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Research Article

Development of Levodon Dosage Form with Controlled Release of the Active Substance

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ABSTRACT

Antibacterial therapy remains a cornerstone of modern medicine due to the persistent prevalence of infectious diseases and the growing challenge of antimicrobial resistance. This study reports the comprehensive development of *Levodon*, a novel effervescent tablet formulation based on a polymeric complex of levofloxacin with polyvinylpyrrolidone (PVP). The formulation was designed to provide controlled release of the active pharmaceutical ingredient, thereby enhancing the therapeutic efficacy of antibacterial treatment. Preclinical in vivo investigations demonstrated significant dose-dependent antibacterial activity of the developed complex. The formulation and manufacturing process of high-dose effervescent tablets (1110 mg) were successfully optimized. Quality evaluation confirmed that the finished dosage form complied with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan for key pharmaceutical parameters, including identity, disintegration, hardness, and assay. In vitro biopharmaceutical studies revealed a prolonged release profile of levofloxacin across media with varying pH conditions, indicating sustained drug release characteristics. Toxicological assessment further demonstrated that the formulation possesses low acute toxicity (LD_{50} > 5000 mg/kg) and weak cumulative properties. These findings suggest that *Levodon* is a promising controlled-release antibacterial dosage form with potential therapeutic advantages in the management of infectious diseases.

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1. INTRODUCTION

The continuous development of pharmaceutical technologies plays a crucial role in improving the efficacy, safety, and quality of medicinal products. Advances in formulation science, including the use of innovative excipients and modern dosage forms, have enabled the optimization of physicochemical and biopharmaceutical properties of active pharmaceutical ingredients. In particular, significant attention has been devoted to the design of dosage forms that enhance solubility, stability, and bioavailability, thereby improving therapeutic outcomes. At the same time, antibacterial agents remain essential in clinical practice due to the widespread prevalence of infectious diseases and the growing threat of antimicrobial resistance (Battu et al., 2025; Ramirez et al., 2024; Salihu et al., 2024; Kadir et al., 2022; Azhar and Salleh, 2020; Salleh et al., 2015).

Antibacterial therapy remains a cornerstone of modern medicine due to the persistent burden of infectious diseases and the continuous increase in antimicrobial resistance worldwide (Karnwal et al., 2025; Reza et al., 2025). Among broad-spectrum antibacterial agents, fluoroquinolones play a significant role, with levofloxacin being one of the most widely prescribed representatives of this class. Despite its pronounced antimicrobial activity, the clinical effectiveness of levofloxacin is largely governed by its physicochemical and biopharmaceutical properties, including solubility, stability, and the drug release profile from the dosage form. Limited aqueous solubility and rapid release kinetics may result in fluctuations in plasma drug concentrations, which can compromise therapeutic efficacy and increase the likelihood of adverse effects (Awofisayo et al., 2025; Izadi et al., 2019; Koeppe et al., 2011).

Levofloxacin is a rapidly and almost completely absorbed drug, with an oral bioavailability approaching 100%. Following a single oral dose of 500 mg, the maximum plasma concentration (Cmax) reaches 5.2-6.9 μg/mL, the time to reach Cmax (Tmax) is approximately 1.3 h, and the elimination half-life (T1/2) ranges from 6 to 8 h. Despite these favorable pharmacokinetic properties, conventional immediate-release levofloxacin tablets have several limitations. First, the rapid achievement of peak plasma concentration (Cmax within 1-2 h) is associated with dose-dependent adverse effects, including nausea, dizziness, and gastrointestinal irritation (Rodvold and Neuhauser, 2001). Second, the large tablet size may reduce compliance in patients with dysphagia, elderly individuals, and pediatric populations. Third, the relatively short half-life (6-8 h) necessitates multiple daily dosing for certain indications, which may affect adherence to therapy. To address these limitations, we developed a novel prolonged-release effervescent formulation of levofloxacin (*Levodon*). The effervescent matrix provides rapid disintegration and improved ease of swallowing, particularly for patients with swallowing difficulties, while enabling prolonged drug release that may reduce peak plasma concentrations without compromising therapeutic efficacy. To our knowledge, no effervescent prolonged-release levofloxacin formulation has been previously reported, and the combination of effervescent technology with a PVP-based polymeric complex represents a novel approach in fluoroquinolone formulation design.

