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FABRICATION OF LEVOFLOXACIN-LOADED PH-SENSITIVE EUDRAGIT POLYMERIC FLOATING MICROBALLOON BIOMATERIAL FOR GASTRORETENTIVE DRUG DELIVERY

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ABSTRACT

Background: The design of improved biomaterials for medication administration is vital in overcoming problems associated with standard therapy for *Helicobacter pylori (H. pylori)*-induced stomach ulcers. This study aims to develop and characterize floating biomaterial of levofloxacin microballoon biomaterials based on a fluoroquinolone-benzoxazine system conjugated with methylated piperazine and carboxylic acid groups, strategically designed for prolonged gastric delivery. **Methodology:** Using the emulsion solvent diffusion method, thirteen preparations were developed by different polymer ratios (pH-sensitive Eudragit RS-100 and Ethyl Cellulose), stirring speeds, and temperatures. **Results and Discussion:** In the buoyancy study simulated gastric fluid (pH 1.2), the best formulation (F9) shows superior encapsulation efficiency (90.2%) and sustained drug release profile (91.2% over 8 hours) that increases its effectiveness against *H. pylori*. FTIR and SEM analyses conducted during characterization studies verified the drug stability and the spherical microballoon morphology, with a particle size of 81.2 µm. Levofloxacin-loaded microballoon biomaterials provide a unique gastro-retentive delivery system that improves patient compliance, reduces off-target effects, and maintains effective drug concentrations at the infection site, thereby strengthening the therapeutic efficacy of levofloxacin against *H. pylori*. **Conclusion:** This creative method offers a viable substitute for traditional therapies for stomach ulcers and is consistent with the overarching objectives of targeted delivery systems and structure-based drug development.

INTRODUCTION

Advanced drug delivery systems called floating microballoon biomaterials are made to allow for prolonged release of encapsulation of its drug in the stomach and extended gastric retention. Since these are hollow, spherical structures of low density, they float on gastric fluids, keeping the drug at the therapeutic level in the GI environment for a prolonged time. *Helicobacter pylori*, commonly known as *H. pylori*, is a significant Gram-negative bacterium that causes peptic ulcers and chronic gastritis and is classified as a Group I carcinogen due to its association with more severe gastrointestinal conditions, including gastric adenocarcinoma and MALT

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lymphoma [1]. This bacterium invades between 30% and 50% of the adult population within developed nations and up to 90% of the adult population in developing nations [2,3]. The current cases of stomach cancer have made treatment strategies against *H. pylori* to be very important since cases are rising around the world. Some standard treatment guidelines for *H. pylori* infection include the American College of Gastroenterology (ACG), the Asia-Pacific Consensus Guidelines, and the Maastricht/Florence Consensus Reports. Those guidelines recommend combination regimens that usually include a PPI and other antimicrobials such as amoxicillin, clarithromycin, or other antibiotics [4]. Among these first-line therapies, however, they pose some disadvantages, including increased antibiotic resistance and 5–50% eradication rates, meaning that failure to treat the condition is relatively common. Levofloxacin, an optical isomer of ofloxacin with the second-generation fluoroquinolone group chemical formula $C_{18}H_{20}FN_3O_4$, is still an essential second-line therapy in *H. pylori*.

Its complex heterocyclic structure, comprising a fluorinated quinolone core, methylated piperazine ring, and carboxylic acid group (IUPAC: This compound, called (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid), allows the covalent incorporation of broad-spectrum antimicrobial activity. However, passive targeting cannot sustain adequate drug concentrations at the site of infection, which is a drawback of conventional delivery systems. The foremost problem with *H. pylori* treatment is maintaining the necessary drug concentration at the microsite of the target infection, which is not feasible with standard drug delivery mechanisms. Despite the second-line regimens such as levofloxacin combinations, no treatment regimen is one hundred percent effective in eradicating the disease once it occurs. In response to these challenges, useful floating microballoon techniques have been introduced using different polymers to target and maintain drug delivery at the gastric mucosa surface [5]. Therefore, the gastroprotective mechanism increases the effective concentration of the drug, Bioavailability, and efficacy at the site of infection, hence offering better therapeutic benefits for *H. pylori*-related gastric ulcers [6,7]. Low-density polymers are used to create floating microballoons, a promising subtype of gastroretentive drug delivery systems (GRDDS) that are perfect for increasing the bioavailability of antibiotics like levofloxacin because they give buoyancy and longer gastric residence [8]. The principal aim is developing a GRDDS that offers targeted and sustained release of levofloxacin at the gastric mucosal surface, thereby addressing the shortcomings of current *H. pylori* therapy. Some of the specific research objectives are creating floating microballoons with different polymer blends, assessing their physical characteristics, and assessing the effects of these formulations on in vitro drug release profiles.

