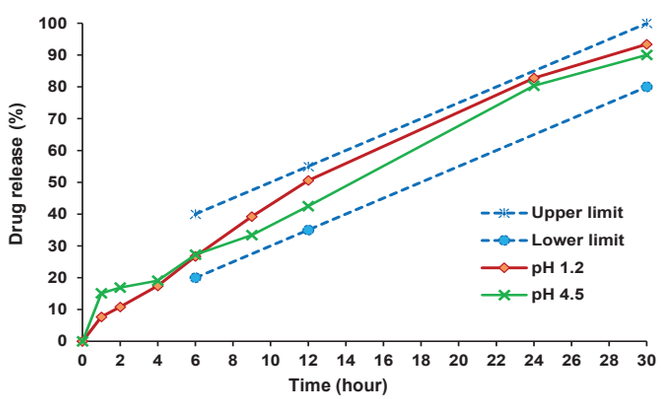

Fig. 11. Dissolution profile of the optimised tablets in different pH environments.

Drug release kinetics from the optimised tablet formulation: The dissolution data for the optimised tablet formulation was fitted to various mathematical models. The results of the model fitting analysis are summarised in Table 8.

Table 8. Results of model fitting analysis.

Models	Adjusted R^2	AIC
Zero-order	0.9624	54.2856
First-order	0.9811	48.0995
Higuchi	0.9248	60.5196
Korsmeyer-Peppas	0.9957	35.5342
Hixson-Crowell	0.9962	33.7527
Weibull	0.9973	31.9019

Based on the AIC and adjusted R^2 values, the drug release process in the tablets follows the Weibull model. This is an empirical model and does not fully explain the kinetic characteristics of drug release. The Korsmeyer-Peppas and Hixson-Crowell models also fit the experimental drug release process well. In other studies of sustained-release floating DTZ tablets in hydrophilic matrix form, the most appropriate drug release kinetic model was found to be the Korsmeyer-Peppas model, which describes drug release as being influenced by two mechanisms: diffusion and erosion [11, 12].

3.3.5. Characteristics of the polymeric matrix during drug release

The data on water uptake, swelling, and erosion of the tablets during the dissolution test are shown in Fig. 12.

The swelling and erosion of the tablets occurred simultaneously. During the first 12 hours, the swelling and water uptake of the tablets were rapid, followed by a predominance of erosion after 12 hours, while the swelling of the tablets decreased. This is consistent with the drug release kinetics observed in the tablets. In the early stages, the tablets absorbed water and swelled, creating channels for the drug to diffuse into the dissolution medium. Later, the polymeric matrix was gradually dissolved and eroded, and the main mechanism of drug release was dissolution and erosion.

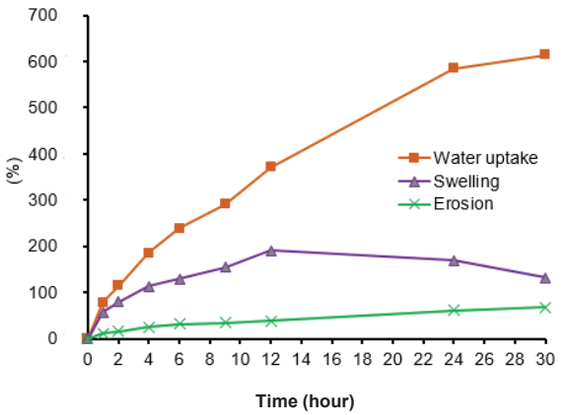

Fig. 12. Water uptake, swelling, and erosion of tablets.

3.4. Development of a manufacturing process for sustained-release floating tablets of diltiazem hydrochloride

Effect of powder mixing time: The powder blend was transferred to a GHL-10 high-speed mixer-granulator. Since the drug content in the powder blend was greater than 10% of the total blend mass, single-stage mixing was employed. The order of addition of ingredients to the mixer was: HPMC K100M CR, $NaHCO_3$, DTZ, and Avicel PH-101. Based on preliminary evaluations, the mixing speed of the impeller was set to 8 Hz, and the cutting speed was set to 0 Hz (no air blowing). Samples were taken at 4, 8, and 12 minutes to determine the distribution of drug content. Ten samples were taken at each time point; the mass of each sample is 1 gram. The sampling locations are described in Fig. 13.

