Optimising verapamil hydrochloride floating tablets formula

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Abstract:

This study aimed to optimise the formulation of verapamil hydrochloride (VH) floating tablets to improve bioavailability and sustain drug release. The tablets were prepared using the wet granulation method, and VH quantification was conducted via high-performance liquid chromatography (HPLC). A categorical and continuous factors (CCF) experimental design was employed using Modde Pro 13.1 software, while formulation optimisation was conducted with INForm 3.1 software. The key formulation factors, including the concentrations of hydroxypropyl methylcellulose (HPMC) K4M, HPMC E6, and sodium bicarbonate, were systematically varied to assess their influence on drug release and floating properties. The optimised formulation consisted of 120 mg VH, 59 mg HPMC K4M, 35 mg HPMC E6, 29.3 mg sodium bicarbonate, 50 mg Avicel, 98.7 mg lactose, 8 mg magnesium stearate, and sufficient 10% PVP K30 in 96% ethanol. The *in vitro* dissolution study demonstrated that the optimised formulation met the United States Pharmacopeia (USP) 47 requirements for extended-release VH tablets, with a similarity factor (f_2) of 92.13 when compared to the predicted release profile. The floating lag time (T_{lag}) was minimised while ensuring sustained drug release over eight hours. The release kinetics followed the Korsmeyer-Peppas model with a high correlation coefficient (R^2=0.997). In conclusion, the optimised VH floating tablet formulation successfully enhances gastric retention and controlled drug release, offering a promising approach for improving the therapeutic efficacy of VH.

Keywords: **floating tablets, optimising, verapamil hydrochloride.**

Classification numbers: **3.3, 3.5**

1. Introduction

Verapamil hydrochloride is a calcium channel blocker medication used to treat conditions such as angina, hypertension, and arrhythmias. The use of this drug is limited due to its low bioavailability (<20%) and short elimination half-life (2.8-7.4 hours), requiring patients to take it multiple times a day [1, 2]. VH is a salt form with solubility decreasing with increasing pH [3], while the pH of the gastrointestinal tract gradually increases. Therefore, formulating VH as a gastric-retentive dosage form is advantageous for drug dissolution and absorption in the upper gastrointestinal tract [4]. The narrow pH range in the stomach facilitates better control over drug release rates and minimises uncontrolled interactions that may occur when the drug reaches the lower gastrointestinal tract, where pH fluctuations are greater and various digestive enzymes are present [5]. N.P. Dong, et al. (2018) [6] studied the effect of certain excipients on the dissolution rate of extended-release floating VH tablets. N.P. Dong, et al. (2018) [6] used the direct compression method on an eccentric tablet press, which poses significant risks when scaling up to commercial production. Additionally, their research only focused on independent parameter evaluations without conducting an optimisation process. In this study, VH floating tablets were formulated using Modde Pro 13.1 employed for experimental design and INForm 3.1 for formula optimisation. The *in vitro* bioavailability of the formulation was required to meet the USP 47 specifications. This research will utilise experimental design methods and statistical analysis using Modde 13.1 and INForm 3.1 software to optimise the VH floating tablet formula to meet USP dissolution requirements [7].

2. Materials and methods

2.1. Materials and equipment

VH and sodium bicarbonate (India), HPMC K4M and HPMC E6 (Belgium), lactose, MCC, and PVP K30 meeting USP standards; 96% ethanol; magnesium stearate (Vietnam) meeting the Vietnamese Pharmacopoeia V standards. Reference standard of VH (National Institute for Drug Quality Control, Vietnamese Pharmacopoeia V standard, Certificate No. QT 242.010914, potency 100.52%).

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Shakti rotary tablet press (India), Copley DIS 8000 dissolution tester (UK), Labomed UVD-2960 UV-Vis spectrophotometer (USA), Alliance Waters 2695D HPLC system (USA), and Mettler Toledo analytical balance (Switzerland).