As shown in our *in vitro* release study, *Levodon* effervescent tablets release levofloxacin over 48 h, suggesting a prolonged absorption profile compared to conventional tablets. Owing to these pharmacokinetic properties, levofloxacin demonstrates extensive tissue distribution, achieving therapeutically relevant concentrations in the lungs, bronchial mucosa, sputum, genitourinary organs, polymorphonuclear leukocytes, and alveolar macrophages. The recommended duration of therapy varies depending on the indication and typically includes 10-14 days for sinusitis, 7-10 days for acute exacerbations of chronic bronchitis, 7-14 days for community-acquired pneumonia, 3 days for uncomplicated urinary tract infections, 28 days for prostatitis, 7-10 days for complicated urinary tract infections including pyelonephritis, and 7-14 days for skin and soft tissue infections (Croom and Goa,2003, Sadahira et.al., 2017).

In recent years, increasing attention has been directed towards the development of polymer-based drug delivery systems (Lu et al., 2024; Sung and Kim, 2020). The use of water-soluble polymers enables modification of the physicochemical and biopharmaceutical properties of active pharmaceutical ingredients without altering their chemical structure, improving technological characteristics and enhancing dissolution and bioavailability (Biswas et al., 2025; Kadajji and Betageri, 2011). Among the most promising polymers, polyvinylpyrrolidone (PVP) is widely employed in pharmaceutical technology due to its biocompatibility, solubility, and ability to form stable complexes with active substances (Luo et al., 2021; Franco and De Marco, 2020; Kurakula and Rao, 2020).

The selection of PVP as the polymeric carrier for levofloxacin was based on several considerations compared to other commonly used pharmaceutical polymers. Unlike polyethylene glycol (PEG), which can accelerate drug release but may cause osmotic diarrhea at high doses (Li et al., 2018), PVP provides better control over drug release kinetics through its high glass transition temperature and hydrogen-bonding capacity (Franco and De Marco, 2020). Compared to hydroxypropyl methylcellulose (HPMC), which requires higher polymer concentrations to achieve prolonged release and may result in

tablet swelling, PVP offers superior solubility in water and alcohol, facilitating effervescent tablet formulation (Kadajji and Betageri, 2011). Polyvinyl alcohol (PVA), while biocompatible, exhibits slower dissolution rates that could delay disintegration of effervescent tablets. Chitosan, although mucoadhesive, has pH-dependent solubility, limiting its use in formulations intended for broad pH range release. Thus, PVP was selected for its unique combination of high aqueous solubility, excellent complexation ability with fluoroquinolones, favorable safety profile, and compatibility with effervescent tablet technology (Kurakula and Rao, 2020).

At the Institute of Bioorganic Chemistry named after Academician A.S. Sadykov of the Academy of Sciences of the Republic of Uzbekistan, the drug *Levodon* was developed as a modified form of levofloxacin in complex with the synthetic polymer polyvinylpyrrolidone (Abrekova et al., 2022). Given the high demand for antibacterial agents, the development of solid dosage forms of new, highly effective and low-toxicity drugs with a broad spectrum of antimicrobial activity remains highly relevant. Recent advances in pharmaceutical technologies, including modern drug delivery systems and the development of biologically active compounds with antibacterial properties, have significantly contributed to improving the effectiveness of pharmaceutical formulations. The clinical significance of *Levodon* lies in its potential to improve patient compliance through its palatable effervescent formulation and to reduce systemic toxicity by avoiding high Cmax values, while maintaining the broad antimicrobial spectrum of levofloxacin. This is particularly relevant for prolonged treatment courses, such as those required for prostatitis (28 days) and complicated urinary tract infections. Therefore, the aim of this study was to develop a solid dosage form of the antibacterial agent *Levodon* and to evaluate its quality, as well as its biopharmaceutical and pharmacological properties.

