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Design and Evaluation of The Floating Oral *In Situ* Gelling System of Levofloxacin Hemihydrate to Dysphagia Patients

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ABSTRACT

Pediatric, geriatric, and dysphagic patients often experience difficulty swallowing solid dosage forms and discomfort with injectable administration. Levofloxacin, a fluoroquinolone antibiotic, is primarily available in tablet and injection forms, as in Indonesia. This study aimed to develop an aqueous dispersion formulation for a floating oral *in situ* gelling system of levofloxacin hemihydrate with sustained-release delivery as a practical and patient-friendly dosage form. Hydroxypropyl methylcellulose (HPMC) and sodium alginate were combined as polymers to form an *in situ* gel in an acidic environment. Formula optimization was conducted using the simplex lattice mixture design method. The formulations were evaluated for physical appearance, pH, *in vitro* floating behavior, *in vitro* gelation, viscosity, and *in vitro* drug release. Drug release kinetics were analyzed using both mathematical and compartmental modelling approaches. The results showed that variations in polymer concentration significantly affected the viscosity of the formulations. The developed formula exhibited rapid gelation and floating behavior that persisted for more than 24 hours. The optimum formula contained 0.378% sodium alginate and 0.122% HPMC, with a cumulative drug release of 86% within 6 hours, following the Korsmeyer-Peppas model for release mechanism. Based on compartmental modeling, the drug release mechanism fitted a two-compartment model. The developed formulation demonstrated enhanced gastric retention of levofloxacin hemihydrate, offering improved therapeutic efficacy and potential for greater patient compliance.

Keywords: floating oral, in situ gel, innovation, levofloxacin hemihydrate, sustained release

INTRODUCTION

Levofloxacin is a broad-spectrum antibiotic effective against both gram-positive and gram-negative bacteria (Arshad et al., 2022). It belongs to the fluoroquinolone class and is commonly prescribed as part of a second-line therapy regimen in combination with omeprazole and amoxicillin when first-line therapy—comprising lansoprazole, amoxicillin, and clarithromycin—fails in the treatment of peptic ulcer disease caused by *Helicobacter pylori* (*H. pylori*). This bacterium is highly adapted to colonize the human stomach, with the majority residing freely within the gastric mucus layer, while only about 20% remain in close contact with epithelial cells. The eradication of *H. pylori* is challenging due to increasing antibiotic resistance, poor patient adherence to treatment regimens, and drug-related adverse effects. Successful eradication requires maintaining high antibiotic concentrations in the gastric mucosa for an extended period (Arshad et al., 2022; El-Zahaby et al., 2014a).

Currently, levofloxacin is only available in tablet and injectable forms, as in Indonesia (Direktorat Registrasi Obat, 2024). These dosage forms pose challenges for certain patient groups, such as pediatric, geriatric, and dysphagic patients, who often experience difficulty swallowing solid preparations like tablets. Moreover, the pain associated with injections can significantly reduce patient comfort. These factors can negatively affect patient compliance, increasing the risk of antibiotic resistance. Therefore, alternative liquid formulations that are easier to swallow and more practical, without causing discomfort, are necessary to improve patient

adherence and therapeutic outcomes (Sharma et al., 2019).

A floating system is an oral controlled drug delivery system designed to prolong gastric residence time, thereby enhancing the sustained release of active substances absorbed in the stomach. This system allows for the controlled release of the active substance at a desired rate, after which the residual system is cleared from the gastric site (Bruschi, 2015). It holds significant potential as a drug delivery system for levofloxacin hemihydrate, optimizing its antibacterial effect by ensuring prolonged exposure to bacteria residing in the gastrointestinal tract. Recent studies have developed various floating systems for levofloxacin, including floating tablets, beads, and mucoadhesive formulations (El-Zahaby et al., 2014a, 2014b; Patil et al., 2016).

Several formulations of oral liquid *in situ* gels have been developed to sustain drug release. *In situ* gel systems are initially in liquid form, exhibiting rheological properties that allow easy spreading, and they gelify upon contact with the absorption site (Bruschi, 2015). This system supports site-specific drug delivery in the stomach, optimizing the efficiency of levofloxacin hemihydrate in eradicating bacteria in the gastrointestinal tract (Hani et al., 2021). The implementation of liquid drug-polymer formulations leads to gel formation at the administration site due to reversible sol-gel transitions in response to changes in temperature, pH, or ionic composition, thereby preventing rapid drug clearance. Additionally, this system offers several advantages, such as ease of administration, reduced dosing frequency, improved patient compliance, and enhanced comfort (Bashir et al., 2019). To the best of our knowledge, no oral liquid formulation combining floating and *in situ* gel systems for levofloxacin hemihydrate has been developed to date.

