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Development and Characterization of Stomach-Specific Gastro-Retentive Drug Delivery of Levofloxacin Hemihydrate for *Helicobacter Pylori* Eradication

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Helicobacter pylori (*H. pylori*) is a significant gastric pathogen, often linked to chronic gastritis, peptic ulcers, and various gastric cancers. Current first-line therapies, including proton pump inhibitors and antibiotics, such as clarithromycin and amoxicillin, have variable eradication success, with failure rates ranging from 5% to 50%. A major challenge in effectively treating *H. pylori* infections is ensuring adequate antibiotic concentration at the infection site for sustained periods. This study aims to develop a gastro-retentive drug-delivery system (GRDDS) utilizing novel mucoadhesive alginate beads containing levofloxacin hemihydrate to enhance therapeutic efficacy. Sodium alginate and carbopol 974P are employed to create beads through ionotropic gelation, facilitating prolonged drug release in the gastric mucosal environment. A standard calibration curve is developed for levofloxacin hemihydrate in 0.1 N HCl, to ensure accurate drug measurement. The formulations' efficacy in prolonging drug retention in the stomach aims to improve *H. pylori* eradication rates. The results are expected to demonstrate that sustained release of levofloxacin *via* GRDDS increases significantly local drug concentration at the infection site, offering a promising approach to enhance the treatment outcomes for *H. pylori* infections. This innovative delivery system not only addresses the limitations of current treatments, but also stands to impact clinical practices in managing gastric infections effectively.

Helicobacter pylori (*H. pylori*) — це істотний шлунковий патоген, часто

пов'язаний із хронічним гастритом, виразковою хворобою та різними видами раку шлунка. Сучасні методи лікування першої лінії, включаючи інгібітори протонної помпи й антибіотики, такі як кларитроміцин та амоксицилін, мають різний успіх усунення з рівнем невдачі від 5% до 50%. Основною проблемою ефективного лікування інфекцій *H. pylori* є забезпечення адекватної концентрації антибіотика у місці інфекції впродовж тривалого часу. Метою цього дослідження є розробка шлунковоутримувальної системи доставки ліків (GRDDS) з використанням нових мукоадгезивних альгінатних кульок, що містять левофлоксацину гемігідрат, для підвищення терапевтичної ефективности. Альгінат Натрію та карбопол 974P було використано для створення кульок шляхом йонотропного ґелеутворення, що сприяє тривалому вивільненню ліків у слизовій оболонці шлунка. Було розроблено стандартну калібрувальну криву для левофлоксацину гемігідрату в 0,1 N HCl для забезпечення точного вимірювання препарату. Ефективність препарату в подовженні затримки ліків у шлунку спрямовано на поліпшення показників знищення *H. pylori*. Очікується, що результати продемонструють, що пролонговане вивільнення левофлоксацину через GRDDS значно підвищує локальну концентрацію препарату в місці інфекції, пропонуючи перспективний підхід щодо поліпшення результатів лікування інфекцій *H. pylori*. Ця інноваційна система доставки не лише усуває обмеження сучасних методів лікування, але й може вплинути на клінічну практику ефективного лікування шлункових інфекцій.

Key words: *Helicobacter pylori*, gastro-retentive drug delivery, levofloxacin hemihydrate, mucoadhesive alginate beads, peptic ulcers, antibiotic efficacy.

Ключові слова: *Helicobacter pylori*, шлунковоутримувальна доставка ліків, левофлоксацину гемігідрат, мукоадгезивні альгінатні кульки, пептичні виразки, ефективність антибіотиків.

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1. INTRODUCTION

Helicobacter pylori (H. pylori) is the predominant gram-negative microaerophilic gastric bacterium that causes stomach ulcers [1–3]. It is primarily found in the mucus layer that covers the gastric epithelium and is responsible for less than 20% of stomach infections. It can be found in up to 80% of central host populations. The infection typically results in chronic gastritis and peptic ulcer disease, which can last a lifetime. *Helicobacter pylori* infection has been linked to stomach adenocarcinoma, peptic ulcer disease, and gastric *B*-cell lymphoid tissue associated with mucosa (MALT) lymphoma [3–5]. Additionally, *H. pylori* is estimated to be responsible for 65–80% of stomach cancers and is projected to rank among the tenth leading causes of death worldwide [5, 7]. Based on scientific evi-

dence, *H. pylori* is a group I carcinogen and the known cause of stomach malignancies in humans, according to the International Agency for Research on Cancer (IARC, USA). The American College of Gastroenterology (ACG) Guidelines, the Asia–Pacific Consensus Guidelines (APC), the Maastricht/Florence Consensus Reports, and other sources all recommend proton pump inhibitors (PPI), clarithromycin, and amoxicillin as routine first-line therapies [8–10].

