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Floating tablets incorporating curcumin solid dispersion as a potential pharmaceutical dosage form for stomach cancer treatment

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ABSTRACT

Curcumin, a well-known compound commonly used for stomach cancer treatment, possesses inadequate oral bioavailability due to its low water solubility and instability in the digestive-tract alkaline pH. To overcome these issues, this study formulated the curcumin solid dispersion (CSD) (to enhance curcumin solubility) and incorporated this solid dispersion in the floating tablet formula (to bypass the alkaline pH in the intestine). The tablets were optimized by varying numerous parameters including (1) the granulating solvent, (2) the binder excipient, (3) the type of gas-generating excipients, (4) the ratio of gas-generating excipients, (5) the type/amount of matrix generator, and (6) the tablet hardness. The product was then fully characterized in terms of floating potential, floating time, tablet integrity, curcumin solubility/dissolution profiles, long-term and accelerated stability study, *in-vitro* cytotoxicity, and other physicochemical properties. The best formula possesses a short floating potential of 35 ± 1 seconds, a long floating retention time of >8 hours, good tablet integrity during the floating duration, enhanced curcumin solubility/dissolution profiles to >200 times, and perfect physicochemical stability for at least 2 years in the normal storage condition. Furthermore, the tablets reserve the curcumin cytotoxicity on the N87 stomach cell lines, with a better efficacy compared to the standard drug 5-FU. Finally, the tablets significantly potentiate and enhance the anticancer effect of 5-FU in a synergistic mechanism. Conclusively, the floating tablet incorporating the CSD could be a potential pharmaceutical product for stomach cancer treatment.

INTRODUCTION

Herbal medicines, medicines with active ingredients made from plant parts such as roots, leaves, and flowers, have demonstrated their outstanding beneficial activities in various diseases (Huynh *et al*., 2022; Nguyen *et al*., 2021b; Pham *et al*., 2022; Tran *et al*., 2022). Among numerous herbs, curcumin, a compound commonly found in turmeric (*Curcuma longa* L., Zingiberaceae), has been extensively researched due to its potential multi-purpose therapeutic actions (Fuloria *et al*., 2022; Hewlings and Kalman, 2017). Specifically, curcumin is a prospective chemotherapeutic agent for stomach cancer, as it has been proven both effective in inhibiting tumor initiation, promotion, and metastasis and safe, with no dose-limiting toxicity in clinical trials at doses up to 10 g/day (Aggarwal *et al*., 2003; Pari *et al*., 2008). Despite demonstrating much potential, no clinical trial has been reported on curcumin for stomach cancer treatment, to the best of our knowledge. Only one related study has been conducted on curcumin's ability in preventing gastric cancer (Clinical Trials, n.d.). This fact could be attributed to the inherent drawbacks of unmodified curcumin as an oral drug. For instance, curcumin possesses a very low water solubility of 0.6 µg/ml (Patel *et al*., 2009). Additionally, curcumin in conventional oral dosage forms is generally released in the intestine and is broken down by intestinal enzymes and alkaline pH (Prashar *et al*., 2011). Moreover, orally absorbed curcumin is rapidly metabolized in the

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liver by the glucuronidation pathway (Aggarwal and Sung, 2009). Consequently, the curcumin oral bioavailability in conventional dosage forms such as traditional tablets is unacceptable (i.e., for tablet, the oral bioavailability of curcumin is only 1%, and the maximum plasma concentration is 0.06 ± 0.01 µg/ml, compared to the intravenous route, with a concentration of 0.36 ± 0.05 µg/ml) (Liu *et al*., 2016; Pouton, 2006). Therefore, further research to solve these issues is necessary.

The solubility and dissolution rate of a drug substance are important factors determining the extent and rate of drug release and absorption from the oral administration route (Papich and Martinez, 2015). Thus, to improve curcumin oral bioavailability, these two factors must be critically considered. For the solubility enhancement, formulation methods such as creating a curcumin solid dispersion (CSD) to reduce the drug molecular sizes and alter its polymorph are beneficial (Pan-On *et al*., 2018, 2022; Phothi *et al*., 2022). Solid dispersion, defined as a homogeneous mixture of one or more active compounds in an appropriate inert carrier or matrix in a solid state, is one of the most widely recognized strategies to increase the poorly water-soluble drug solubility and release rate (Alshehri *et al*., 2020; Vo *et al*., 2013). For absorption enhancement, it is necessary to increase the curcumin residence time in the gastrointestinal tract, as well as to avoid curcumin degradation by the alkaline pH of the small intestine environment. To this end, the gastric drug delivery systems prove their effectiveness. The gastric drug delivery system is a method for sustaining the drug release while the formulations/active ingredients retain/float in the gastrointestinal tract, without being affected by the rate of gastric emptying, thereby preventing curcumin from being broken down by the small intestine's alkaline pH (Wook Huh *et al*., 2021). These systems include a mucoadhesive system, floating system, high-density system, magnetic system, and swelling system (Tripathi *et al*., 2019). Among them, the floating systems (i.e., floating tablets) that possess a density lower than the gastric juice density (1.004 g/cm^3) have gained much attention.

With the main aim of increasing the oral bioavailability of curcumin, this work employed both the aforementioned approaches by incorporating the CSD in the floating tablet dosage form for the application of gastric cancer treatment. The CSD was first formulated to enhance curcumin solubility. Then, the CSD was incorporated into the floating tablet formula to bypass the alkaline pH in the intestine. The physicochemical properties of the product were fully evaluated, and its pharmacological effects were tested in the *in-vitro* cytotoxic model on the stomach cancer cell line N87.