2. METHODOLOGY

2.1. Evaluation of Antibacterial Activity and Physicochemical Properties

All animal manipulations were performed in accordance with Directive 2010/63/EU (Hartung, 2010). The antibacterial efficacy of *Levodon* substance (polymeric complex of levofloxacin with PVP) was compared with levofloxacin reference substance (Topharman Shanghai Co., Ltd., China). Animals and infection model involved fifty male outbred white rats (180–200 g, 3 months old) maintained under standard vivarium conditions at 22 ± 2°C and 65 ± 10% humidity with free access to food and water, while experimental infectious peritonitis was induced by intraperitoneal administration of 3 mL of a polymicrobial suspension containing Staphylococcus aureus and Escherichia coli in a 1:1 ratio prepared in physiological saline. For the treatment protocol, rats received oral administration of Levodon at doses of 48, 95, or 190 mg/kg, 24 h after infection induction. The reference group was treated with levofloxacin at 95 mg/kg, whereas the control group received no treatment.

For microbiological assessment, the bacterial inoculum used for infection consisted of a polymicrobial suspension containing approximately 1-2 × 10^8 CFU/mL of *Staphylococcus aureus* and *Escherichia coli* in a 1:1 ratio, as determined by turbidimetry. Exudate samples (200 µL) were aseptically collected before treatment (24 h post-infection) and 7 h after treatment. Serial tenfold dilutions were prepared, and 100 µL aliquots from each dilution were plated in triplicate on meat-peptone agar. Following incubation at 37°C for 24 h, colony-forming units (CFU) per mL of exudate were counted according to the methods of Sandberg et al. (2009) and Frimodt-Moller (1993). The mean CFU value was calculated from three replicate plates for each dilution, followed by statistical analysis of the CFU data.

For physicochemical characterization, particle morphology was examined using a Leica Microsystems Leica DM 500 optical microscope, while particle size distribution, flowability, bulk density, angle of repose, and moisture content were determined according to the State Pharmacopoeia of the Republic of Uzbekistan (2021). Hygroscopicity was evaluated following the European Pharmacopoeia 7.0 (2010), and loss on drying was measured using an SF-1 moisture analyzer.

2.2. Evaluation of Pharmaceutical and Technological Properties

Hygroscopicity was evaluated according to EuPh 7, using a Memmert HPP 110 climatic chamber. Loss on drying was determined by the State Pharmacopoeia of the Republic of Uzbekistan (2021). Compressibility and flowability were assessed using Carr's Compressibility Index (CI) and Hausner Ratio (I_H). Flowability and angle of repose were measured using an ERWEKA GTD-63150 flowability tester. Bulk density before compaction (ρ_a) and tapped density after compaction (ρ_c) were determined using an ERWEKA SVM 221 bulk density tester. The following equations were used:

$$\rho = \frac{m}{V} \quad (1)$$

$$I_H = \frac{\rho_c}{\rho_a} \quad (2)$$

$$CI = \frac{\rho_c - \rho_a}{\rho_c} \times 100\% \quad (3)$$

where ρ is bulk density, m is mass, V is volume, ρ_a is bulk density before compaction, and ρ_c is tapped density after compaction.

2.3. Development of Dosage Form

The high daily dose of Levodon made capsule formulations unsuitable, as hard gelatin capsules (size 000) could not accommodate more than 1000 mg of active substance, and the addition of excipients would further exceed the capsule capacity; therefore, effervescent tablets were selected as the optimal dosage form.

2.4. Quality Control and In-vitro Release Study

Quality control was performed by visual inspection of tablet appearance using samples from three production batches (010124, 020124, and 030124), while identification was carried out by HPLC. Disintegration time was determined using an LB-2D disintegration tester in 500 mL distilled water at 37±2°C. Average tablet mass and deviation were determined according to the State Pharmacopoeia of the Republic of Uzbekistan (2021) using 20 tablets per batch. Friability was evaluated with a CJY-300D apparatus by rotating 10 tablets for 5 min; the test was performed in triplicate. Foreign impurities were assessed by TLC on Silufol UV-294 plates using a mobile phase of ethanol:25% ammonia:water (4:1:1, v/v/v). After ascending development, spots were visualized at 294 nm. No additional spots were detected in any batch, and Rf values matched the levofloxacin reference standard (Rf ≈ 0.65).