2.2. Methods

2.2.1. Preparation method

VH floating tablets were prepared using the wet granulation method. The active pharmaceutical ingredient, HPMC, $NaHCO_3$, MCC, and lactose were weighed according to specified ratios. The individual powders were ground and sieved through a 0.35 mm mesh, then blended using the geometric dilution method. A 10% PVP K30 solution in 96% ethanol was gradually added and mixed thoroughly to form a wet mass, which was allowed to rest for 30 minutes. The wet mass was sieved through a 0.71 mm mesh and dried at 50-60°C for 10 minutes. The dried granules were re-sieved through a 0.8 mm mesh and further dried for an additional 45 minutes until the moisture content was reduced to 2-3%. Magnesium stearate was sieved through a 0.125 mm mesh and mixed with the granules. The tablets were compressed using a single-punch tablet press with punches of ϕ 11 mm diameter. Each tablet had a weight of 400 mg and a hardness of 10±0.5 kp.

2.2.2. Quantification method

The VH content in the floating tablets was determined using a HPLC method, as follows: A reference standard of VH or tablet powder was dissolved in methanol to achieve a concentration of approximately 20 µg/ml. Chromatographic analysis was conducted, and the peak areas obtained were compared.

Chromatographic conditions: SunFire™ column (4.6x250 mm; 5 µm), detector 2998 PDA set at 278 nm, flow rate: 1.0 ml/min, injection volume 20 µl. The drug content in the floating tablets was calculated using the following formula:

$$\mathrm{HL} = \frac{\mathrm{St}.C_S.m_{20}}{20.\mathrm{Ss}.m_t}\ (\mathrm{mg/unit})$$

where S_t and S_s are the peak areas of VH in the chromatograms of the sample and standard solutions, respectively (µV.s); C_s is the concentration of the standard solution (µg/ml); m_t is the weight of the tablet powder used for analysis (g); m_{20} is the total weight of 20 randomly selected tablets used for quantification (g) [7, 8].

2.2.3. Evaluation of verapamil hydrochloride floating tablet dissolution

The dissolution test for VH floating tablets was conducted according to the monograph "VH extended-release tablets, test 3" in USP 47, using the following specific conditions: Apparatus: Paddle-type dissolution tester. Rotation speed: 50 revolutions per minute. Dissolution medium: 900 ml of 0.1 N HCl solution. Test temperature: 37.0±0.5°C. Sampling times: 1, 2, 3.5, 5, and 8 hours. The amount of drug released was calculated based on the VH calibration curve in 0.1 N HCl medium using UV spectrophotometry [7].

2.2.4. In vitro floating ability evaluation

The *in vitro* floating ability of the tablets was assessed concurrently with the dissolution test. The evaluation was based on the T_{lag} parameter (seconds), which represents the time interval from when the tablet first contacts the dissolution medium until it stably floats on the surface of the medium (also referred to as the floating lag time) [9].

2.2.5. Experimental design and formula optimisation

The experimental design was carried out using Modde Pro 13.1 software, while formula optimisation was performed using INForm 3.1 software. Based on the obtained experimental results, INForm 3.1 was utilised to establish a causal model between independent and dependent variables. Subsequently, the formula was optimised, the optimal formulation was prepared, and its evaluation was conducted [10].

3. Results and discussion

3.1. Experimental design

The basic formulation for VH floating tablets was selected with the following composition: VH 120 mg, HPMC K4M 60 mg, HPMC E6 40 mg, $NaHCO_3$ 50 mg, Avicel 50 mg, lactose up to 400 mg, magnesium stearate 8 mg, PVP K30 sufficiently.

Selection of independent variables: Key factors strongly influencing drug release and T_{lag} were selected, including the amounts of HPMC K4M, HPMC E6, and $NaHCO_3$. The levels and variation ranges of these independent variables are shown in Table 1.

Table 1. Independent variables and their variation levels.