MATERIALS AND METHODS

Materials

Curcumin (95.5%) was imported from India. Xanthan gum, hydroxypropyl methylcellulose (HPMC) K4M, K15M, and 615, lactose, and poly(vinyl pyrrolidone) (PVP) K30 were purchased from the USA. Aerosil, magnesium stearate, $CaCO_3$, $NaHCO_3$, citric acid, KCl, and HCl were bought from China. All the other reagents, chemicals, and solvents were of pharmaceutical grades or higher.

The stomach cancer cell line N87 (ATCC) and the CellTiter 96® non-radioactive cell proliferation assay-3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) (Promega) were imported from the USA. 5-Fluorouracil (5-FU) (Ebewe® 500 mg/10 ml) was bought from Austria. Fetal bovine serum (FBS), Roswell Park Memorial Institute (RPMI) culture media, penicillin-streptomycin (Pen-Strep), trypan blue, trypsin-Ethylenediaminetetraacetic acid (EDTA), L-glutamine, and dimethyl sulfoxide were bought from Sigma-Aldrich, Singapore.

CSD formulation

The CSD was formulated based on our published study (Pan-On *et al*., 2018), with slight modifications. Briefly, the CSD was fabricated using the simple solvent (with ethanol) or melting solvent method with different polymers including β-cyclodextrin, poly(ethylene glycol) 6000, PVP K30, and HPMC 606, with or without the surfactant Tween 80, at various ratios (data not shown). The best formula, in terms of curcumin solubility and stability, was the formulation with a ratio of curcumin:PVP K30:Tween 80 of 1:4:0.22 w/w/w, fabricated by the solvent method. This condition was then employed to make the CSD.

Floating tablets incorporating CSD formulation

Firstly, the blank floating tablets were fabricated to find the optimal formulation with the fastest floating potential, longest floating time, and highest integrity during the floating duration. For this, the tablets were formulated using the simple wet granulation method, with slight modifications (Shishu and Aggarwal, 2008). The compositions included the SD (without curcumin) as the main ingredient, lactose as a diluent, xanthan gum/HPMC K4M/HPMC K15M/HPMC 615 as matrix generator, PVP K30 as a binder, $NaHCO_3$/$CaCO_3$ and citric acid as gas-generating excipients, and aerosil and magnesium stearate as glidant and lubricant. The process starts with homogeneous mixing of the SD (without curcumin), the matrix generator, lactose, and citric acid. Then, the mixture was moistened and wet-granulated with EtOH:water and PVP K30 through a 2 mm sieve. The granules were dried at 50°C–60°C to a moisture of ≤7%, passed through a 0.5 mm sieve, and mixed with gas-generating excipients, glidant, and lubricant. Finally, the powder was compressed on a rotary tablet press (Rimek, India) with a tablet weight of ~1,000 mg.

To obtain the optimal blank floating tablet, six parameters were varied, namely (1) the granulating solvent (EtOH:water at the ratio of 10:0, 9:1, 7:3, and 5:5 v/v), (2) the binder (PVP K30) concentrations in the formula (1%, 2%, 3%, 4%, and 5% w/w), (3) the type of gas-generating excipients ($NaHCO_3$ and $CaCO_3$), (4) the ratio of $NaHCO_3$/$CaCO_3$ and citric acid (1:0.2, 1:0.5, and 1:0.76 w/w), (5) the type/amount of matrix generator (xanthan gum, HPMC K4M, HPMC K15M, and HPMC 615), and (6) the tablet hardness. The tablet floating potential, floating time, and integrity during the floating duration were determined to select the optimal formula.

Secondly, the optimal blank floating tablet formula was then selected to incorporate the CSD, with a curcumin content of 100 mg/tablet. The process of preparing floating tablets containing CSD was similar to the process of preparing the blank floating tablets; however, in the first step, the blank SD was replaced with the CSD containing 100 mg of curcumin. The matrix generators

and gas-generating excipients compositions of the final products were further adjusted to maximize the tablet potency. The complete best formulation is shown in Table 1.

Physicochemical characterizations

Floating potential

The floating ability of the floating tablets was tested in 200 ml of HCl buffer pH 1.2, by determining the time when the tablet fully emerges in the liquid. The tablets should float as quickly as possible (≤180 seconds) (Jaimini *et al*., 2007; Kanwar *et al*., 2016). Each experiment was repeated six times.

Floating time

The tablets were subjected to a dissolution tester (Erweka, Germany) using the paddle type I as the mixer. The parameters were set at a paddle speed of 100 rpm, at a temperature of 37°C ± 0.5°C, and a medium consisting of 900 ml HCl buffer pH 1.2. The tablets should float as long as possible (≥8 hours). Each experiment was repeated six times.

Tablet integrity

During and after the floating experiments, the tablet's integrities were frequently observed and their physical stability was visually assessed by three levels of (1) good (intact tablets), (2) acceptable (partially broken tablets), and (3) poor (completely broken tablets). Each experiment was repeated six times.

In-vivo floating ability

To further confirm the tablet's floating potential and floating time, an *in-vivo* gastric X-ray model in dogs has been applied. To this end, barium sulfate was used as a tracer in the formulation of floating tablets. The dogs weighing 11–15 kg were fasted overnight and anesthetized; and after 15 minutes, the floating tablets were subjected orally into the dog digestive system with 150 ml of water. Then, the dog's stomach X-ray images were taken at different time intervals, namely immediately after taking the drug (0 minute), 30, 90, 150, 210, and 270 minutes, and continued until the tablet signal disappeared in the dog's stomach. The floating potential and floating time were then assessed accordingly.

Tablet mass uniformity

The tablets (20 units) were randomly selected and individually weighed. The acceptance criteria were those of no more than two units whose weights were outside the ±5% range of the average weight.