For pH determination, one tablet from each batch was dissolved in 200 mL of water at 25°C, and the pH was measured, with an acceptable range of 5.5-6.5. Dissolution testing was performed using a rotating basket apparatus (RCZ-6C) in 500 mL of KH_2PO_4 buffer (pH 3.3) at 37±0.5°C, 200 rpm, for 5 min. Dissolved levofloxacin was quantified by HPLC using a Beckman Ultrasphere Si column (5 µm, 25 × 4.6 mm) with UV detection at 294 nm. The mobile phase was pH 3.3 buffer (orthophosphoric acid/triethylamine):acetonitrile (20:80, v/v) at 1.0 mL/min. Injection volume was 20 µL, and run time was 10 min. The content of levofloxacin (% of labeled amount) was calculated using the following equation:

$$X = \frac{S_1 \cdot a_0 \cdot P \cdot G}{S_0 \cdot a_1 \cdot L} \times 100 \quad (4)$$

where S_1 and S_0 are peak areas of test and reference solutions, a_1 and a_0 are sample and standard weights, P is reference standard potency (%), G is average tablet weight (mg), and L is labeled levofloxacin content per tablet (mg).

An *in-vitro* release study of Levofloxacin from Levodon effervescent tablets was conducted using the dialysis bag method (MWCO 12-14 kDa). Each bag was filled with a solution obtained from one effervescent tablet dissolved in 200 mL of warm water. Bags were placed into vessels containing 1000 mL of three different media: 0.1 M HCl (pH 2.0), phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4), maintained at 37±0.5°C with constant stirring at 100 rpm. Samples from the external medium were collected at 8, 12, 28, 40, and 48 h, and levofloxacin content was quantified by HPLC.

Kinetic modeling of drug release was performed by fitting the release data to zero-order, first-order, Higuchi, and Korsmeyer-Peppas mathematical models. The best-fit model was selected based on the highest coefficient of determination (R^2). The release exponent (n) from the Korsmeyer-Peppas model was used to characterize the release mechanism: $n \leq 0.45$ indicates Fickian diffusion, $0.45 < n < 0.89$ indicates anomalous (non-Fickian) transport, and $n \geq 0.89$ indicates Case II transport (polymer erosion). The in vitro release profile was studied according to State Pharmacopoeia of the Republic of Uzbekistan (2021) and United States Pharmacopeia and National Formulary (2015).

2.5. Toxicity Studies

Acute toxicity and the median lethal dose (LD_{50}) of Levodon effervescent tablets were evaluated in male outbred white mice (18 ± 2 g) using the fixed-dose procedure following a single intragastric administration at 5000 mg/kg. The animals were observed for 14 days, and toxicity class was determined

according to OECD criteria (Stallard, 2004). Cumulative toxicity was evaluated using the Lim scheme, in which doses were increased every four days from 0.1 to 1.12 of the LD_{50} over 24 ± 4 days. The cumulative median lethal dose after repeated administration ($LD_{50}n$) was calculated using a probit analysis program (Schoofs and Willhite, 1984), and the cumulative coefficient (Cc) was determined as follows:

$$C_c = \frac{LD_{50n}}{LD_{50}} \quad (5)$$

where LD_{50n} is the cumulative median lethal dose after n-repeated administration and LD_{50} is the median lethal dose after single administration. Cumulative properties were classified based on the cumulative coefficient (Cc) as follows: Cc <1.0, super-cumulation; 1.0-2.2, pronounced cumulation; 2.2-5.0, moderate cumulation; and >5.0, weak cumulation.

2.6. Statistical analysis

All data are presented as mean ± standard deviation (SD). Comparisons between two groups were performed using an unpaired two-tailed Student's t-test. A p-value <0.05 was considered statistically significant. Statistical analyses were conducted using Statplus 9.0.

3. RESULTS AND DISCUSSION

The polymicrobial peritonitis model was confirmed by bacterial contamination of the peritoneal exudate. The control group showed a bacterial load of 2418 ± 198 CFU/mL, indicating successful and reproducible infection induction. Oral administration of Levodon at doses of 48, 95, and 190 mg/kg, as well as levofloxacin at 95 mg/kg, significantly reduced bacterial load in a dose-dependent manner. Levodon reduced bacterial counts to 974 ± 71 CFU/mL at 48 mg/kg and 405 ± 38 CFU/mL at 95 mg/kg, while no bacterial growth was detected at 190 mg/kg. Reference levofloxacin (95 mg/kg) reduced the bacterial count to 358 ± 39 CFU/mL. Since PVP has no intrinsic antibacterial activity (Luo et al., 2021; Abrekova et al., 2022), the antibacterial effect was attributed to levofloxacin. No significant difference was observed between Levodon and pure levofloxacin at 95 mg/kg (p = 0.058), indicating comparable antibacterial efficacy.