Independent variables	Symbol	Variation levels			
		Upper (+1)	*Base (0)*	*Lower (-1)*	*Range*
HPMC K4M amount (mg)	X1	100	70	40	30
HPMC E6 amount (mg)	X2	60	40	20	20
Sodium bicarbonate amount (mg)	X3	60	40	20	20

Selection of dependent variables: The objective of the optimisation process was to identify a formulation that meets the requirements outlined in the USP 47 monograph "VH extended-release tablets", while ensuring that the T_{lag} is not more than 180 seconds. The selected dependent variables included: The percentage (%) of drug released at specific time points: 1, 2, 3.5, 5, and 8 hours, and T_{lag} (floating lag time). The requirements are detailed in Table 2.

Table 2. Requirements for dependent variables.

Dependent variables	Symbol	Requirement (%)
VH release percentage after 1 hour	Y1	8-20
VH release percentage after 2 hours	Y2	15-35
VH release percentage after 3.5 hours	Y3.5	27-57
VH release percentage after 5 hours	Y5	45-75
VH release percentage after 8 hours	Y8	≥80
T_{lag} (s)	Y	Minimum and not more than 180 s

The experiments were designed using the CCF design model with the assistance of Modde Pro 13.1 software. The VH floating tablet formulations were designed and arranged according to the experimental layout presented in Table 3.

Table 3. Experimental formulations of verapamil hydrochloride floating tablets.

Formulations	HPMC K4M	HPMC E6	$NaHCO_3$	Lactose
N1	40	20	20	142
N2	80	20	20	82
N3	40	60	20	102
N4	100	60	20	42
N5	40	20	60	102
N6	100	20	60	42
N7	40	60	60	62
N8	100	60	60	2
N9	40	40	40	102
N10	100	40	40	42
N11	70	20	40	92
N12	70	60	40	52
N13	70	40	20	92
N14	70	40	60	52
N15	70	40	40	72
N16	70	40	40	72
N17	70	40	40	72

Additionally, VH (120 mg), Avicel PH-101 (50 mg), magnesium stearate (8 mg), and PVP K30 (sufficiently) were kept constant across all formulations.

3.2. Experimental procedure

The formulations listed in Table 3 were prepared using the described method, with each formulation produced in a batch of 100 tablets. The VH content in the prepared tablets for each formulation is presented in Table 4.

Table 4. Verapamil hydrochloride content in tablets compared to labelled amount (n=6, Mean±SD).

Formulations	Content compared to labelled amount (%)	Formulations	Content compared to labelled amount (%)
N1	99.61±0.43	N10	100.96±1.15
N2	100.38±0.91	N11	97.22±1.27
N3	95.22±1.05	N12	100.20±0.79
N4	93.83±0.99	N13	100.78±0.76
N5	98.79±0.67	N14	100.44±1.11
N6	101.09±1.02	N15	98.33±1.31
N7	91.82±0.99	N16	100.21±0.41
N8	94.58±1.24	N17	90.03±0.84
N9	96.87±1.05		

The results in Table 4 indicate that the VH floating tablets prepared according to the experimental formulations all had a drug content within the acceptable limits of USP 47, which ranges from 90.0 to 110.0% of the labelled amount. The percentage (%) of drug released from the VH floating tablets at different time points and T_{lag} are presented in Table 5.

Table 5. Percentage (%) of verapamil hydrochloride released from prepared verapamil hydrochloride floating tablets for different formulations.