MATERIALS AND METHODS

Preparation of microballoons

Levofloxacin and the polymer were dissolved in a homogeneous solution in an organic solvent, such as ethanol or dichloromethane, to make microballoons. The PVA concentration (0.5% to 1.25%) and stirring speed (100–600 rpm) help produce better microballoons. Lower PVA reduces viscosity to improve filling success and specific stirring rates, maintaining droplet spread and particle sizes without losing encapsulation quality [9]. To develop a fine emulsion, this organic phase was gradually added to an aqueous phase that included a stabilizer while vigorously stirred. Solid microballoons were formed by the drug and polymer precipitating with the organic solvent dripped throughout the aqueous phase. Afterward, the microballoons were separated by centrifugation or filtration and cleaned with distilled water to remove any leftover solvent and drugs that weren't encapsulated and dried using either air drying or freeze-drying techniques. The emulsion solvent diffusion method proved better than spray-drying or coacervation because it successfully created floating microballoons with desired drug-release properties [10,11]. The resultant microballoons were then analyzed for their size, shape, drug loading efficiency, and release profile, utilizing techniques such as SEM and drug release experiments, verifying their appropriateness as effective drug delivery.

Formulation Yield and Encapsulation Efficiency

By weighing the cultivated microballoons about the original dosage form of the levofloxacin-based therapy, Eudragit RS-100, and ethyl cellulose utilized in the formulation, the collection of microballoons carrying the drug was evaluated. The following formula was used to calculate the percentage yield:

$$Percentage\ Yield(\%) = \frac{Total\ measured weight of microballoons\ obtained}{Total\ weight\ of\ all\ initial\ materials\ used} x100$$

The encapsulation efficiency, or how much of the medicine was entrapped in the microballoons, was analyzed using

spectrophotometry [12]. Ultra-sonication was used by dissolving the microballoons in a dichloromethane-ethanol combination (1:1 v/v). The drug content and encapsulation efficiency were calculated by comparing the weight of the medication in microballoons to the theoretical weight of the drug initially placed therein. The following formula was utilized to estimate the encapsulation efficiency:

$$Encapsulation\ Efficiency(\%) = \frac{Amount\ of\ drug\ encapsulated}{Total\ amount\ of\ drug\ added} x100$$

Particle Size and Morphology

A Malvern particle size analyzer, which uses laser diffraction as its basis of operation, was used to analyze the particle sizes of the prepared microballoons. The particle size distribution of the microballoons was ascertained by diffraction patterns in laser light after they were scattered in a suitable medium and added to the analyzer. Measuring essential parameters, including D10, D50, and D90, provided information about the microballoon's homogeneity and mean size, necessary for understanding their particle size properties [13]. SEM, which produced detailed images verifying the microballoon's spherical morphology and smooth surface, both crucial for their performance in drug delivery applications, was used further to assess the microballoon's shape and surface structure.

Buoyancy Studies

We tested microballoon buoyancy by adding 100 mg of microballoons to 300 ml of acidic solution at pH 1.2 with 0.02% w/v Tween 20 at 37°C while stirring at 100 rpm. We experimented three times to verify accuracy and picked the floating microballoons from the water aseptically before weighing them after 12 hours. We measured the floating microballoon weight percentage and reported standard deviations to show our findings were reliable [14]. The following formula was used to determine the buoyancy percentage:

$$Buoyancy\ (\%) = \frac{Weight\ of\ microballoons\ that\ float}{Weight\ of\ floating\ microballoons + Settled\ microballoons\ weight} x100$$