If this empirical first-line treatment fails, bismuth quadruple therapy or triple therapy with levofloxacin is recommended (a PPI plus levofloxacin and amoxicillin). If bismuth quadruple therapy does not work, levofloxacin triple therapy should be used [11–13].

The Maastricht guidelines' current threshold for an acceptable level of eradication is based on intention to treat (ITT) analysis; unfortunately, these strategies have not achieved maximum eradication rates [14, 15]. Despite this, overall failure rates have been observed to vary from 5–50% and no regimen has achieved a 100% eradication rate. Lack of a sufficient concentration of antibiotics that localizes to the infection site for adequate time duration is the main obstacle to the effective eradication of *H. pylori* [16, 17]. The oral drug-delivery systems, which are now on the market, are not made to remain in the stomach long enough to provide antibiotics with an effective extended-release. Therefore, in addition to the existing conventional systems, we needed a new delivery system for the continuous administration of drugs on the gastric mucosal surface [18–20].

Because gastro-retentive drug delivery offers a longer stomach residence period and so enhances the distribution of antibiotics to the mucus layer, they may prove beneficial in this situation on a wide scale [20, 21]. Due to extended exposure, *in vivo* investigations revealed a greater eradication of *H. pylori* following the administration of amoxicillin and clarithromycin *via* GRDDS in the stomach [22].

In this work, we use a combination of synthetic and natural polymers to create and assess novel mucoadhesive alginate beads containing levofloxacin hemihydrate. Developing a gastro-protective medication delivery method that guarantees sustained drug release and improves *H. pylori* eradication is the aim. This novel strategy targets the gastric mucosal surface to increase levofloxacin therapeutic efficacy against *H. pylori* infections.

2. EXPERIMENTAL METHODS

Goldsun Pharmaceuticals Limited in Mumbai provided the levofloxacin hemihydrate used in this investigation. Mumbai-based Macleods Pharmaceuticals Limited was the supplier of carbopol 974P.

Nice Chemical in Bangalore provided the calcium chloride and sodium alginate. We purchased periodic acid, iodomethane, N-methyl pyrrolidone, basic fuchsine, and mucin (type II) from Aldrich Co. The remaining reagents were all analytical grades and were used exactly as supplied.

2.1. Levofloxacin Hemihydrate Standard Curve in 0.1 N HCl

Levofloxacin hemihydrate (100 μg/mL) was made into a stock solution in 0.1 N HCl. This procedure was carried out three days in a row, with measurements taken in repeat each day to assess intra- and interday variations.

To create standard solutions in the 1–10 μg/mL range, the stock solution was further diluted.

An ultraviolet/visible Shimadzu spectrophotometer (Tokyo, Japan, Model 2100) was used to measure absorbance spectrophotometrically at 293 nm. A calibration curve was constructed, using averaged values derived from nine independent measurements. The regression equation produced from the calibration curve was used to calculate the concentration of the dissolved drugs.

2.2. Formation of Sodium Alginate–Carbopol 974P Beads

The ionotropic-gelation method was used to create levofloxacin hemihydrate beads. Ten millilitres of filtered water were used as a vehicle to create sodium alginate solutions with three distinct concentrations (of 1%, 2%, and 3% w/v) (Table 1). A sigma blade mixer was used to add carbopol 974P (of 1% w/v) to the alginate solution and swirl it for five minutes in order to prevent aggregation. After that, powdered levofloxacin hemihydrate was added to the mixture and agitated for five more minutes to ensure equitable dispersion. Using a syringe (number 20), the resultant dispersion was manually injected dropwise into calcium chloride solutions of varying concentrations (of 2%, 3%, and 4% w/v). Using a syringe (number 20), the resultant dispersion was manually injected dropwise into calcium chloride solutions of varying concentrations (of 2%, 3%, and 4% w/v).