Tablet hardness

The tablets' hardness (20 units) was separately determined by the hardness tester (Erweka, Germany) following the manufacturer's protocol. The acceptance criteria were set at the hardness of 40–60 N.

Tablet dissolution profile

The dissolution profile of the CSD and the floating tablet incorporating CSD were conducted following the standardized protocol with the dissolution tester (Erweka, Germany) for 8 hours using the paddle apparatus, in 900 ml buffer pH 1.2, at a speed of 100 rpm, and in a temperature of 37°C ± 0.5°C. At each time interval, 10 ml of the dissolution media was withdrawn, diluted with methanol and acetonitrile, filtered through a 0.45 µm membrane, and subjected to the high performance liquid chromatography (HPLC) analysis with the same condition in the *Curcumin Quantification* section. The percentage of released/dissolved curcumin was calculated based on the following equation:

$$\text{Curcumin} = \frac{S_t}{S_C} \times 25 \times C_0 \times \frac{900}{m \times 1{,}000} \times 100 \quad (1)$$

Where, C_0 is the standarld curcumin concentration (µg/ml), S_c, S_t is the curcumin peak area of the test sample and the reference sample, respectively, and m is the initial curcumin amount (mg).

Curcumin quantification

The curcumin in the floating tablets was extracted using methanol and subjected to the HPLC analysis for quantification. The conditions were set as follows: RP_{18} column (250 × 4.6 mm, 5 µm), mobile phase: acetonitrile:phosphoric acid pH 3.0 (50:50 v/v), flow rate: 1 ml/minute, injection volume: 10 µl, column temperature: 50°C, and detector: UV-Vis at a wavelength of 428 nm. The method has been validated based on the ICH guideline,

Table 1. Floating tablet incorporating CSD formulation.

Ingredient	Function	Amount (mg)
Blank/CSD[a]	Active ingredient	500
Xanthan gum	Matrix generator	49.5
HPMC K15M	Matrix generator	198.1
PVP K30	Binder	40
$NaHCO_3$	Gas-generating excipient	101.5
Citric acid	Gas-generating excipient	50.8
Aerosil	Glidant/Lubricant	5
Magnesium stearate	Glidant/Lubricant	15
Lactose	Diluent	ad. 1,000

[a] Blank solid dispersion was used in the blank floating tablet; CSD (ratio of curcumin: PVP K30:Tween of 1:4:0.22 w/w/w) was used in the floating tablet incorporating CSD.

including the specificity, linearity/range, accuracy, precision, limit of detection, and limit of quantitation.

Stability study

The long-term and accelerated stabilities of the floating tablets incorporating CSD have been assessed following the guidelines on the stability testing in the ASEAN region, zone IVB condition (i.e., hot and very humid region) (European Medicines Agency, n.d.). For this, the condition for the long-term stability test and for the accelerated stability test is set at the temperature of 30°C ± 2°C with a relative humidity of 75% ± 5% and at the temperature of 40°C ± 2°C with a relative humidity of 75% ± 5%, respectively. After 0, 3, 6, 9, 12, 18, and 24 months for the long-term stability test and 0, 1, 2, 3, 4, 5, and 6 months for the accelerated stability test, the physicochemical properties of the tablets were re-analyzed, including floating potential, floating time, tablet integrity, tablet hardness, tablet dissolution profile, and curcumin quantification.

Then, based on the stability results, the tablet shelf-life (t_{90}) was calculated following Equations (2)–(4). Equations (2) and (3) were used to determine the tablet shelf-life based on the long-term stability results. For the accelerated condition, the tablet shelf-life was similarly determined based on Equations (2) and (3); however, the t_{90} value was then adjusted by Equation (4), following Van't Hoff rule as follows:

$$k = \frac{-2.303 \times \log \frac{D}{D_0}}{t} \quad (2)$$

$$t_{90} = \frac{0.1053}{k} \quad (3)$$

where, k is the constant calculated based on the remaining drug amount (D), the initial drug amount (D_0), and the testing time (t). Moreover,

$$t_{90} = A^{\frac{\Delta t}{10}} \times t_{90\text{-accelerated condition}} = 2 \times t_{90\text{-accelerated condition}} \quad (4)$$

where $A^{\frac{\Delta t}{10}}$ is the temperature constant, indicating the difference in two storage temperatures. In our case, the constant was calculated to be 2.

Finally, the optimal storage temperature to reach the determined tablet shelf-life was calculated based on the following equation:

$$T^0_{th} = T_{bq}{}^0 + \frac{10}{\log A} \log \frac{C_{bq}}{C_{mm}} \quad (5)$$

where T^0_{th} is the optimal storage temperature, T^0_{bq} is the ambient storage temperature (30°C), C_{bq} is the tablet shelf-life (t_{90}) at ambient temperature (30°C), C_{mm} is the optimal tablet shelf-life, and A is the temperature constant, which was set at 2.

***In-vitro* cytotoxicity assay**

The stomach cancer N87 cell line was cultured in a 75 cm^2 flask using the RPMI culture medium supplemented with 10% FBS and 1% Pen-Strep. The cells were then kept in an incubator at 37°C, 5% CO_2, and 70% humidity. Cells were replaced with a culture medium every even day and confluence cells were subcultured with trypsin-EDTA following the standardized protocol.