***In-Vitro* Drug Release**

The diffusion technique in a dialysis tube was used to assess the levofloxacin release from the microballoons in an *in vitro* setting. A 100 mg sample of microballoons was suspended in beakers with 100 millilitres of simulated stomach fluid (SGF, pH 1.2 level) after being put into dialysis tubes with a molecular weight cut-off (MWCO) of 10–12 kDa and sealed [14]. The temperature of the receptor compartments was kept at 37 ± 1°C while they were being shaken at 100 rpm. To keep the volume of the system constant, samples were taken at predetermined intervals and an equal volume of fresh SGF was introduced. Levofloxacin release concentration was measured at the drug wavelength using a UV–vis spectrophotometer. The following calculation was employed to ascertain the proportion of drug release:

$$\%\ Drug\ Release = \frac{Amount\ of\ drug\ released\ at\ a\ specific\ time}{Total\ amount\ of\ drug\ encapsulated} x100$$

RESULTS AND DISCUSSION

To increase the gastroretentive administration of levofloxacin and especially treat *H. pylori*-induced stomach ulcers, the research emphasizes developing and characterizing levofloxacin-loaded floating microballoons. Thirteen distinct formulations (designated F1 through F13) were meticulously designed to accomplish this by adjusting a count of important factors, including the concentrations of polyvinyl alcohol (PVA), the ratios of polymers (pH-sensitive Eudragit RS-100 (ethyl acrylate- co-methyl Methacrylate- co-trimethylammoniethyl methacrylate chloride) and ethyl cellulose), the drug-to-polymer ratios, stirring speeds during the preparation process, and the processing temperatures. Eudragit RS-100 helps levofloxacin release slowly because it changes its action at different pH levels. Ethylcellulose helps the drug stay floating and absorb better, creating an ideal delivery system for gastric treatment [15]. Each of these factors was changed to maximize the performance of the microballoons and provide a perfect retention and release profile of levofloxacin in the stomach environment.

Compatibility and Stability

Levofloxacin remained stable inside the microballoons, as validated by Fourier-transform infrared (FTIR) spectroscopy, which revealed no notable interactions between the drug and the polymers [15]. FTIR spectroscopy was employed to evaluate the compatibility of levofloxacin with excipients in a physical mixture prepared in a 1:1 ratio. The FTIR spectrum of pure levofloxacin displayed distinct peaks, as shown in Figure. 1 at 1004.84 cm^{-1} (corresponding to C-F stretching), 1091.09 cm^{-1}

(C-N stretching), 1290.91 cm^{-1} (C-N stretching in amines), and 1725.05 cm^{-1} (C=O stretching in ketones), confirming the drug's identity and purity. These characteristic peaks were preserved in the physical mixture without notable shifts or the appearance of new peaks, indicating that there were no chemical interactions between the drug and the excipients. For example, the carbonyl stretching peak at 1725.05 cm^{-1} remained unchanged. [16] This demonstrates that levofloxacin is compatible and stable within the formulation.

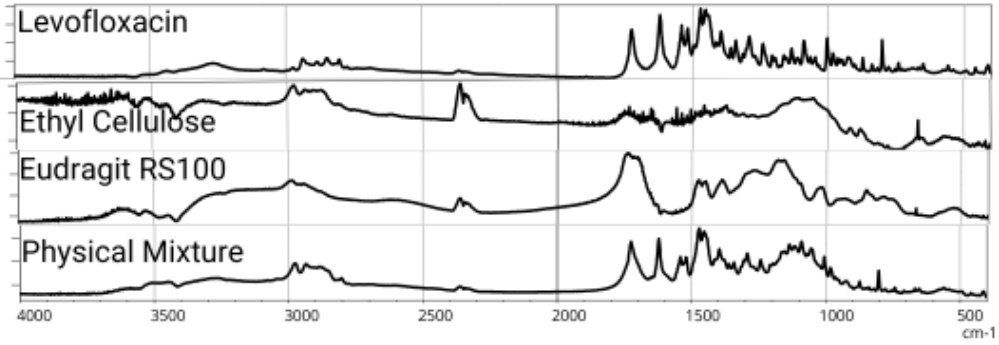

Figure 1: FTIR spectrum of drug, excipients and physical mixture

Table 1: Fabrication of levofloxacin-loaded floating microballoons biomaterials.