Importantly, PVP as a carrier did not diminish the antibacterial activity of levofloxacin, while control experiments confirmed that PVP itself lacks antimicrobial effects, acting solely as a solubilizer and stabilizer. These data support the feasibility of developing a finished dosage form based on the *Levodon* complex. However, the transition from substance to final dosage form presents technological challenges related to the physicochemical properties of the polymer complex powder. *Levodon* substance is an amorphous, light yellow to yellow powder with a faint hay-like odor, readily soluble in water and alcohol, but practically insoluble in acetone, chloroform, hexane, and petroleum ether. The daily therapeutic dose of *Levodon* is 1110 mg, a key factor in dosage form selection.

Particle morphology of the *Levodon* substance was examined using a Leica DM 500 microscope (10×10/0.22 objective). Figure 1 shows that the substance has needle-shaped and web-like particles forming agglomerates of different sizes. These agglomerates may improve compressibility by increasing particle adhesion and powder density during compression, which supports tablet processing and product stability. Other technological properties of Levodon, including particle size, flowability, angle of repose, bulk density, and moisture content, were evaluated according to approved standards. The results are shown in Table 1.

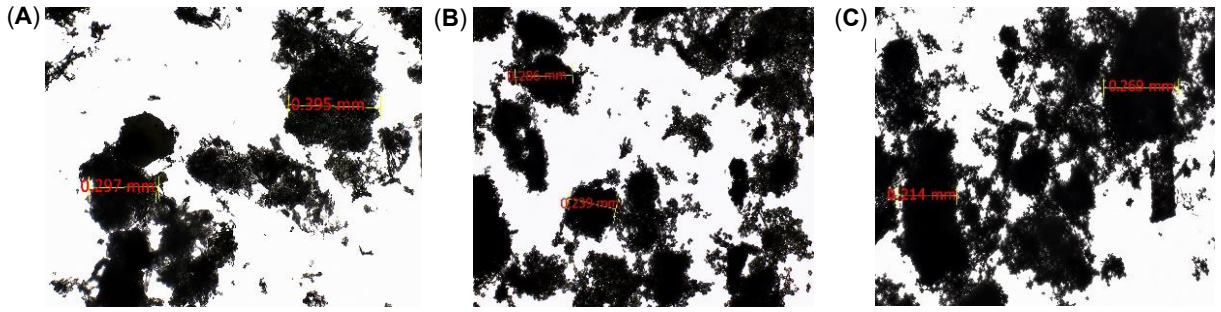

Figure 1. Micrographs of *Levodon* substance particles at different magnifications: (**A**) ×100, scale bar 0.395 mm; (**B**) ×200, scale bar 0.286 mm; (**C**) ×400, scale bar 0.214 mm. The substance consists of needle-shaped and web-like particles that interweave to form agglomerates of variable sizes.

Table 1. Results of the study of pharmaceutical and technological properties of the *Levodon* substance.

Parameters	x_1	x_2	x_3	x_4	x_5	x_{cp}	SD	Unit
Particle size distribution, μm:								%
+800	-	-	-	-	-	-		
-800+500	21.3	24.1	17.6	18.2	17.3	19.7	2.8	
-500 +300	10.5	12.3	11.8	10.9	12.5	11.6	0.8	
-300 +200	19.4	16.2	19.3	18.1	16.5	17.9	1.5	
-200 +150	22.6	19.2	22.3	21.6	20.3	21.2	1.4	
-150 +100	25.0	26.9	27.9	29.6	31.6	28.2	2.6	
-100	1.2	1.3	1.1	1.6	1.8	1.4	0.3	
Angle of repose	47.1	46.5	47.0	45.7	47.8	46.8	0.8	°
Flowability of powder	0.17	0.29	0.36	0.25	0.33	0.27	0.07	g/s
Bulk density (before compaction, m/V_0)	0.192	0.204	0.204	0.196	0.200	0.199	0.005	g/mL
Tapped density (after compaction, m/V_{2500})	0.243	0.238	0.250	0.250	0.250	0.246	0.005	g/mL
Internal porosity	1.09	0.70	0.90	1.10	1.00	0.96	0.16	-
Hausner ratio	1.26	1.16	1.22	1.27	1.25	1.23	0.04	-
Carr index	20.9	14.2	18.4	21.6	20.0	19.1	2.9	-
Residual moisture	4.8	5.5	5.3	4.6	4.5	4.94	0.42	%
Hygroscopicity	15.6	16.1	15.02	14.7	15.3	15.34	0.53	%