The cytotoxicity of the products on the cells was assessed using the CellTiter 96® non-radioactive cell proliferation assay (MTT assay) (Gerlier and Thomasset, 1986) following the manufacturer's protocol. Briefly, prior to the cytotoxicity test, N87 cells were seeded into a 96-well culture plate with a concentration of 10,000 cells/well (each well contains 180 µl of culture medium). The plate was then incubated at 37°C, 5% CO_2, and 70% humidity for 24 hours. After that, the samples (20 µl) were added to the cells and incubated for another 48 hours at the same condition. There were four sets of samples, with varying concentrations, including (1) the reference chemotherapeutic drug, 5-FU, at concentrations of 200, 100, 50, 25, 12.5, 6.25, and 3.125 µg/ml; (2) the floating tablet excipients (without curcumin), at concentrations of 450, 225, 112.5, 56.25, 28.125, 14.06, and 7.03 µg/ml; (3) the complete floating tablets incorporating the CSD, at concentrations of 500, 250, 125, 62.5, 31.25, 15.6, and 7.8 µg/ml; (4) the mixtures of the complete floating tablets incorporating the CSD and 5-FU, at concentrations (tablet/5-FU µg/ml) of 250/100, 125/50, 62.5/25, 31.25/12.5, 15.6/6.25, and 7.8/3.13 µg/ml. The sample concentration ranges were selected based on our preliminary work and previous studies (Liu *et al*., 2014; Tian *et al*., 2012). After 48 hours incubation, 20 µl of the MTT reagent was subjected to the cells and the plate was further incubated for 4 hours at 37°C. Finally, the supernatants were withdrawn and 100 µl of the dissolving/stopping solution mixture was added to solubilize the formed crystals for 1 hour. The solutions were spectroscopically measured using a microplate reader at a wavelength of 490 nm. All experiments were repeated four times. The percent of cell viability was calculated based on Equation (6). Based on the obtained results, the inhibitory concentrations at 50% (IC50) values were then determined and reported as follows:

$$\%\text{Cell viability} = \frac{\text{OD sample} - \text{OD blank}}{\text{OD negative control} - \text{OD blank}} \times 100\% \quad (6)$$

where, the OD is the optical density, the blank was the sample without cells, and the negative control was the cells treated with the medium only.

RESULTS

Blank floating tablets formulation

The blank floating tablet was formulated, with numerous parameters, to select the optimal formulation (Table 2). Each factor varied sequentially one by one, with other factors/ingredient values being fixed. Firstly, the best granulating solvent (EtOH:water v/v ratio) was determined. A higher amount of EtOH significantly increases the floating potential from 38 seconds in the 10:0 ratio to 110 seconds in the 5:5 ratio. Furthermore, we noticed that the 7:3 and 5:5 ratios yielded incoherent and coarse granules. Thus, the 9:1 ratio was selected for the next factor variation. Secondly, the PVP K30 concentration of 3% w/w was chosen, since lower concentrations yielded short-floating-time tablets and higher concentrations resulted in long-floating-potential tablets. Thirdly, $NaHCO_3$ was decided to be the main gas-generating excipient, as the $CaCO_3$ made the tablet non-floatable for the first

Table 2. Optimizations of the blank floating tablets with various parameters. For each parameter, the other factors/ingredients were set at constant (n = 3).

No.	Parameter	Floating potential (second)	Floating time (hour)	Tablet integrity
		Granulating solvent (EtOH:water v/v ratio)		
1	10:0	38 ± 3	>8	Poor
2	**9:1**	**60 ± 5**	**>8**	**Acceptable**
3	7:3	96 ± 7	>8	Acceptable
4	5:5	110 ± 7	>8	Good
		Binder concentration (PVP K30 amount, % w/w)		
5	1%	20 ± 1	2	Poor
6	2%	57 ± 3	4	Poor
7	**3%**	**60 ± 6**	**>8**	**Acceptable**
8	4%	152 ± 10	>8	Acceptable
9	5%	191 ± 12	>8	Good
		Type of gas-generating excipients		
10	**$NaHCO_3$**	**98 ± 11**	**>8**	**Acceptable**
11	$CaCO_3$	860 ± 58	>8	Poor
		Ratio of $NaHCO_3$/$CaCO_3$ and citric acid (w/w)		
12	1:0.2	131 ± 12	>8	Acceptable
13	**1:0.5**	**60 ± 4**	**>8**	**Acceptable**
14	1:0.76	36 ± 2	>8	Poor
		Type/amount (mg) of matrix generator		
15	**Xanthan gum/150**	**746 ± 41**	**>8**	**Good**
16	**Xanthan gum/200**	**338 ± 25**	**>8**	**Good**
17	**Xanthan gum/250**	**270 ± 20**	**>8**	**Good**
18	HPMC K4M/150	231 ± 18	0.75	Poor
19	**HPMC K4M/200**	**120 ± 8**	**>8**	**Acceptable**
20	**HPMC K4M/250**	**60 ± 8**	**>8**	**Acceptable**
21	HPMC K15M/150	200 ± 19	3	Poor
22	**HPMC K15M/200**	**58 ± 7**	**>8**	**Acceptable**
23	**HPMC K15M/250**	**23 ± 3**	**>8**	**Acceptable**
24	HPMC 615/150	N/A	N/A	Poor
25	HPMC 615/200	N/A	N/A	Poor
26	HPMC 615/250	N/A	N/A	Poor
		Mixture of matrix generator (mg)		
27	Xanthan gum/100 HPMC K4M/100	311 ± 28	>8	Good
28	Xanthan gum/50 HPMC K4M/150	223 ± 17	>8	Good
29	Xanthan gum/33 HPMC K4M/167	130 ± 16	>8	Good
30	Xanthan gum/20 HPMC K4M/180	45 ± 4	>8	Acceptable
31	Xanthan gum/50 HPMC K4M/75 HPMC K15M/75	230 ± 20	>8	Good
32	Xanthan gum/100 HPMC K15M/100	306 ± 32	>8	Good
33	Xanthan gum/50 HPMC K15M/150	216 ± 19	>8	Good

Continued

No.	Parameter	Floating potential (second)	Floating time (hour)	Tablet integrity
34	**Xanthan gum/33 HPMC K15M/167**	**100 ± 9**	**>8**	**Good**
35	Xanthan gum/20 HPMC K15M/180	40 ± 5	>8	Acceptable
		Tablet hardness (*N*)		
36	**40–60**	**40 ± 3**	**>8**	**Good**
37	70–90	128 ± 16	>8	Good
38	100–120	147 ± 18	>8	Good
39	130–150	167 ± 20	>8	Good

N/A: not available due to non-floatable tablets.
The best formula (in **bold**) for each factor was selected to test the next factors.