Therefore, this study aimed to develop an oral liquid preparation of a floating *in situ* gel system for levofloxacin hemihydrate. The system can be formulated using hydroxypropyl methylcellulose (HPMC) and sodium alginate. Sodium alginate is widely recognized as a leading raft-forming agent, while HPMC has been successfully utilized in sustained-release formulations. Both polymers are non-toxic, biocompatible, and biodegradable (Deshmukh et al., 2017; Wiwattanapatapee et al., 2023).

In this study, both polymers were combined at varying concentrations to develop the formulation. The evaluation of the developed formulations included assessments of physical appearance, pH, viscosity, *in vitro* floating and gelation behavior, gelation time, and *in vitro* drug release. In addition, the drug release mechanism was analyzed. This study is intended as an initial evaluation to identify the optimal formulation and explore the potential of oral floating *in situ* gel preparations of levofloxacin as an alternative product for geriatric, pediatric, and dysphagic patients undergoing infection treatment with sustained-release delivery systems.

MATERIALS AND METHODS

Levofloxacin hemihydrate (PT. Pharos Indonesia Tbk., Indonesia), sodium alginate, sodium citrate, HPMC K100, calcium carbonate ($CaCO_3$), and methylparaben were of pharmaceutical grade (purchased from CV. Poleba, Indonesia). Deionized water (Onemed, Indonesia), hydrochloric acid (HCl), and other chemical reagents were of analytical grade.

Preparation of levofloxacin hemihydrate floating oral in situ gel

The composition of the formula is presented (Table I). The target potency of the formula was set at 10 mg/mL of levofloxacin hemihydrate per 1 mL. The formula was designed using Simplex Lattice Mixture Design generated by Design Expert 10 software. Sodium alginate was dispersed in deionized water containing sodium citrate at 70°C until fully dissolved. After cooling to below 40°C, pre-dissolved HPMC K100 from a separate container was added to the sodium alginate solution. Calcium carbonate ($CaCO_3$) and methylparaben were then incorporated and stirred continuously until a homogeneous mixture was achieved. Finally, levofloxacin hemihydrate, dispersed in deionized water, was added to the *in situ* gel system. The resulting formulation was stored in airtight bottles, protected from light, until further evaluation (Siripruekpong et al., 2017).

Evaluation of physical appearance and pH

All formulations were evaluated for color through visual inspection. The pH of each formulation was measured at room temperature in triplicate using a calibrated pH meter (Hanna) (Rajendra Suryawanshi et al., 2022; Solanki et al., 2018).

Table I. Composition of floating oral in-situ gel designed using simplex lattice mixture design

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Levofloxacin hemihydrate (mg)	1000	1000	1000	1000	1000	1000	1000	1000
HPMC K100 (%)	0.35	0.2	0.05	0.05	0.125	0.275	0.35	0.2
Sodium Alginate (%)	0.15	0.3	0.45	0.45	0.375	0.225	0.15	0.3
Sodium citrate (%)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
$CaCO_3$ (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methyl Paraben (%)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15

***In vitro* floating studies**

A total of 100 mL of 0.1 N HCl was placed in a beaker glass, and 10 mL of the formulated gel was added to the HCl solution. The floating lag time and total floating time (floating duration) were then measured. Floating lag time refers to the time required for the sample to rise and float on the surface of the medium, while floating duration represents the total time the gel remained buoyant on the surface without disintegration (Adnan et al., 2023).

***In vitro* gelation studies**

The study evaluated the gel formation by visualizing the coagulation or agglomeration state of the sample solution after direct pouring into 0.1 N HCl maintained at 37°C (S. Sharma et al., 2019). The stiffness of the formed gel was classified based on visual observation, with the following criteria: (−) no gelation, (+) gelation occurring after a few minutes following rapid dispersion, (++) immediate gelation persisting for a few hours, and (+++) instantaneous gelation persisting for an extended period (Hani et al., 2021).

Measurement of viscosity

The viscosity of the floating oral *in situ* gel formulation of levofloxacin hemihydrate was measured using a Brookfield digital viscometer with an appropriate spindle at room temperature. (Solanki et al., 2018).