Formulations	Verapamil hydrochloride release percentage (%)					T_{lag} (s)
	1 h	*2 h*	*3.5 h*	*5 h*	*8 h*	
N1	39.38±1.11	45.38±1.35	64.02±1.43	75.13±1.10	93.03±3.63	202±11
N2	17.86±0.63	22.28±0.77	33.44±1.24	43.89±1.14	74.92±1.35	900±15
N3	26.19±0.50	33.10±0.60	48.82±1.59	64.65±1.70	88.92±1.76	not float
N4	17.60±0.51	18.82±0.44	28.53±1.00	37.89±1.19	53.46±1.81	900±33
N5	99.12±1.02	-	-	-	-	203±13
N6	18.03±0.87	17.55±0.60	24.10±0.58	30.97±0.89	47.29±1.39	24±4
N7	92.08±1.51	-	-	-	-	145±10
N8	12.27±0.63	13.15±0.51	22.34±0.77	31.67±0.67	47.18±1.02	22±4
N9	98.71±0.78	-	-	-	-	95±5
N10	14.26±0.60	14.44±0.75	23.25±0.81	32.44±1.23	48.35±1.38	130±10
N11	21.74±0.69	27.20±0.67	37.64±1.49	46.56±1.36	64.27±1.27	43±5
N12	13.83±0.58	17.74±0.62	27.34±1.04	36.08±0.89	54.97±1.64	63±2
N13	16.74±0.70	20.03±0.62	30.96±0.74	41.71±1.18	62.58±2.26	1168±23
N14	61.51±1.13	66.46±1.37	72.43±0.44	78.23±2.52	85.60±1.11	42±3
N15	17.71±0.50	20.08±0.84	29.49±0.75	38.02±0.80	62.71±0.96	69±5
N16	21.27±0.64	22.63±0.52	30.71±0.87	39.72±1.08	62.70±0.66	67±4
N17	20.26±0.51	21.30±0.38	32.58±0.88	42.42±0.89	66.16±1.44	60±9

The results in the table indicate that formulations N5, N7, N9, and N14 exhibited poor drug release control due to their low HPMC K4M content and high $NaHCO_3$ ratio. Formulations N1, N2, N3, and N13 showed unstable floating behaviour, with T_{lag} values failing to meet the requirements due to their low $NaHCO_3$ content. The remaining formulations exhibited stable floating characteristics and effective drug release control. The dissolution results of the 17 experimental formulations were consistent with the principles derived from the preliminary evaluation of the basic formulations.

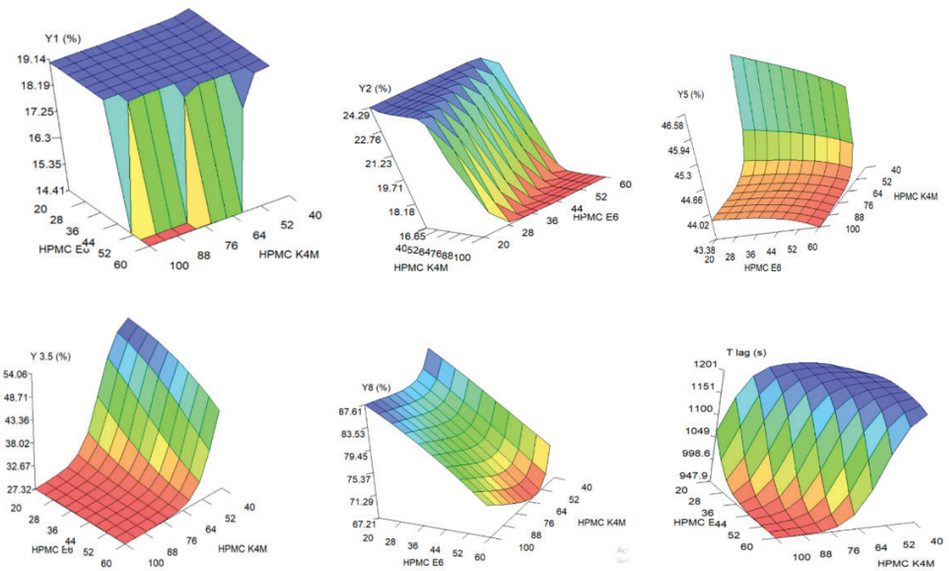

Fig. 1. Response surface of dependent variables as a function of hydroxypropyl methylcellulose K4M and hydroxypropyl methylcellulose E6.