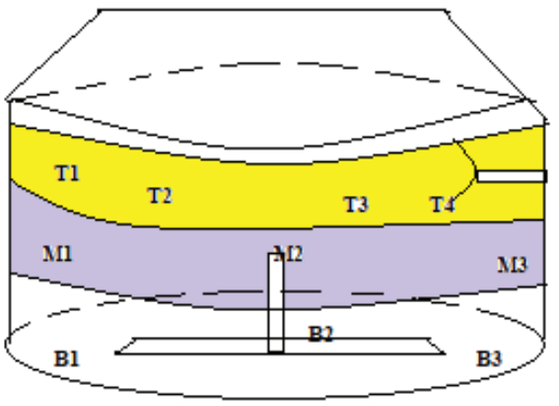

Fig. 13. Sampling positions on the high-speed mixer-granulator GHL-10.

The results of determining the drug content distribution in the samples are summarised in Table 9.

Table 9. Evaluation of drug content distribution during the powder blend mixing stage.

Positions	Drug content (%)				
	Batch 1			*Batch 2*	*Batch 3*
	4 minutes	*8 minutes*	*12 minutes*	*8 minutes*	*8 minutes*
1	98.12	98.49	101.17	98.76	99.48
2	101.33	101.86	98.92	101.17	99.61
3	103.39	100.96	100.47	97.56	99.05
4	101.62	101.46	101.11	99.21	101.47
5	102.96	98.50	101.96	99.17	98.91
6	99.10	100.46	99.01	101.50	101.63
7	100.00	101.18	100.02	100.66	100.20
8	98.73	101.41	101.75	100.92	102.12
9	98.56	100.07	101.56	100.06	99.80
10	97.77	100.89	98.40	100.02	99.94
Mean±SD	100.16±2.04	100.52±1.19	100.43±1.29	99.90±1.23	100.22±1.13
RSD	2.03	1.18	1.28	1.23	1.12

At a mixing time of 4 minutes, the powder blend did not achieve uniformity in drug content distribution (RSD>2%). Increasing the powder blend mixing time to 8 or 12 minutes improved the uniformity of drug content distribution in the powder blend (RSD≤2%). Based on this result, the selected powder blend mixing time was 8 minutes with a mixing impeller speed of 8 Hz, a cutting impeller speed of 0 Hz, and no air blowing on the GHL-10 high-speed mixer-granulator.

The powder blend was mixed with the selected parameters for batches 2 and 3, and the drug content distribution in the powder blend was evaluated. The results of the drug content distribution evaluation are summarised in Table 9, which shows that the RSD values are all less than 2%, indicating that the drug content distribution is similar among the three batches.

Effect of lubricant mixing time: After the granulation process, the granules and lubricants (magnesium stearate, talc, and Aerosil 200) were transferred to a Shakti V-mixer with a BY800 mixer head. The equipment was operated at a mixing speed of 44 rpm, and samples were taken at 2, 4, and 6 minutes to determine the drug content distribution. Samples were taken at 10 positions. Since there was no dedicated sampling device, the powder in the mixer was poured onto a stainless steel tray, and samples were taken from 10 different positions. The results are shown in Table 10.

Table 10. Evaluation of drug content distribution during lubricant mixing stage.

Positions	Drug content (%)				
	Batch 1			***Batch 2***	***Batch 3***
	2 minutes	*4 minutes*	*6 minutes*	*4 minutes*	*4 minutes*
1	100.10	100.09	99.74	98.89	98.50
2	104.74	100.99	101.24	98.03	101.03
3	99.57	100.06	100.03	100.83	100.35
4	99.65	99.84	101.26	102.27	102.77
5	97.71	98.97	97.72	102.35	101.37
6	97.29	98.67	99.16	98.80	98.80
7	98.99	98.78	98.78	100.00	100.23
8	100.16	99.50	100.59	101.82	101.64
9	101.37	99.60	99.41	97.86	98.97
10	103.33	101.70	102.16	98.95	99.09
Mean±SD	100.28±2.65	99.82±0.96	100.01±1.33	99.98±1.73	100.27±1.45
RSD	2.65	0.96	1.33	1.73	1.45

At a mixing time of 2 minutes, the powder blend did not achieve uniformity in drug content distribution (RSD > 2%). With mixing times of 4 and 6 minutes, the powder blend achieved uniformity in drug content distribution. However, prolonged mixing tended to cause the powder blend to delaminate. Therefore, to ensure uniformity in drug content distribution, a mixing time of 4 minutes with a mixing speed of 44 rpm was chosen.