***In vitro* drug release study**

The drug release from the prepared floating oral *in situ* gel formulation was evaluated using a USP II dissolution apparatus (paddle method). Ten milliliters of the floating oral *in situ* gel was added to 900 mL of 0.1 N HCl, which served as the dissolution medium. The study was conducted at an operating speed of 50 rpm, with the medium maintained at 37 ± 0.5°C to simulate gastric conditions. Aliquots (5 mL) were withdrawn at predetermined intervals of 5, 10, 15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes and immediately replaced with fresh medium to maintain sink conditions. The drug concentrations in the collected samples were analyzed using a UV-Vis spectrophotometer at a maximum absorbance wavelength of 294 nm. The cumulative percentage of drug release was calculated for each time point (Sharma et al., 2019).

Optimization of formula

The optimum formula was determined by setting goal criteria and assigning priority values (importance) to each parameter in the software based on the response data obtained. The formula with the highest desirability value was selected as the optimum formulation (Pawestri et al., 2021b).

Modelling of drug release kinetics of optimum formula

The modeling of drug release was conducted using two different approaches. The dissolution profile of the optimum formulation was fitted to various mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas, to describe the drug release kinetics using DD Solver software (Ahmed et al., 2017; Zhang et al., 2010). The coefficient of determination (R^2) and Akaike's Information Criterion (AIC) were evaluated to determine the best-fitting model for the drug release profile. In addition, a compart-mental modeling approach was implemented to further investigate the drug release mechanism (Pawestri et al., 2021). This approach utilized WinSAAM software (version 3.3.0) running on Windows 11 to simulate the drug release process. The proposed model consisted of two compartments: compartment 1 representing the drug within the formulation and compartment 2 representing the dissolution medium.

The compartmental-based models were applied to the drug release data, and individual data fitting was conducted using a naïve pooling approach to enable visual evaluation of the data.

Table II. Evaluation of levofloxacin floating oral in situ gelling system

Formula	pH*	Floating Lag time (s)	Duration of floating (h)	*In vitro* gelation**	Viscosity *(cP)	% Cumulative drug release* (at 6 h)
F1	7.81±0.01	38	>24	+++	28.38±1.28	86.39±2.62
F2	7.83±0.01	17	>24	+++	35.01±0.83	80.69±1.85
F3	7.82±0.01	46	>24	+++	39.88±0.98	83.48±1.05
F4	7.82±0.01	42	>24	+++	31.65±1.30	87.73±1.01
F5	7.78±0.05	40	>24	+++	37.39±0.90	96.51±1.07
F6	7.81±0.01	67	>24	+++	24.11±0.58	83.97±2.25
F7	7.79±0.02	44	>24	+++	20.25±1.27	91.98±0.20
F8	7.80±0.02	80	>24	+++	25.94±0.58	95.36±0.06

*The results were mean±SD from three data replicates.
**(−) no gelation, (+) gelation after a few minutes following rapid dispersion, (++) immediate gelations persists for a few hours, and (+++) instantaneous gelation persists for an extended period

The notation rules in WinSAAM were utilized to represent mass transfer flow within the model and to define the model parameters. Several notations were applied, including: 1) IC(1), representing the initial dose amount, and 2) L(2,1), denoting the rate constant of drug transport from compartment 1 to compartment 2 (Pawestri et al., 2021a).

RESULTS AND DISCUSSION

The results of the physical properties of the formulation are presented (Table II). The data were analyzed using Analysis of Variance (ANOVA) to determine whether the factors significantly influenced the responses. A p-value of less than 0.05 ($p < 0.05$) indicated that the factors had a statistically significant effect on the response variables.

Physical appearance and pH measurements

All prepared formulations exhibited a yellowish, pourable, viscous liquid appearance. The pH values ranged from 7.78 to 7.83, indicating that the formulations maintained their liquid state. This stability is attributed to sodium alginate's high stability within a pH range of 4–10, while it precipitates at pH levels below 3, potentially affecting the formula's appearance (Rowe et al., 2009). Based on the analysis, the pH values indicated that variations in the concentrations of both polymers had an insignificant influence on the pH of the formulations.

In vitro floating study

An *in vitro* floating study was conducted in simulated gastric fluid to assess the floating behavior of the formulations, which is a critical step before proceeding to *in vivo* evaluation (Hani et al., 2021). This study ensured a comprehensive understanding of floating performance in terms of floating lag time and duration. The results demonstrated that all formulations floated immediately upon contact with the medium (0.1 N HCl), with lag times ranging from 17 to 80 seconds. The floating duration for all formulations exceeded 24 hours. The *in vitro* floating study revealed that variations in the concentrations of both polymers had an insignificant effect on the floating performance.