10 minutes. Fourthly, the higher amount of citric acid significantly decreases the floating potential and, however, reduces the tablet integrity. Thus, the ratio of $NaHCO_3$ and citric acid of 1:0.5 w/w was selected. Fifthly, regarding the matrix generator types, HPMC 615 formed a rigid tablet framework that could not float. Xanthan gum has the outstanding advantage of being able to maintain tablet integrity, but it has the disadvantage of a long floating time. In contrast, formulas using HPMC K4M or HPMC K15M help tablets float quickly, but with poor integrity. Therefore, we combined these polymers to optimize the floating tablets with short floating potential, long floating time, and good integrity. For this (formulae 27–35 in Table 2), the ratio of xanthan gum and HPMC K15M of 33:167 w/w possessed a floating time ≥8 hours with good integrity, and thus, this ratio was selected. Finally, the tablet hardness was investigated, and the floating potential increased with the hardness values. Hence, the hardness of 40–60 N was chosen.

Floating tablets incorporating CSD formulations

Prior to the floating tablet formulation, the CSD physical stability, as well as the aqueous solubility of curcumin in CSD (formula curcumin:PVP K30:Tween 80 (1:4:0.22) w/w/w), was investigated at the initial timepoint, after 1 year (12 months), and after 2 years (24 months) of storage at room temperature (Fig. 1). Obviously, the curcumin possesses low solubility of 0.6 ± 0.1 µg/ml for the entire 2-year storage. On the other hand, CSD could significantly increase the drug solubility to 50.5 ± 5.7 µg/ml (nearly 100 times enhancement). Moreover, no observable alterations in the CSD's physical appearance and its solubility were noted after 2 years of storage, indicating the high stability of the CSD.

The optimal blank floating tablet formula was then utilized to load the CSD. For this, to confirm that the best final product was obtained, especially in terms of the floating potential, we re-varied the two main factors, namely the matrix generator (mixture of the xanthan gum and HPMC K15M, with a ratio of 1:5 w/w) and the gas-generating excipient $NaHCO_3$ percentages in the formula (Table 3). The factor values were selected based on the design of the experimental approach, and the results were analyzed by the program BCPharSoft OPT (data not shown). The model was fit and reliable with a predicted R^2 of 0.95 and an adjusted R^2 of 0.9, and the optimal parameters were the matrix generator percentage of 24.8% and the $NaHCO_3$ percentage of 10.2%. This condition yielded the wet-lab formula with a floating potential of 33 ± 2 seconds, a floating time of >8 hours, and good

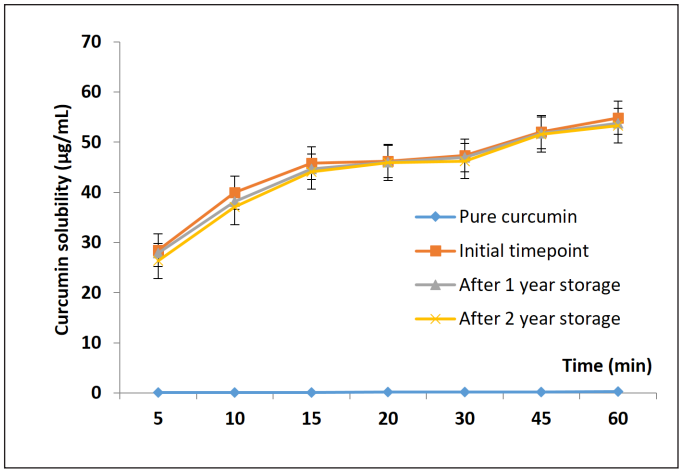

Figure 1. Aqueous solubility of the pure curcumin and the curcumin in solid dispersion at the initial timepoint, after 1 year, and after 2 years storage at room temperature ($n = 3$).

tablet integrity. These results were in agreement with the model-predicted value, with an insignificant difference between the actual and theoretical values ($F = 1.15 < F_{crit} = 12.32$), indicating that the model was fit and reliable.

Floating tablets physicochemical properties

The physicochemical properties of the final product, the floating tablets incorporating CSD, have been investigated in terms of the tablet appearance, hardness, floating potential, floating time, integrity, curcumin determination, curcumin quantification (assay), and curcumin dissolution profile. Additionally, for the stability tests, these properties were also re-investigated on tablets that were kept for 6 months in accelerated conditions (i.e., the temperature of 40°C ± 2°C and relative humidity of 75% ± 5%) and for 24 months in normal conditions (i.e., the temperature of 30°C ± 2°C and relative humidity of 75% ± 5%). Firstly, Figure 2 shows that after 8 hours of testing, the floating tablets significantly enhance the solubility and dissolution of curcumin approximately 241 times higher than that of the floating tablet containing raw curcumin. Secondly, in the *in-vivo* study, these floating tablets could maintain their floating ability in the dog's stomach for at least 4.5 hours, since the tablet was X-ray observed at the 4.5 hour time point, but not at the 5.5 hours point (Fig. 3). Thirdly,

Table 3. Design of experimental model of two independent variables, the matrix generator percentage (%) and the $NaHCO_3$ percentage (%), and their effects on the three responses, the floating potential, the floating time, and the tablet integrity.