Formulation	Temperature (°C)	Eudragit RS-100: Ethyl cellulose (% w/w)	PVA Con. (%)	Stirring Speed (rpm)	Drug: Polymer (% w/w)
F1	25	1:1	0.5	100	1:0.5
F2	25	1:1	0.5	300	1:0.5
F3	25	1:1	0.5	600	1:0.5
F4	37	1:2	0.75	100	1:1
F5	37	1:2	0.75	300	1:1
F6	37	1:2	0.75	600	1:1
F7	45	1:3	1	100	1:1.5
F8	45	1:3	1	300	1:1.5
F9	45	1:3	1	600	1:1.5
F10	25	1:4	1.25	100	1:2
F11	25	1:4	1.25	300	1:2
F12	25	1:4	1.25	600	1:2
F13	37	1:4	1.25	600	1:2

Using the emulsion solvent diffusion method, which involves emulsifying a polymer-drug solution, typically a combination of ethanol and dichloromethane into an aqueous phase with polyvinyl alcohol (PVA) acting as a stabilizer, floating microballoons were developed [17,18]. In the procedure, the drug and polymer co-precipitated at the droplet interface, surrounding each droplet with a solid shell as the organic solvents diffused outer droplets of the emulsion into the surrounding aqueous phase. The solvents were subsequently removed, which caused the microballoon structures to interior voids that significantly increased buoyancy. The regulated drug release from these microballoons allowed them ideal for prolonged retention in gastric fluids and enhanced drug delivery directly to the stomach.

Emulsion solvent diffusion technique and mechanism of levofloxacin floating microballoon development

One of the distinctive methods of gastroretentive delivery of drugs is the use of floating microballoons. The microballoons float in gastric fluid, causing their bulk density to be lower than the stomach's contents. The drug is released by the microballoons at a regulated rate that maintains the drug concentration for an extended amount of time while they float on the contents of the stomach [17,19]. Upon completion of the

drug release, the stomach eliminates any residual system. As a result, this technology raises gastroretentive duration and offers efficient sustain over fluctuations in plasma drug level. The drug (Levofloxacin 250 mg) and polymers (pH-sensitive Eudragit RS-100 and EC) in the Ethanol: CH_2Cl_2 solution finely dispersed into separate droplets when added to an aqueous solution while being stirred, creating an oil-in-water (o/w) form of emulsion. Figure l shows the ethanol and CH_2Cl_2 concentrations that were measured in the external aqueous phase of the microballoon development process. The straight and dotted lines indicate the most suitable concentrations of ethanol and CH_2Cl_2 in the aqueous phase, respectively. In a closed system (a flask with a glass stopper), 200 milliliters of aqueous polyvinyl alcohol solution were saturated with 10 mL of the two solvent combinations (1:1, v/v). A few seconds after the solvent mixture was discharged, the aqueous medium absorbed all of the ethanol that had diffused from the dispersed droplets, and the microballoons developed to their optimal concentration of ethanol [18]. Rather than entirely diffusing outside of the droplets into the aqueous phase, CH_2Cl_2 stayed partially in the droplets. The solubility character of the polymer in the droplets may have been reduced since the polymer (pH-sensitive Eudragit RS-100) was hydrophobic in CH_2Cl_2 and rapidly diffused into the aqueous phase via ethanol, a suitable solvent. At the droplet surface, the polymer precipitated quickly, forming a shell that encased Eudragit RS-100 and EC, encasing the CH_2Cl_2 that was dissolving the drug. The model system used to investigate the microballoon development process pictorially is shown in Figure 2. A pipette added the drug and polymer solution to the liquid in a 400°C-heated petri plate. The released droplet became slightly hollow as it dropped to the bottom of the serve due to gravity.

The droplet surface developed a gel-like coating, making it instantaneously opaque (Figure 2). After a few minutes, as shown in Figures B and C, a few CH_2Cl_2 bubbles appeared when a crushed gel-like droplet with a pincette. This indicates that before the droplet wholly solidified, the gaseous state of dichloromethane was created in the droplet encased in a film-like gel layer. The gas phase ought to cause the formation of microballoon. The method proposed in this work is quite different from the emulsion-solvent evaporation methods. Where the liquid in the emulsion droplet evaporates, the droplet mostly solidifies. The polymer solubility was significantly decreased in the current system as a result of the transfer of ethanol, an excellent solvent for Eudragit RS-100, before the evaporation of DCM, a weak solvent for the polymer, by an emulsion droplet from water into the aqueous medium. A film-like gel also formed on the surface [15,16].