2.3. Evaluation of Mucoadhesive Beads

The percentage yield of beads. A digital balance was used to weigh precisely the dried beads after they were gathered.

The following formula was used to determine the prepared beads' yield [%]:

TABLE 1. Composition of calcium alginate beads loaded with levofloxacin hemihydrate and made using the ion-gelation technique.

Formulation code	Levofloxacin hemihydrate, % w/v	Sodium alginate, % w/v	Calcium chloride, % w/v	Carbopol 1974P, % w/v
LMB1	2.5	1	2	1
LMB2	2.5	2	2	1
LMB3	2.5	3	2	1
LMB4	2.5	1	3	1
LMB5	2.5	2	3	1
LMB6	2.5	3	3	1
LMB7	2.5	1	4	1
LMB8	2.5	2	4	1
LMB9	2.5	3	4	1

$$\text{Yield percentage of beads} = \frac{\text{Weight of the collected beads}}{\text{Total drug and polymer weight}} \cdot 100\% .$$

Drug content and effectiveness of encapsulation. The extraction procedure was used to determine the drug content of the beads. A glass mortar and pestle was used to grind five milligrams of meticulously weighed mucoadhesive beads into a powder. After that, the crushed beads were put in one hundred millilitres of 0.1 N HCl (pH 1.2) and agitated with a magnetic stirrer for two hours at 37 ± 0.5°C. High-performance liquid chromatography (HPLC) was used to assess the drug content after the samples had been filtered to produce a clear solution [25, 26]. The following formula is utilized to determine the drug content and encapsulation efficiency:

$$\text{Efficiency of encapsulation (EE, [\%])} = (W_t/W_i) \cdot 100\% .$$

Particle size analysis. A laser-based particle size analyser (Particle Sizing Systems Inc., U.S.A., Model 780 AccuSizer) was used to measure the particle sizes produced by the drugs, excipients, and beads. After being dispersed in *n*-hexane, the particles were me-

chanically suspended, during the analysis using magnetic stirring [27].

Shape and surface characterization. Using a scanning electron microscope (SEM) (Model S-450, Hitachi High-Technologies), both the qualities of the beads' surface and shape were investigated. To prepare the samples, double-sided tape was used to place the beads onto the SEM holder. A 200 nm thick layer of gold was then applied under reduced pressure (of 0.001 Torr) before to photography [28].

***In vitro* evaluation of mucoadhesiveness.** A colorimetric method that employed periodic acid/Schiff (PAS) to measure the concentration of free mucin was used to evaluate the amount of mucin that was adsorbed within the levofloxacin mucoadhesive beads and how that affected the beads' ability to adhere to mucosa. Schiff reagent (20 mL of 1 M HCl and 100 mL of one percent basic fuchsine in an aqueous solution) and periodic acid reagent (10 µL of 50% periodic acid solution in 7 mL of 7% acetic acid solution) were prepared. Schiff reagent was used to treat standard mucin solutions (0.125, 0.25, 0.375, and 0.5 mg/mL), following an incubation period at 37°C. Absorbance at 555 nm was measured using a UV spectrophotometer. The mucin content was determined, using the standard calibration curve.

Adsorption of mucin on alginate beads. Aqueous solutions of mucin were made in 0.05, 0.1, 0.2, 0.5, and 0.025 mg/mL among different amounts. These mucin solutions were then combined with 20 mg of levofloxacin hemihydrate mucoadhesive beads shaken and vortexed at room temperature. After centrifuging the solutions for two minutes at 4000 rpm, the amount of free mucin in the supernatant was measured. The Freundlich's and Langmuir's equations were used to assess the data and describe the adsorption isotherms.

Compatibility studies. An FT-IR spectrophotometer (Model 84005, Shimadzu) equipped with the potassium-bromate disk method was used to produce FT-IR spectra of blank beads, levofloxacin hemihydrate mucoadhesive beads, and drug. Within a scanning range of 450 to 4000 cm, the pure drug, formulations, and blank beads were thermally analysed using a Universal V4.2E TA instrument DSC. Over a temperature range of 10–300°C, a 40 µL aluminium pan with 3 mg of samples was sealed with a perforated cover and heated at a rate of 10°C/min with a nitrogen purge of 50 mL/min [31].