HPMC and sodium alginate act as key polymers in the formulation. When exposed to gastric fluid, water hydrates these polymers, forming a colloidal gel barrier around the surface. This hydration and subsequent swelling of the surface polymers create a floating mass (Bruschi, 2015). In addition, calcium carbonate ($CaCO_3$) serves as a gas-forming agent, releasing carbon dioxide (CO_2) upon reaction with hydrochloric acid (HCl) in the stomach.

The interaction between HCl and calcium carbonate ($CaCO_3$) produces calcium chloride, water, and carbon dioxide (CO_2). The ability of polymers to form cross-links traps CO_2 bubbles within the gel matrix, reducing the gel's density and creating buoyancy (Hani et al., 2021). The floating performance of the prepared formulations indicates that they can provide sustained drug release over a prolonged period.

In vitro gelation study

In *in situ* gelling systems, it is expected that the formulation will immediately form a gel upon exposure to body fluids. Based on the data obtained, the developed formulations demonstrated the ability to form gels instantly and

maintain their structure for extended periods (Figure 1). The divalent ions in sodium alginate interact with sodium citrate, which is subsequently broken down in the acidic environment of the stomach, releasing free divalent calcium ions (Ca^{2+}). These free calcium ions are trapped by the sodium alginate polymer chains, facilitating cross-linking and forming a stable gel matrix structure.

Figure 1. The typical floated oral in situ gel appearance of in vitro floating and gelation study

Viscosity

The viscosity of the formulations ranged from 20.25 to 39.88 cP. The concentration variations of HPMC and sodium alginate significantly influenced the viscosity of the formulations. An increase in polymer concentration resulted in higher viscosity, with sodium alginate having the most dominant effect. These results suggest that higher polymer concentrations bring the polymer chains closer together, leading to increased interactions and the formation of a denser network structure (Xu et al., 2014). This dense network enhances resistance to liquid flow (Wiwattanapatapee et al., 2023). Despite the increase in viscosity, all the prepared floating oral *in situ* gels exhibited adequate pourability, meeting the criteria for patient-friendly medication administration.

***In vitro* drug release**

The results of *in vitro* drug release studies for the formulations are presented (Table II). The analysis indicated that variations in polymer concentration did not significantly influence the *in vitro* drug release, which ranged from 80.69% to 96.51%. Both polymers were sufficiently strong to retain levofloxacin for the intended release period. The drug molecules were entrapped within the polymer matrix and cross-linked to form a gel structure. All *in situ* gel formulations exhibited a significant burst release within the first hour, likely due to the immediate dissolution of levofloxacin hemihydrate present on the gel surface upon contact with the dissolution medium (0.1 N HCl) (A. Sharma et al., 2014).

Optimization of the formula

The optimization process was conducted by setting criteria for each response parameter and generating desirability plots. The criteria were defined as pH, floating lag time, and viscosity within the acceptable range, while *in vitro* drug release was set to be maximized. The predicted optimum formula yielded a desirability value of 0.907. The optimal formulation consisted of 0.122% HPMC and 0.378% sodium alginate. Verification experiments were carried out to validate the predicted procedure. The results indicated that the physical properties of the experimental formulation, particularly the viscosity parameter, were not significantly different from the software predictions.

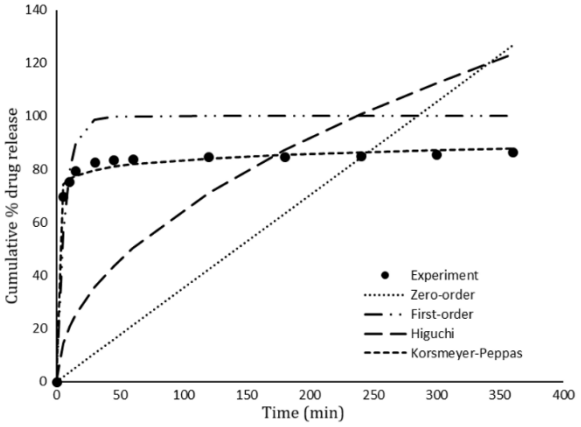

Figure 2. The fitting result of observed and predicted data of optimum formula applied with zero-order, first-order, Higuchi, and Korsmeyer-Peppas models (n=3).

Drug release kinetics of optimum formula

When the percent drug release was plotted against time (Figure 2), the optimized formulation showed a gradual release of levofloxacin hemihydrate, achieving a cumulative release of 86% within 6 hours. The release behavior appeared to follow the Korsmeyer-Peppas model, as confirmed by visual observation and further verified by the coefficient of determination (R^2) and Akaike's Information Criterion (AIC), which indicated a better fit compared to the zero-order, first-order, and Higuchi models (Table III).