3.3. The effects of the investigated excipients on dissolution and flotation ability

The data in Table 5 was used for optimisation in INForm 3.1. Test data were selected as 10% of the experiments using the smart select method. The outcomes were trained separately, with the training parameters including one hidden layer with two nodes, an Asymmetric Sigmoid activation function, a Linear output function, and the RPROP backpropagation algorithm. The Target MS Error was set to 0.0001, the Target Epochs to 1000, and the Random Seed to 10000. The results of the statistical model are shown in Table 6.

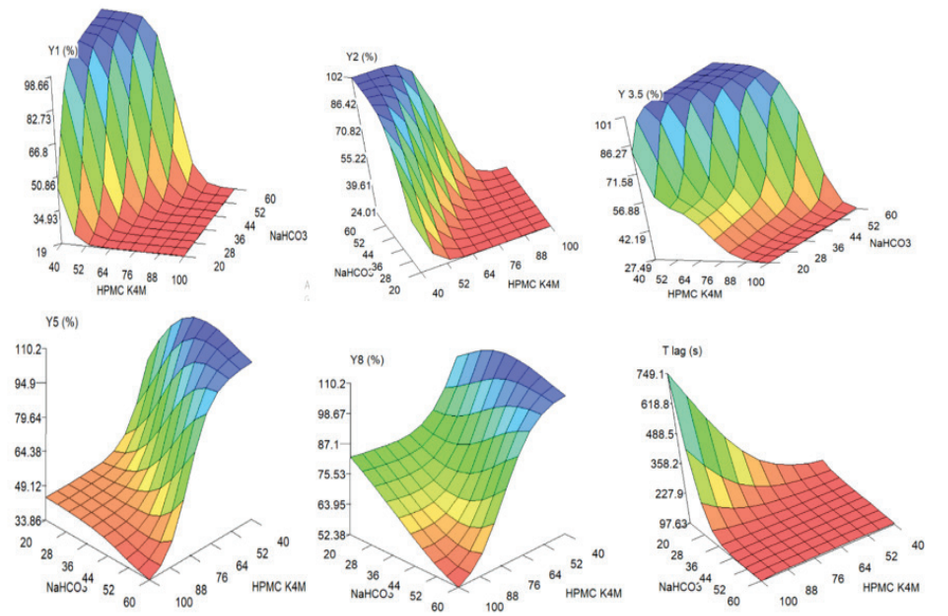

Fig. 2. Response surface of dependent variables as a function of hydroxypropyl methylcellulose K4M and $NaHCO_3$.

Table 6. Statistical model results by INForm 3.1 software.

	Y1	Y2	Y3.5	Y5	Y8	Y
Train set R-squared	99.76	99.81	99.38	99.88	98.64	97.78
Test set R-squared	100	100	100	100	100	100
Computed F ratio	226.4	22.1	50.9	8.5	24.2	419.6

The analysis was conducted using INForm 3.1 software, with the requirement that the correlation coefficients R^2 for training and testing fall within the range of 80-100. The software training results were: R^2_{test} = 100 and R^2_{train} from 97.76 to 99.88%, all within the acceptable range. Therefore, the model demonstrated a strong correlation between independent and dependent variables. Further response surface analysis was performed to examine the influence of independent factors on drug release from the experimental formulations and the floating lag time (T_{lag}) of the tablets.

The impact of HPMC K4M, HPMC E6, and sodium bicarbonate on drug release and T_{lag} was assessed. The results are represented through response surface plots at different time points, derived from the experimental formulations. The findings are illustrated in Figs. 1 and 2.