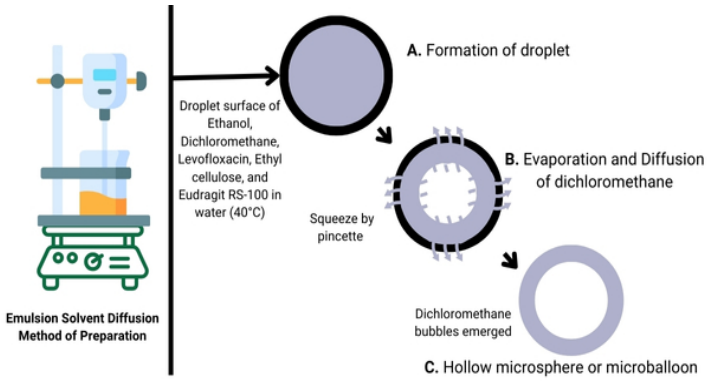

Figure 2: Illustrations of the ethanol droplet Levofloxacin, EC, and Eudragit RS-100 DCM solution in water (400C) on a vessel called a both before the pincette squeeze (A) and following it (B&C).

The model research demonstrated how the mechanically strong solidified layer (shell) created at the droplet's surface with subsequent ethanol depletion prevented the formulation from rupturing and contracting during the droplet's dichloromethane evaporation. The droplet's internal pressure dropped due to CH_2Cl_2 evaporation, allowing water to progressively fill the gap that resulted from the gas phase's development. The proposed microballoon was created by extracting the water within the microballoon with the use of a drying process [18]. The emulsifying agent, fully hydrolyzed polyvinyl alcohol, significantly inhibited the formation of droplets using solid exterior shells during the entire procedure. Because the polyvinyl alcohol complied with the droplets' aqueous medium border, creating a stable dispersed layer, it was anticipated that an effective hydrated layer would form over the droplets. Moreover, the model experiment showed that the droplets were prevented from merging by rapidly forming an outer layer that resembled a film above them.

As a result, the size ranges of microballoons and their droplet sizes produced during the drug and polymer solution pouring phase may be the same. The polymer and drug ratios in the design, the pace at which the drug and polymer combination was poured, and the system's agitation rate were discovered to be the primary determinants of the micro balloon sizes [19]. Levofloxacin yields and average sizes of floating microballoons

as a function of temperature in the aqueous dispersed media are displayed in Figure 3. The recovery was expressed as the percentage of microballoons with a diameter of 72±1.08 to 86±1.1 micrometers that were recovered about the amounts of polymeric material and medication added to the system, accounting for aggregates. When the temperature was adjusted between 30 and 40°C, the recall rate of micro balloons reached 70–80%, indicating the optimal range [20]. The recovery was greatly retarded because the ruptured microballoon aggregated into a more significant mass, and their outer covering broke down around 40°C. Severe dichloromethane evaporation caused the emulsion droplet to become unstable at higher temperatures. Because of the increased aggregates made by the connecting activity of polyvinyl alcohol, which produced the particles during the washing procedure, the recovery was quickly reduced at lower temperatures.

Figure 3: shows the levofloxacin floating microballoons in the following views: (a) microscopic, (b) normal, (c) floating, (d) emulsion development, and (e) SEM picture of the floating microballoons.

Formulation Yield and Encapsulation Efficiency

All formulations' encapsulation efficiency and yield were satisfactory, underscoring the efficacy of the emulsion solvent diffusion method employed in their manufacture. Between 50.2% and 94.2% was the range of encapsulation efficiency for each formulation; the best formulation, F9, achieved an impressive 90.2% encapsulation efficiency. Encapsulation efficiency also exhibited significant variability, with F2 achieving an efficiency of 50.3%. ANOVA indicated that these differences were statistically significant ($p < 0.05$), suggesting that formulation parameters greatly influence yield and encapsulation efficiency. High encapsulation efficiency is essential to best-formulated levofloxacin therapeutic potential. We analyzed statistical results to show if formulation types differed significantly in their drug loading rates and drug release patterns. This is because it guarantees that a sufficient amount of the drug is loaded into the microballoons, enabling prolonged and efficient drug release while treating stomach ulcers [21].