***In vitro* dissolution studies.** Using a USP dissolve test apparatus 2 (paddle) at 100 rpm, the mucoadhesive beads' *in vitro* drug release was investigated (Disso 2000, Labindia). At 37 ± 0.2°C, beads were submerged in 0.1 N HCl (pH 1.2) in 900 mL. The absorbance was measured spectrophotometrically at 293 nm after samples were obtained at predefined intervals, replaced with new dissolving medium, and filtered through a 0.45 µm syringe [32].

Drug release kinetics. A number of models, such as the Peppas's, Higuchi's, zero-order, and first-order ones, were employed to determine the kinetics and mechanism of drug release. Values for the regression coefficient (R_2) were computed and examined [32].
Accelerated stability testing. The optimized formulation was kept for six months at stability chamber with 40 ± 2°C and 75 ± 5% relative humidity (Model Remi CHM-10 S®, REMI Laboratory Instruments) in accordance with ICH Q1A (R_2). *In vitro* drug release, mucoadhesiveness, and drug content were assessed at 30 days, 90 days, and 180 days. As controls, zero-time samples were employed.
Statistical analysis. A one-way ANOVA with GraphPad Prism software was used to evaluate the beads' manufacturing yield, encapsulation efficiency, particle size, *in vitro* release assays, and *in vivo* research. A significance criterion of $p < 0.05$ was determined.

3. RESULTS AND DISCUSSION

The ion-gelation process was effectively used to create levofloxacin-hemihydrate mucoadhesive beads. The results confirmed the long-held belief that, when the mucoadhesive polymer is distributed, mucoadhesive systems adhere to mucosal membranes more strongly [92]. Mucoadhesive polymers were added to the microspheres to accomplish this that improved mucoadhesion. Additionally, a levofloxacin hemihydrate standard curve was created at 37°C in 0.1 N HCl (pH 1.2). The results confirmed the validity of the selected method for levofloxacin hemihydrate quantification, showing a linear relationship between concentration and absorbance within the range of 0.1 μg/mL to 10 μg/mL ($R_2 = 0.9961$) (Fig. 1).
Percentage yield of microspheres. Levofloxacin hemihydrate-loaded microspheres had a yield percentage ranging from 33.18 ± 1.37% to

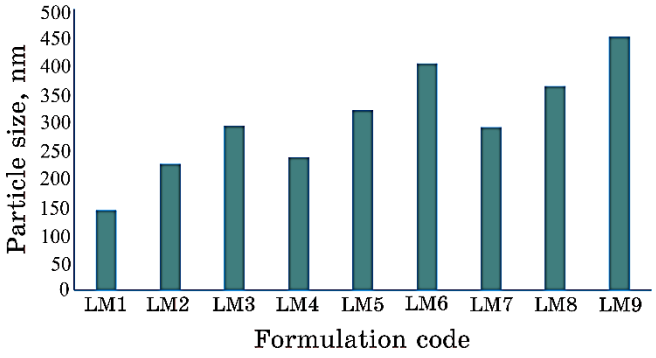

Fig. 1. Particle-sizes' distribution of levofloxacin hemihydrate-loaded mucoadhesive bead.

88.16 ± 0.82%. Higher calcium chloride and sodium alginate concentrations were associated with a substantial increase in yield ($P < 0.05$). This pattern implies that greater concentrations of polymers offer enough material to wrap completely the drug particles, increasing yield.

Drug content and encapsulation efficiency. The concentration of the polymer had a substantial impact on the microspheres' drug content and encapsulation effectiveness. The range of encapsulation efficiency was of 52.31 ± 0.23% to 79.55 ± 0.55%, while the range of drug content was of 20.58 ± 0.82% to 29.90 ± 0.61%. Better drug loading and encapsulation efficiency were the outcomes of higher polymer concentrations ($P < 0.05$). This is explained by the polymer chains-enhanced availability of active calcium binding sites, which promotes stronger cross-linking and drug entrapment.