Batches 2 and 3 were mixed using the parameters selected during the evaluation of Batch 1. The results of evaluating the uniformity of drug content distribution in these two batches are summarised in Table 10. The results show that the RSD values are all less than 2%, indicating that the drug content distribution is consistent among the batches.

The change in powder flowability before and after lubricant mixing was also evaluated. The results show that the powder flowability was significantly improved after lubricant mixing, with the flowability changing from poor (26-31) to fair (16-20).

Table 11. Summary of some tablet characteristics.

Parameter	Batch 1	Batch 2	Batch 3
Appearance	White tablets	White tablets	White tablets
Breaking force (kp), (mean±SD, n=10)	6.44±0.22	6.54±0.31	6.47±0.28
Abrasion (%)	0.034	0.061	0.059
Tablet weight uniformity	Within limit ±5% average weight	Within limit ±5% average weight	Within limit ±5% average weight
Content (%), (mean±SD, n=10)	102.16±0.35	98.06±1.67	98.79±1.41

Evaluation of tablet quality from three batches of 1000 tablets: The appearance, breaking force, abrasion, and weight uniformity of the three batches of 1000 tablets each are presented in Table 11.

The floating and dissolution properties of three batches of 1000 tablets each are presented in Table 12.

The buoyancy and dissolution performance of the optimised sustained-release floating tablets were evaluated

Table 12. Results of floating and dissolution evaluation on 3 batches of 1000 tablets.

	Batch 1	Batch 2	Batch 3
Floating lag time (min)	<1	<1	<1
Floating time (hour)	30	30	30
Drug release (%, n=6, mean±SD)			
0	0	0	0
1	7.71±0.65	6.78±0.34	7.64±0.55
2	10.02±1.08	9.57±0.34	10.88±0.17
4	17.93±1.76	18.04±1.85	20.71±1.30
6	26.96±1.13	28.13±0.37	27.29±1.08
9	37.82±0.25	37.42±2.38	37.53±0.23
12	48.30±1.74	46.25±2.19	46.46±2.38
24	77.35±2.72	73.95±3.93	78.50±3.22
30	90.77±0.83	89.94±0.93	90.90±0.71
f2	f2 (Batch 1 vs Batch 2)=87.45	f2 (Batch 2 vs Batch 3)=83.32	f2 (Batch 1 vs Batch 3)=89.97
f2	f2 (Batch 1 vs 100 tablets/batch)=88.37	f2 (Batch 2 vs 100 tablets/batch)=92.50	f2 (Batch 3 vs 100 tablets/batch)=92.01

across three batches. All three batches exhibited satisfactory buoyancy, maintaining buoyancy throughout the 30-hour *in vitro* dissolution test. The dissolution profiles of the three batches were compared using the similarity factor f2. The f2 values for all three batches were above 80%, indicating a high degree of similarity in their dissolution performance. Additionally, the dissolution profiles of the 1000-tablet batches were compared to those of the 100-tablet batches from the screening study. The f2 values for these comparisons were also above 80%, demonstrating that the dissolution performance was consistent across different batch sizes.

4. Conclusions

A quality by design (QbD) approach was successfully employed to develop a sustained-release floating diltiazem hydrochloride tablet formulation with a target dose of 120 mg. The optimised tablet composition was as follows: diltiazem hydrochloride: 120 mg; HPMC K100M CR: 501.5 mg; $NaHCO_3$: 244.8 mg; PVP K30: 32.4 mg; Avicel PH-101: 56.3 mg; magnesium stearate: 16 mg; talc: 16 mg; Aerosil-200: 13 mg; ethanol 96%: 0.4 ml; the average tablet weight was 1000 mg. The optimised formulation exhibited a floating lag time of less than 1 minute, maintained buoyancy throughout the 30-hour *in vitro* dissolution test, and met the dissolution criteria according to United States Pharmacopeia 2023. A manufacturing process for the sustained-release floating diltiazem hydrochloride tablets (1000 tablets per batch) was established following the investigation of various process parameters. The tablet properties across three 1000-tablet batches were consistent and similar to those observed in the 100-tablet per batch screening study.