Particle Size and Morphology

As given in Table 2, the microballoons particle sizes varied from 79.8 µm to 152.14 µm, with the optimized formulation F9 showing an average size of 81.2 µm. Our statistical results show that raising polymer concentration led to the apparent size growth of particles ($p < 0.05$). Our results match research that shows that when polymer concentrations become thicker, they make particles bigger because emulsification shearing weakens. The spherical form of the microballoons, a crucial component that contributes to their buoyancy and controlled drug release properties, was validated by scanning electron microscopy (SEM). The microballoons surface texture and internal spaces demonstrate their ability to release drugs over an extended period. Smaller particle sizes, such as those found in F9, are beneficial because they improve localized delivery by improving gastric retention and enhancing contact with the gastric mucosa [22]. Here, we observed that the particle size of levofloxacin floating microballoons decreased as the system's stirring speed increased.

Buoyancy Studies

Because buoyancy directly impacts the duration of time the drugs remain in the stomach, floating is a crucial consideration for floating drug delivery. All formulations with floating percentages ranging from 72% to 86% over eight hours demonstrated outstanding buoyancy (as seen in Figure 4). The floating ability of the formulation depended on the polymer amount and the method used to make them. ANOVA results show that these changes produce statistically significant outcomes ($p < 0.05$), which prove that different formulations affect buoyancy properties. Interestingly, formulation F9 demonstrated 83% buoyancy in gastric simulated fluid (pH 1.2), indicating that it can function as a viable gastroretentive system. Levofloxacin may be continuously released at the site of infection thanks to prolonged buoyancy, which keeps the microballoons buoyant in the stomach [23, 24]. This is essential for maximizing the effectiveness of treatment against *H. pylori*.

***In-Vitro* Drug Release**

To ensure that the conditions with the stomach were duplicated, the i*n-vitro* release of drug experiments (given in Table 2) were carried out in simulated gastric fluid (pH 1.2) [25,26]. Formulation F9 ability to deliver a prolonged therapeutic effect was demonstrated by its cumulative drug release of 91.2% over eight hours. The statistical tests revealed important differences

between drug release patterns from our formulations ($p < 0.05$). More polymers in the matrix block drug release because they create longer pathways for the drug molecules to move through [27,28]. The drug delivery system released levofloxacin in two distinct phases: an initial high dose followed by a steady release. The fast drug release at the microballoon surface results from levofloxacin molecules moving through concentration gradients and weak bonds with the polymer material. The first part of treatment gives patients the right amount of drug to fight *H. pylori* infections. The Eudragit RS-100 and ethyl cellulose matrix dissolve slowly to control levofloxacin release and maintain effective drug delivery throughout treatment.