No.	Matrix generator percentage (%)[a]	Gas-generating $NaHCO_3$ percentage	Floating potential (second)	Floating time (hour)	Tablet integrity
1	23.1	9.4	35	>8	Good
2	21.3	11.2	42	>8	Acceptable
3	25.0	7.5	82	>8	Good
4	22.5	10.0	31	>8	Good
5	20.0	12.5	25	>8	Acceptable
6	23.7	8.8	45	>8	Good
7	20.0	12.5	22	>8	Acceptable
8	20.6	11.9	27	>8	Acceptable
9	25.0	7.5	86	>8	Good
10	22.5	10.0	34	>8	Good
11	25.0	7.5	88	>8	Good
12	24.4	8.1	49	>8	Good

[a] Xanthan gum: HPMC K15M of 1:5 w/w.

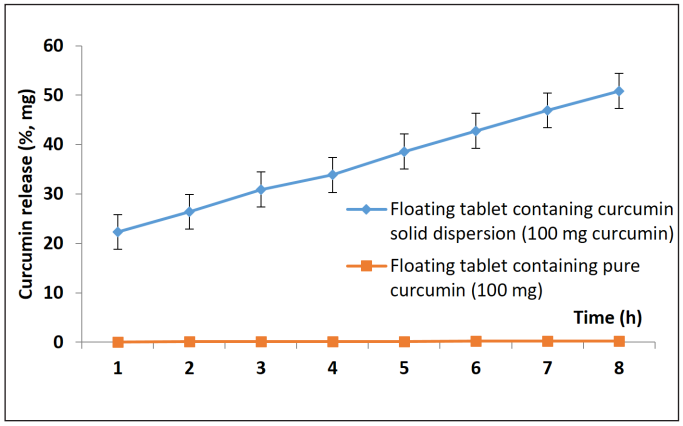

Figure 2. Dissolution profiles during 8 hours of the floating tablet incorporating the curcumin-solid-dispersion and the corresponding floating tablet incorporating the pure curcumin ($n = 3$).

Table 4 demonstrates that all physicochemical properties of the tablets at the initial time (i.e., after formulation), after 6 months preserved in accelerated condition, and after 24 months preserved in normal condition were in acceptance criteria. These results indicate that the tablets could protect the curcumin and CSD from degradation as well as maintain their properties properly. Thus, the product shelf-life was calculated to be 24 months (2 years), and the recommended storage condition is the normal condition at a temperature of 30°C ± 2°C and relative humidity of 75% ± 5%.

Floating tablets cytotoxicity on N87 stomach cancer cell line

To investigate the *in-vitro* ability to treat stomach cancer of the newly formed floating tablets incorporating the CSD, we first evaluate the effects of the tablet and SD excipients on the cells. The results show that the excipient samples did not alter the cell morphology, as well as did not significantly affect the cell viability (data not shown). Regarding the effect of the floating tablet, alone or in conjunction with a well-known stomach cancer treatment (5-FU), our data indicate that the curcumin in the floating tablet possessed an IC_{50} of 24.01 µM, lower than that of the reference drug 5-FU (46.86 µM), suggesting the effectiveness of the product (Table 5). Interestingly, the IC_{50} of the combined chemotherapy of the floating tablet and 5-FU was statistically lower than the IC_{50} of each individual therapy. This fact could be attributed to the synergistic effects of curcumin and 5-FU, which will be discussed in detail in the Discussion section.

DISCUSSION

To protect curcumin from being degraded by the alkaline environment of the small intestine and reduce the rapid metabolism by the liver and prolong its half-life to increase the oral bioavailability of curcumin, this work incorporated the CSD in the floating tablet dosage form for the application of gastric cancer treatment. To this end, the formulation was first optimized by various factors. To prevent the tablet from being pushed out of the stomach quickly, the tablet should possess a short floating potential (i.e., <180 seconds), a long retention time (i.e., >8 hours), and good integrity. The best formula is shown in Table 1, with a floating potential of 35 ± 1 seconds, a retention time of >8 hours, and perfect integrity. Other general tablet parameters have also been satisfied (Table 4).

Regarding the effects of the excipient type/amount on the tablet properties, for the granulating solvent, the formula with ethanol-water (10:0) provided the shortest floating potential; however, the polymer frame structure was not stable, and the rapid ethanol evaporation yielded weak bridges between the particles (Tank *et al.*, 2018). Moreover, without water, the matrix polymer could not expand effectively (Nokhodchi *et al.*, 2012), resulting in poor tablet integrity. With the ethanol-water ratio of 5:5, the integrity of the pellets was the best. Nevertheless, due to a high amount of water, the wet granulation process was very difficult, time-consuming, and unproductive with lots of granules sticking to the sieve. Therefore, the formula using ethanol-water (9:1) was selected.

For the binder, PVP K30 was chosen due to its high solubility in alcohol and has its high binding affinity, even in the

dry state, which made it suitable for the wet granulation method (Becker *et al*., 1997; Nguyen *et al*., 2021a). Our results showed that a low PVP K30 content (1%, 2%) was not able to bind the granules cohesively, thus making the dissolution medium easy to contact with $NaHCO_3$ and quickly generating CO_2. Consequently, the floating potential was shortened. However, because the particles are not well adhered to, they cannot withstand the pressure when the CO_2 gas is generated, causing the polymer framework to disintegrate. In contrast, with 5% PVP K30, the polymer frame is well bonded with good tablet integrity, but the floating potential was prolonged. Conclusively, the formulation with 3% PVP-K30 possessed a short floating potential, slow pellets corrosion, and a maintained tablet shape throughout the floating process.