Results and discussion from response surface analysis (Figs. 1 and 2):

Effect of hydroxypropyl methylcellulose K4M: The amount of HPMC K4M significantly influenced the percentage of VH released. A higher HPMC K4M concentration resulted in a thicker gel layer, which slowed down the VH release rate into the medium. However, when HPMC K4M was reduced to below 52 mg, the formulation exhibited poor drug release control. Thus, HPMC K4M serves as the primary release-controlling excipient in the core matrix, enabling a sustained release of VH to meet therapeutic requirements. Additionally, an increase in HPMC K4M concentration led to a reduction in T_{lag}, enhancing the floating behaviour of the tablets.

Effect of hydroxypropyl methylcellulose E6: At early times, HPMC E6 had minimal influence on drug release. However, at 8 hours, HPMC E6 significantly impacted VH dissolution. Keeping the levels of HPMC K4M and $NaHCO_3$ constant while increasing HPMC E6 from 20 to 60 mg resulted in a decrease in drug release from 74.9 to 53.5%. Furthermore, HPMC E6 enhanced the floating ability of the tablets by reducing T_{lag}. This phenomenon can be explained by the fact that higher HPMC E6 levels improved gas entrapment within the tablet, allowing it to float more quickly.

Effect of sodium bicarbonate ($NaHCO_3$): When the HPMC K4M concentration exceeded 75 mg, $NaHCO_3$ had little effect on drug release. Conversely, when HPMC K4M was below 75 mg, $NaHCO_3$ significantly influenced VH release. Keeping HPMC K4M at 40 mg and HPMC E6 at 20 mg, an increase in $NaHCO_3$ from 20 to 60 mg led to an increase in VH release from 39.4 to 99.1%. Moreover, $NaHCO_3$ played a crucial role in the floating ability of the tablets. Increasing $NaHCO_3$ from 20 to 44 mg rapidly decreased T_{lag} from 749 to 97 s. However, further increasing $NaHCO_3$ beyond this point resulted in only a negligible reduction in T_{lag}. This can be attributed to the reaction between $NaHCO_3$ and H^+ ions in the medium, generating CO_2, which facilitates tablet buoyancy.

The floating mechanism of the optimised VH tablet is primarily determined by the CO_2 generation from $NaHCO_3$ upon contact with gastric fluid. The generated CO_2 gas is retained within the polymer matrix, contributing to the buoyancy of the tablet [4]. HPMC K4M, a high-viscosity polymer, forms a thick gel layer upon hydration. This gel layer not only modulates drug release but also plays a crucial role in CO_2 entrapment. As the concentration of HPMC K4M increases, the gel network becomes denser, reducing CO_2 diffusion from the tablet core and thereby prolonging the floating duration. Conversely, HPMC E6, a lower-viscosity polymer [11], facilitates initial hydration and gas expansion, which in turn reduces T_{lag} (floating lag time).

The interaction between $NaHCO_3$ concentration, polymer viscosity, and matrix porosity dictates the CO_2 release kinetics and the overall floating performance of the tablet. Increasing the amount of $NaHCO_3$ enhances gas production; however, without sufficient polymeric support, the gas may escape too quickly, reducing the floating duration. Therefore, maintaining a balance between gas generation and matrix viscosity is essential for optimising the floating behaviour of the tablet formulation.

3.4. Optimisation results of the formulation

Based on the experimental data and the USP 47 criteria, the optimisation requirements for the dependent variables were established as follows: 8%≤Y1≤20%; 15% ≤Y2≤35%; 27%≤Y3.5≤57%; 45%≤Y5≤75%; Y8≥80%; Y: minimum and not more than 180 s.

Optimisation results: X1 (HPMC K4M)=59.0 mg; X2 (HPMC E6)=35.0 mg; X3 ($NaHCO_3$)=29.3 mg.

Predicted values for the dependent variables: Y1=17.96 (%); Y2=30.15 (%); Y3.5=51.94 (%); Y5=63.63 (%); Y8=86.10 (%); Y=107.57 (s).