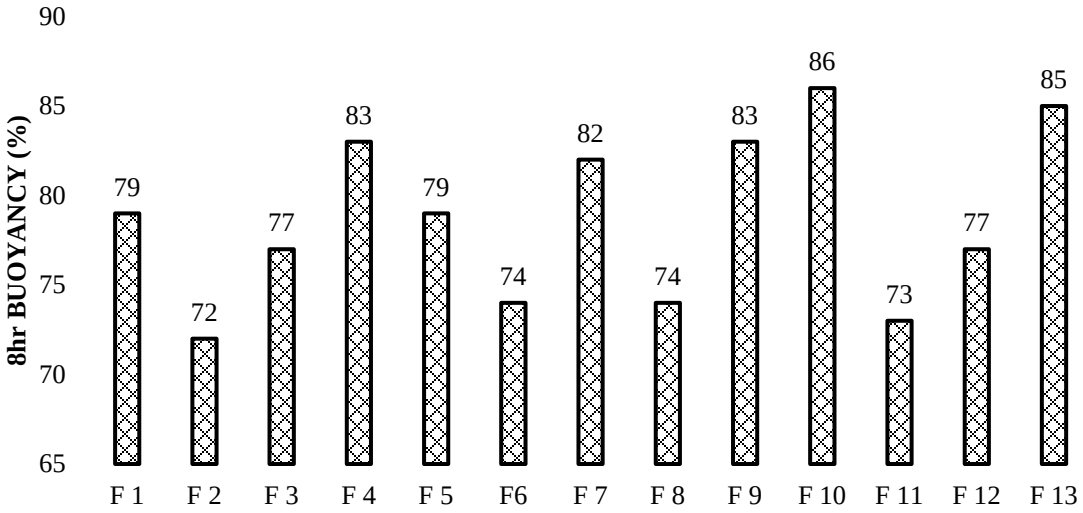

Figure 4: Buoyancy Studies of levofloxacin floating microballoons

Table 2: Characterisation of levofloxacin-loaded floating microballoons biomaterials.

Formulation	Yield (%)	Encapsulation Efficiency(%)	Particle Size (µm)	8hrs Buoyancy (%)	Cumulative Drug Release (%)-8hrs SGF (pH 1.2)
F 1	78.45	84.2±1.40	82.8±0.06	79±1.34	81.4 ± 1.40
F 2	80.27	50.3±0.40	107.8±1.40	72±1.08	63.2 ± 1.41
F 3	81.46	74.2±1.50	79.8±1.42	77±1.31	59.2 ± 0.30
F 4	77.45	62.4±1.09	118.15±1.04	83±1.03	79.5 ± 1.31
F 5	76.47	80.9±0.43	151.45±1.70	79±0.04	97.2 ± 1.10
F6	82.49	71.4±0.90	152	74±1.13	92
F 7	73	89.1±0.41	149.45±1.40	82±0.54	95
F 8	76	69.3±0.16	109.46±0.41	74±1.14	94.4 ± 1.60
F 9	78	90.2±0.30	81.2±0.91	83±0.60	91.2 ± 1.50
F 10	75	59.5±1.20	134.25±0.40	86±1.10	90.4 ± 0.16
F 11	49	75.2±1.80	94.19±1.50	73±1.09	81.9 ± 0.40
F 12	53	81.1±1.70	83.46±0.40	77±0.04	84.1 ± 0.26
F 13	59	77.2±0.40	94.49±1.80	85±1.14	79.3 ± 1.50

n=3; values are expressed in mean ± SD (standard deviation)

CONCLUSION

Using the emulsion solvent diffusion approach, the current study successfully developed levofloxacin-loaded floating microballoons by optimising critical formulation factors like polymer ratios, drug-polymer concentrations, PVA levels, stirring speeds, and processing temperatures. Among the 13 formulations evaluated, F9 emerged as the most promising, demonstrating high drug entrapment effectiveness of 90.2±3.4%, confirmed spherical morphology, and an ideal particle size of 81.2±2.9 µm. F9 sustained release capability was

shown in *in vitro* tests, wherein it demonstrated superior buoyancy in SGF (pH 1.2 level) and a cumulative drug release of 91.2 ± 3.5% over an 8-hours.

These results demonstrate the potential of floating microballoons filled with a complex heterocyclic structure levofloxacin pH-sensitive Eudragit RS-100 and Ethyl Cellulose as a novel gastroretentive delivery system that allows for targeted and prolonged administration of the drug to the gastric mucosa. This newly developed approach has prolonged therapeutic activity and may increase eradication rates, making it a better option for treating *H. pylori* infections than traditional treatments. The developed microballoons for levofloxacin offer significant advantages, particularly for patients with resistance to first-line therapies, by providing enhanced gastric retention and targeted delivery to combat *H. pylori* infections effectively. The development of this floating biomaterial enhances levofloxacin's therapeutic efficacy and safety profile while also advancing treatment approaches for gastrointestinal problems, addressing challenges such as the need for in vivo validation and scalability, and highlighting future directions for clinical trials and patient compliance studies.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Manivasakam Prakash designed the study, conducted experiments, and drafted the manuscript. Venkateswaramurthy Nallasamy supervised and validated the results and refined the writing. Senthil Venkatachalam provided resources and technical support and helped shape the final manuscript. All authors approved the final version.

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