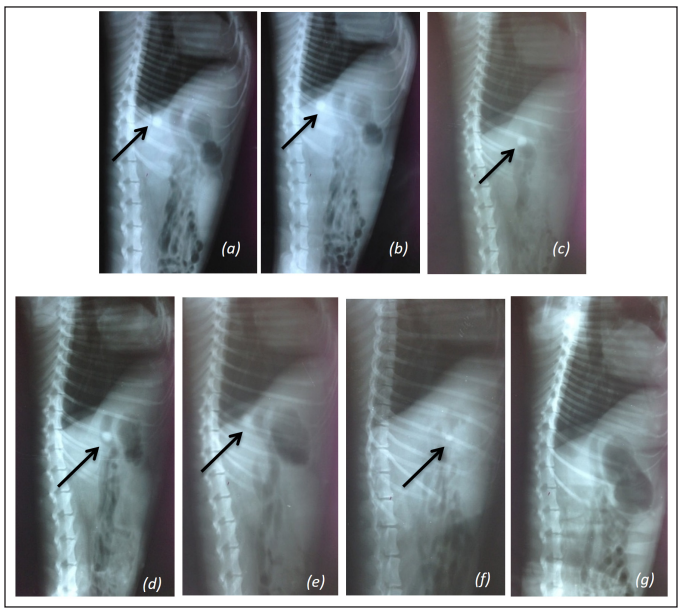

Figure 3. *In-vivo* X-ray investigation of the floating time in the dog stomach of the floating tablet incorporating curcumin solid dispersion. The X-ray images demonstrate the dog stomach (a) at the initial time point, (b) after 0.5 hours, (c) after 1.5 hours, (d) after 2.5 hours, (e) after 3.5 hours, (f) after 4.5 hours, and (g) after 5.5 hours.

Regarding the gas-generating excipients, $NaHCO_3$ produced CO_2 more rapidly than $CaCO_3$, which was consistent with the previous studies (Deb *et al*., 2010; Nguyen *et al*., 2016; Tadros, 2010). To further increase the rate of CO_2 generation in the early stages of short-floating-potential tablets, it is necessary to add a sufficient amount of acid to the formula. Citric acid was selected in our case due to the preliminary studies and the literature (Jaimini *et al*., 2007; Nguyen *et al*., 2016). An increase in the amount of citric acid significantly reduced the tablet's floating potential of the tablet, yet it destroyed its integrity due to fast CO_2 generation. Therefore, the ratio of $NaHCO_3$:citric acid (1:0.5) was selected.

In terms of the matrix generator type/amount, four commonly used excipients were employed, including the xanthan gum, HPMC K4M, HPMC K15M, and HPMC 615. All formulations with HPMC 615 were non-floating and rapidly disintegrated, possibly because the viscosity of HPMC 615 was too low (Perfetti *et al*., 2012) to form a stable gel framework that traps the gas in contact with the dissolved environment. At the same time, HPMC 615 could not withstand the pressure of CO_2 produced, making the pellets not buoyant and rapidly disintegrating. Therefore, HPMC 615 is not a suitable matrix generator, in our case. Among the remaining three polymers, xanthan gum yielded the best tablets with good integrity and long floating time (>8 hours). However, the tablets possessed long floating potential (i.e., >180 seconds), possibly due to the fact that xanthan gum is a natural polymer that takes a long time to expand (Kanwar *et al*., 2016) and to reduce

Table 4. Physicochemical properties of the floating tablets incorporating the CSD at the initial time point, after 6-month storage in accelerated condition, and after 24-month storage in normal condition ($n = 3$).

Parameter	Acceptable criteria	Stability results		
		Initial	After 6-month storage in accelerated condition[a]	After 24-month storage in normal condition[b]
Appearance	Round yellow tablets with no deformations	Pass	Pass	Pass
Tablet mass uniformity	No more than 2 units outside the ±5% range of the average weight	Pass	Pass	Pass
Curcumin determination	Similar R_f of the sample and the references on TLC	Pass	Pass	Pass
Curcumin quantification	90.0%–110.0%	Pass 101.22% ± 0.51%	Pass 91.04% ± 0.25%	Pass 91.09% ± 0.34%
Hardness	40–60 N	Pass 54.8 ± 4.3 N	Pass 48.0 ± 2.2 N	Pass 52.1 ± 1.1 N
Floating potential	<180 seconds	Pass 35 ± 1 seconds	Pass 36 ± 5 seconds	Pass 33 ± 4 seconds
Floating time	≥8 hours	Pass ≥ 8 hours	Pass ≥ 8 hours	Pass ≥ 8 hours
Integrity	Good level (tablet integrity is reserved during floating time)	Pass	Pass	Pass
Dissolution profile	≥30 mg curcumin was released	Pass 34.06 ± 0.42 mg	Pass 32.16 ± 0.81 mg	Pass 32.31 ± 1.03 mg

[a] Accelerated condition is set at the temperature of 40°C ± 2°C and a relative humidity of 75% ± 5%.
[b] Normal condition is set at the temperature of 30°C ± 2°C and a relative humidity of 75% ± 5%.

Table 5. The cytotoxicity data on the N87 stomach cancer cell line of the floating tablet incorporating CSD, the reference drug 5-FU, and the combination of the tablet and 5-FU (n = 3).