Table III. Coefficient determination (R^2) and AIC value in mathematical modelling

		R1	R2	R3
Zero-order	R^2	-4.0140	-4.1958	-4.3204
	AIC	126.4847	124.7470	129.4254
First order	R^2	0.6343	0.1497	0.9143
	AIC	95.0672	103.0272	79.8812
Higuchi	R^2	-1.4341	-1.5657	-1.6768
	AIC	117.8130	116.2794	121.1823
Korsmeyer-Peppas	R^2	0.9884	0.9927	0.9915
	AIC	55.6183	47.9144	54.1383

R1,R2,R3= replication 1,2,3, respectively

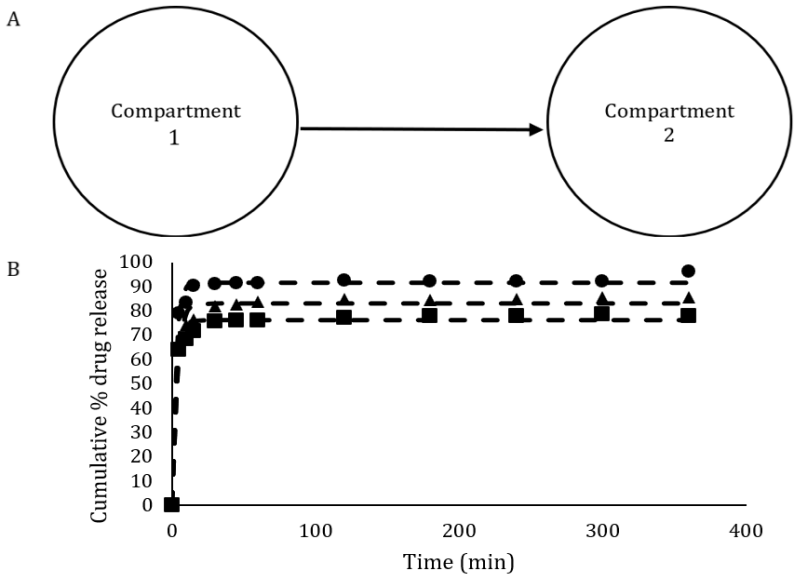

Figure 3. (A) The schematic 2-compartment model for kinetic drug release of optimum formula, (B) The fitting result of observed and predicted data applied with the 2-compartment model (n = 3); ▲, ● , ■ are observed data; dash line (———) was predicted data.

The data revealed that the observed release pattern did not align with other models except for the Korsmeyer-Peppas model. To verify the best-fitting model, the highest R^2 value and the lowest AIC were considered optimal criteria (El-Zahaby et al., 2014a). Therefore, the data demonstrated that the optimum formulation best fitted the Korsmeyer-Peppas model.

Meanwhile, the Korsmeyer-Peppas release exponent (n) for the optimized formulation was found to be less than 0.5, indicating a Fickian diffusion mechanism. The kinetics of this release phenomenon are characterized by diffusivity (Permanadewi et al., 2019). In the Fickian diffusion model (Case I), when n = 0.5, drug release is primarily governed by diffusion, where the rate of solvent transport significantly exceeds the relaxation of the polymeric chains. The rapid absorption equilibrium on the exposed surface of the polymer system results in time-dependent links (Bruschi, 2015). Meanwhile, based on the compartmental approach (Figure 3), the drug release mechanism was best described by a two-compartment model. In the proposed model, compartment 1 represents the aqueous dispersion of the *in situ* gel containing the drug. Upon contact with the dissolution medium (compartment 2), an initial burst release occurred due to the homogeneous distribution of the drug within the *in situ* gel matrix. The drug was simultaneously released while the gel system formed immediately upon contact with the medium.

CONCLUSION

All the prepared formulations exhibited instantaneous gelation that persisted for over 24 hours. Variations in the concentrations of HPMC and sodium alginate significantly influenced the viscosity of the *in situ* gelling systems. The optimum composition of the formula was determined to be 0.122% HPMC and 0.378% sodium alginate. This formulation achieved a cumulative drug release of 86% within 6 hours. The drug release mechanism of the optimum formula followed the Korsmeyer-Peppas model and, based on the compartmental approach, was best described by a two-compartment model. The innovative formulation demonstrated successful sustained-release delivery and represents a promising alternative dosage form for levofloxacin therapy, potentially improving patient compliance.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

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