CRediT author statement

Hung Pham Van: Methodology, Formal analysis, Writing - Reviewing and Editing; Tung Nguyen Thanh: Methodology, Investigation, Formal analysis; Nhat Hoang Thi Anh: Formal analysis, Writing - Reviewing and Editing; Hieu Bui Trung: Methodology, Investigation, Formal analysis; Uyen Dinh Thi Thu: Methodology, Investigation, Formal analysis; Duyen Nguyen Thi Thanh: Supervision, Methodology, Writing - Reviewing and Editing.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Colorcon Inc. (USA) for the generous supply of HPMC (K4M, K15M, and K100M CR) for research purposes.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

[1] Vietnam Ministry of Health (2018), *Vietnamese National Drug Formulary*, Medical Publishing House One Member Company Limited, 1666pp (in Vietnamese).

[2] S. Adepu, S. Ramakrishna (2021), "Controlled drug delivery systems: Current status and future directions", *Molecules*, **26(19)**, DOI: 10.3390/molecules26195905.

[3] H. Lodh, F.R. Sheeba, P.K. Chourasia, et al. (2020), "Floating drug delivery system: A brief review", *Asian Journal of Pharmacy and Technology*, **10(4)**, pp.255-264, DOI: 10.5958/2231-5713.2020.00043.4.

[4] S.B. Sateesha, M.K. Narode, B.D. Vyas, et al. (2010), "Influence of organic acids on diltiazem HCl release kinetics from hydroxypropyl methyl cellulose matrix tablets", *Journal of Young Pharmacists*, **2(3)**, pp.229-233, DOI: 10.4103/0975-1483.66793.

[5] D.L. Heald, J.A. Ziemniak, I.R. Wilding (1993), "The gastrointestinal transit and systemic absorption of diltiazem HCL from a modified release dosage form", *Nuclear Imaging in Drug Discovery, Development, and Approval*, pp.301-320, DOI: 10.1007/978-1-4684-6808-3_16.

[6] G. Suresh, P. Pavan (2013), "Formulation and evaluation of floating gastroretentive drug delivery system of diltiazem hydrochloride", *International Journal of Pharma and Bio Sciences*, **4(2)**, pp.538-548.

[7] B.V. Reddy, K. Navaneetha (2015), "Formulation development and *in vitro* characterization of floating tablets of diltiazem hydrochloride", *Journal of Global Trends in Pharmaceutical Sciences*, pp.2372-2378.

[8] United States Pharmacopeial Convention (2023), "Diltiazem hydrochloride extended-release capsules", *The United States Pharmacopeia*, pp.1-8.

[9] Association of Southeast Asian Nations (2005), *ASEAN Guideline on Stability Study of Drug Product*, ASEAN Consultative Committee for Standard and Quality, Philippines.

[10] R.E. Stevens, V. Gray, A. Dorantes, et al. (2015), "Scientific and regulatory standards for assessing product performance using the similarity factor, f2", *The AAPS Journal*, **17**, pp.301-306, DOI: 10.1208/s12248-015-9723-y.

[11] G. Glatting, P. Kletting, S.N. Reske, et al. (2007), "Choosing the optimal fit function: Comparison of the Akaike information criterion and the F-test", *Medical Physics*, **34(11)**, pp.4285-4292, DOI: 10.1118/1.2794176.

[12] P. Costa, J.M.S. Lobo (2001), "Modeling and comparison of dissolution profiles", *European Journal of Pharmaceutical Sciences*, **13(2)**, pp.123-133, DOI: 10.1016/S0928-0987(01)00095-1.

[13] L. Wang, K. Chen, H. Wen, et al. (2017), "Design and evaluation of hydrophilic matrix system containing polyethylene oxides for the zero-order controlled delivery of water-insoluble drugs", *AAPS PharmSciTech*, **18**, pp.82-92, DOI: 10.1208/s12249-016-0498-y.

[14] T. Brody (2017), "Chapter 3 - Food effect studies", *FDA's Drug Review Process and The Package Label: Strategies for Writing Successful FDA Submissions*, Academic Press, 653pp.