	Floating tablet	5-FU + Floating tablet	5-FU
Regression equation	$y = -0.0008x^3 + 0.1579x^2 - 1.2375x + 7.2495$	Curcumin: $y = 0.0065x^3 - 0.9881x^2 + 48.635x - 730.59$ 5-FU: $y = 0.0026x^3 - 0.3952x^2 + 19.452x - 292.19$	$y = 0.002x^3 - 0.0852x^2 - 0.796x + 49.661$
R^2	0.9962	0.9497	0.9994
IC_{50} (µM)	24.01	Curcumin: 4.32 5-FU: 17.41	46.86

the tablet density (i.e., the tablets sank first and then resurfaced in the testing media). Therefore, xanthan gum should be combined with other matrix generators with rapid expansion ability such as HPMC K4M and HPMC K15M. To that end, Table 2 shows that HPMC K4M, with an inherent moderate-viscosity property, could not maintain the tablet integrity at a low amount of 150 mg. At higher amounts, HPMC K4M yielded acceptable but not perfect integrity. These results were similar to the previous studies (Chowdary and Hussainy, 2012; Someshwar *et al*., 2011). The HPMC K15M provides tablets with the shortest floating potential, compared with the xanthan gum and HPMC K4M. These data were in agreement with a previous study (Someshwar *et al*., 2011). This indicates that HPMC K15M was the suitable candidate for combination with xanthan gum to shorten the floating potential time. Conclusively, the formula of xanthan gum-HPMC K15M with a ratio of 1:5 yielded the best tablets.

Investigating the influences of the tablets' hardness on their floating properties, the results showed that the floating potential increased proportionally to the tablet hardness, in accordance with previous works (Jivraj *et al*., 2000; Someshwar *et al*., 2011). This could be attributed to two reasons, the polymer swelling matrix generator polymer properties and the tablet porosity. In tablets with high hardness, the porosity of the pellets decreases and the polymer molecules on the tablet surface are compacted; thus, they could not be hydrated quickly when in contact with the medium, leading to a long floating potential time. Overall, all these aforementioned formulation factors significantly affected the floating tablet's properties, especially the floating potential and floating time. Thus, critical considerations are necessary to formulate optimal products.

Shifting to another issue, the results of X-ray of the dog's stomach on the floating ability of the tablets demonstrated a good correlation between the *in-vitro* and *in-vivo* tests. This re-confirmed that the tablets, when taken into the stomach of biological living systems, are still capable of maintaining their floating properties. The fact that the floating time in the *in-vivo* study was shorter than that in the *in-vitro* test (>4 *vs.* >8 hours) could be due to the effects of the stomach contractions, gastric volume, and enzymatic functions. This result was in agreement with the literature (Chandira *et al*., 2011).

Another important problem to discuss is the stability of the CSD and the product. One of the most common disadvantages of SD is its poor stability during storage. This phenomenon crucially affects curcumin solubility and oral bioavailability. Hence, we investigated the stability of these floating tablets incorporating CSD under storage conditions at room temperature and accelerated conditions after 1 and 2 years. Interestingly, the results showed that in both conditions the tablet's physicochemical properties (Table 4) and the curcumin solubility (Fig. 1) were well preserved, with no significant differences compared to the initial values. These data re-confirm that the formula was optimal for the delivery of curcumin.

Finally, the cytotoxicity of the best product was determined on the N87 stomach cancer cell line. After 48 hours of incubation, the excipient samples (i.e., tablets without curcumin) did not alter the cell morphology and reduce its survivability, even at the highest concentration of 450 µM. Thus, the excipients did not affect the cytotoxic potential of curcumin. On the other hand, all test samples containing CSD possessed significant cytotoxicity, corresponding to the sample concentrations. This indicates that the formulations could well preserve the anticancer efficacy of curcumin. Surprisingly, the floating tablet cytotoxic effect on N87 cells was statistically higher than on 5-FU, with an IC_{50} of 24.01 and 46.86 µM, respectively. This could be due to the unique action of curcumin on stomach cancer cells, possibly by impairing ATP-sensitive potassium channel opening (Li *et al*., 2014; Liu *et al*., 2014). Moreover, the fact that the IC_{50} of both curcumin and 5-FU was lower in the combination treatments compared to that in the individual treatments suggests that curcumin potentiated and enhanced the 5-FU anticancer effect against stomach cancer N87 cell line. Although this phenomenon has been shown in various cancer cell lines (Tian *et al*., 2012; Yang *et al*., 2017), we, for the first time, reported it on the N87 cells. Hence, these data could contribute to the literature on the potential effects of curcumin on stomach cancer.

CONCLUSION

This study develops and fully characterizes the floating tablets incorporating the CSD for gastric cancer treatment. The optimal formula possesses a short floating potential of 35 ± 1 seconds, a long floating retention time of >8 hours, good tablet integrity during the floating duration, and perfect physicochemical stability for at least 2 years in the normal storage condition. Furthermore, the tablets could enhance the curcumin solubility and dissolution profiles to >200 times compared to the pure curcumin and reserve the curcumin cytotoxicity on the N87 stomach cell lines with a better efficacy compared to the standard drug 5-FU. Finally, the tablets significantly potentiate and enhance the anticancer effect of 5-FU in a synergistic mechanism. Conclusively, the floating tablet incorporating the CSD could be a potential pharmaceutical product for stomach cancer treatment.

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AUTHORS' CONTRIBUTION

Conceptualization was done by D. T. M. H., V.T., and D. T. P.; methodology was done by D. T. M. H., M. T. L., V. H., and V. T.; validation was done by D. T. P.; investigation was done by D. T. M. H., M. T. L., V. H., and V. T.; resources were done by D. T. P.; writing original draft was done by D. T. M. H. and D. T. P.; writing review and editing were done by D. T. M. H., M. T. L., V. T., and D. T. P.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

The research ethics were approved by the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam, code 1454/QD-DHYD-SDH.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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