Thus, the optimised formulation per tablet consists of:

Verapamil hydrochloride	120 (mg)
HPMC K4M	59 (mg)
HPMC E6	35 (mg)
$NaHCO_3$	29.3 (mg)
Avicel	50 (mg)
Lactose	98.7 (mg)
Magnesium stearate	8 (mg)
10% PVP K30 in ethanol 96%	Sufficient

3.5. Evaluation of floating ability and in vitro drug release

The optimised formulation was prepared following the described method. The drug content of the optimised tablet was determined to be 102.1±1.5% of the labelled amount, meeting the USP 47 standards. A dissolution test was conducted on the optimised formulation and compared to the USP 47 requirements. The results are presented in Table 7.

Table 7. Percentage (%) of verapamil hydrochloride released from the optimised floating verapamil hydrochloride tablets (n=6, Mean±SD).

Verapamil hydrochloride release percentage (%)					T_{lag} (s)
1 h	*2 h*	*3.5 h*	*5 h*	*8 h*	
15.38±0.66	26.03±1.29	43.14±1.50	53.12±1.38	81.03±3.07	89±4

The results in Table 7 indicate that the percentage (%) of drug released over time and the T_{lag} of the tablets formulated using the optimised formulation meet the initial optimisation requirements.

The data in Fig. 3 indicate that the dissolution results of the optimised formulation closely match the predicted model values from INForm 3.1, with a similarity factor of f_2=92.13. The release kinetics of VH from the floating tablets followed the Korsmeyer-Peppas model, with an Akaike Information Criterion (AIC) value of 35.18 and an adjusted R-squared (R^2) of 0.997, demonstrating a strong fit to the model.

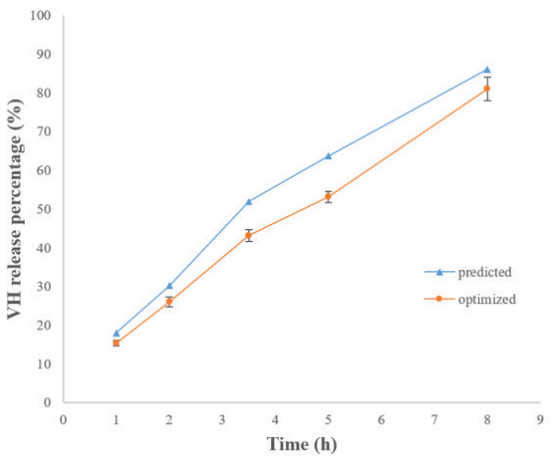

Fig. 3. Dissolution of the optimised tablet: Experimental vs. predicted data.

This study focuses on optimising the formulation to meet USP specifications (in vitro bioavailability) and does not address *in vivo* results. VH is classified as a BCS Class II drug, indicating good permeability [12]. Pharmacokinetic data also show that 90% of the labelled VH dose is well absorbed via oral administration [1, 2, 12]. Therefore, controlling VH dissolution from the formulation plays a crucial role in determining the drug's bioavailability. These data suggest that *in vivo* studies of the formulation are likely to show a strong correlation with *in vitro* results.

4. Conclusions

This study used Modde Pro 13.1 and INForm 3.1 software to optimise the formulation of VH floating tablets. The optimised formulation consists of 120 mg VH, 59 mg HPMC K4M, 35 mg HPMC E6, 29.3 mg $NaHCO_3$, 50 mg Avicel, 98.7 mg lactose, 8 mg magnesium stearate, and sufficient 10% PVP K30 in 96% ethanol. The percentage (%) of VH released from the optimised formulation closely matched the predicted values from INForm 3.1, with a similarity factor of f_2=92.13. The formulation met the USP 47 dissolution requirements.

CRediT author statement

Vu Van Tuan: Experimental, Writing; Trinh Nam Trung, Nguyen Van Bach: Editing and Supervision.

COMPETING INTERESTS

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

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