Particle size analysis and shape characterization. The production of beads was significantly influenced by the viscosity of the polymer solution. Higher concentrations of calcium chloride (2% w/v) and sodium alginate (3% w/v) produced more spherical beads, while lower amounts (1% w/v) caused flake formation. According to Fig. 1, the microspheres' mean diameters varied from 141.2 ± 0.78 μm to 451.04 ± 0.90 μm. Greater viscosity and more thorough cross-linking were probably the causes of the bigger bead sizes seen with increasing polymer content (Figs. 2 and 3).

***In vitro* evaluation of mucoadhesiveness.** With values ranging from 46.52 ± 0.57% to 84.51 ± 0.74%, the microspheres' mucoadhesive qualities were noteworthy (Fig. 4). Mucoadhesion was enhanced by higher calcium-chloride and sodium-alginate concentrations, presumably, as a result of stronger polymer–mucus interactions and increased viscosity. Both targeted drug administration to *H. pylori* and extended stomach retention benefit from this improved mucoadhesion.

Compatibility studies. Levofloxacin hemihydrate and the excipients did not interact significantly, according to FT-IR spectra. The drug remained intact within the polymer matrix, as evidenced by the presence of characteristic peaks, in both pure drug and drug-loaded microspheres. The endothermic peak of pure levofloxacin hemihydrate was detected by DSC at 237.3°C, which agrees with values reported in the literature. The drugs' molecular dispersion within the mucoadhesive beads was confirmed by the modest changes in peak shape observed in all formulations, which suggested no substantial drug–polymer interactions.

***In vitro* dissolution studies.** An initial rapid release was followed by a steadier, persistent release, according to dissolution experiments, which showed a biphasic release pattern. Higher polymer concentrations improved the gel-layers' density and the diffusional paths'

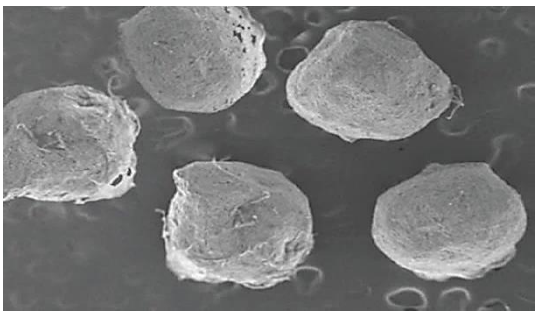

Fig. 2. SEM photograph of formulation LM5.

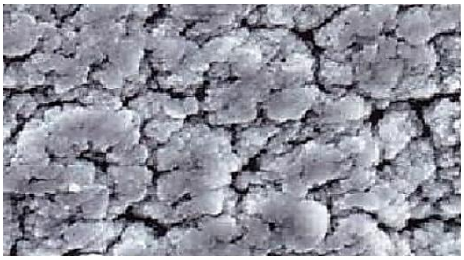

Fig. 3. SEM photograph of formulation LM5 (surface view).

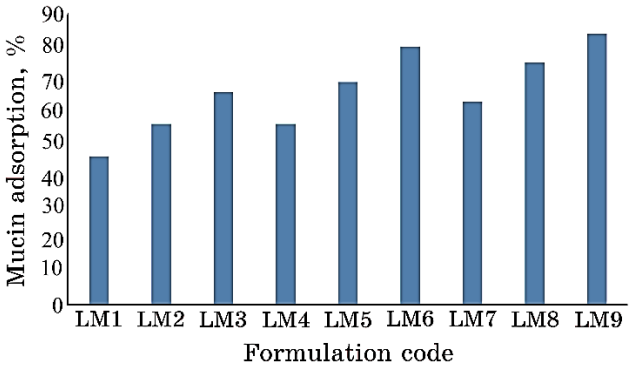

Fig. 4. Mucoadsivenes of levofloxacin hemihydrate loaded.

length, making this pattern easier to manage. Because of greater cross-linking and gel formation, formulations with higher calcium-chloride and sodium-alginate concentrations showed slower drug-release rates (Table 2).

Kinetics of drug release. With high linearity in zero-order kinetics ($R^2 = 0.9842–0.9987$) and a non-Fickian diffusion mechanism, as suggested by the Korsmeyer–Peppas model ($n = 0.5533–0.6541$), the

TABLE 2. Levofloxacin hemihydrate-loaded mucoadhesive beads' *in vitro* release kinetic data.

F Code	Zero-order plot K_0	Zero-order R^2	First-order plot K_1	First-order R^2	Higuchi's R^2	Korsmeyer–Peppas n	Korsmeyer–Peppas R^2
LMB1	18.6210	0.9905	–0.5912	0.8647	0.9939	—**	—**
LMB2	16.1983	0.9962	–0.5275	0.7221	0.9926	—**	—**
LMB3	13.0746	0.9931	–0.1914	0.9103	0.9936	0.6214	0.9987
LMB4	17.0119	0.9958	–0.6890	0.7625	0.9917	—**	—**
LMB5	14.1295	0.9945	–0.3927	0.7206	0.9914	0.5736	0.9989
LMB6	13.5173	0.9976	–0.3109	0.7243	0.9974	0.6478	0.9935
LMB7	19.2157	0.9902	–0.7054	0.7693	0.9943	—**	—**
LMB8	11.6257	0.9829	–0.1589	0.9705	0.9963	0.5498	0.9956
LMB9	09.9124	0.9924	–0.1074	0.9720	0.9945	0.5427	0.9932

Notes: *There were insufficient data points from rapid-release profiles to use kinetics; **seventy percent of the data points could not be explained by the Korsmeyer–Peppas equation. Legend: zero-order rate constant, or K_0; the rate constant of the first order is K_1; regression coefficient, or R^2; the Korsmeyer–Peppas model diffusion exponent is denoted by n.

drug release from the microspheres was by Higuchi's model (Table 2). This implies that the formulation is appropriate for sustained release applications, since drug release is regulated by both diffusion and erosion mechanisms.

Selection of best formulation. Formulation LMB5 was chosen as the optimum formulation due to its ideal balance of stability, drug release, and mucoadhesion. It contains 2% w/v sodium alginate, 1% w/v carbopol 974P, and 3% w/v calcium chloride. Accelerated stability testing demonstrated its appropriateness for extended storage, which verified that LMB5 retained its drug content, mucoadhesiveness, and release profile over six months (Table 3, Fig. 5).

4. CONCLUSION

This work developed and assessed levofloxacin-hemihydrate mucoadhesive alginate beads. The improved formulation displayed excellent yield, encapsulation efficiency, mucoadhesion, and controlled

TABLE 3. Levofloxacin hemihydrate-loaded mucoadhesive beads' accelerated stability results (formulation LMB5), examined in accordance with ICH Q1A (R^2).

No.	Duration, days	Strength of mucoadhesion (mean ± SE) (n = 3)	Mean ± SD for drug content, % (n = 3)	Mean ± SD for drug release, % (n = 3)
1	Zero days before storage	69.45 ± 0.53	25.78 ± 0.46	99.76 ± 0.29
2	30 days (once stored)	68.85 ± 0.45	25.37 ± 0.84	99.36 ± 0.26
3	90 days (once stored)	67.82 ± 0.88	25.11 ± 0.55	99.26 ± 0.13
4	180 days (once stored)	66.98 ± 0.61	24.95 ± 0.43	98.79 ± 0.59

Note: *Storage (n = 3) at 40°C and 75% RH.

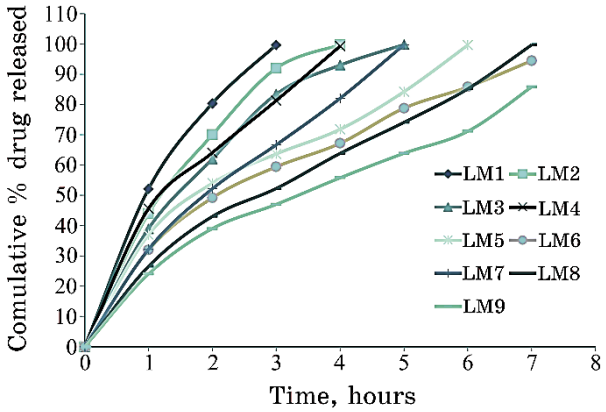

Fig. 5. Drug-release pattern of various formulations of levofloxacin hemihydrate.

drug release, suggesting that it could be a viable option for targeted drug administration and efficient stomach retention. This prolonged retention increases the amount of levofloxacin used, which may lead to better treatment results for *H. pylori* infection.

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