Moisture content and particle size distribution were within pharmacopoeial limits; however, particle adhesion and agglomeration adversely affected flowability, angle of repose, and bulk density, causing these parameters to fall outside the standard specifications. Carr Index and Hausner Ratio values indicated “moderate” compressibility. Therefore, further studies were undertaken to optimize the formulation and select the appropriate dosage form. Due to the high daily dose of *Levodon* (1110 mg), capsule dosage forms were excluded from further development. Hard gelatin capsules (size 000) cannot accommodate more than 1000 mg of active substance, and the addition of necessary excipients would exceed this capacity. Therefore, alternative dosage forms capable of delivering the required dose were investigated. Five tablet formulations differing in disintegrant, binder, and excipient content were investigated (Table 2). Direct compression (Formulations 1, 2, and 4) and wet granulation with 96% ethanol (Formulations 3 and 5) were compared.

Table 2. Formulation samples for the preparation of the *Levodon* tablet dosage form.

Names of the substances used	Formulation samples				
	1	2	3	4	5
Levodon, mg	1110	1110	1110	1110	1110
Magnesium stearate, mg	10	10	10	10	10
Croscarmellose sodium, mg	-	10	10	30	40
Crospovidone, mg	20	25	30	30	30
Pregelatinized starch, mg	90	100	-	110	-
Tablet weight, mg	1230	1255	1160	1290	1190

To improve powder flowability, bulk density, and other tableting parameters, magnesium stearate was used as an antifriction agent. Sodium croscarmellose (E-468) and crospovidone were added as disintegrants, and pregelatinized starch as a binder. For Formulations 3 and 5, wet granulation with 96% ethanol was applied to enhance binding properties. These improvements resulted in powder properties that complied with regulatory requirements. Subsequently, tablets of 14 mm diameter were produced from blends 1-5 at compression pressures of 50, 75, 100, and 150 kgf/cm², and mechanical strength was tested. The results are presented in Figure 2.

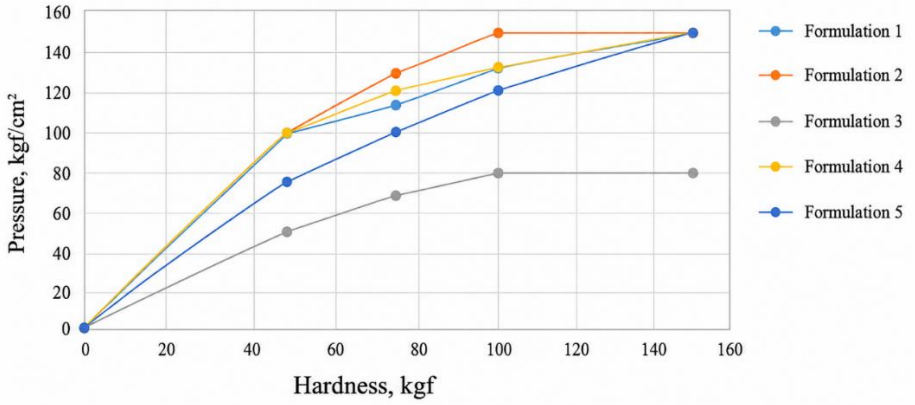

Figure 2. Effect of compression pressure (50, 75, 100, and 150 kgf/cm²) on tablet hardness (N) for Formulations 1–5 (n=3, mean ± SD). Hardness increases with compression pressure for all formulations.

However, disintegration testing according to the State Pharmacopoeia of the Republic of Uzbekistan (2021) yielded unsatisfactory results. Formulation 1 tablets disintegrated in no less than 28 min, Formulation 2 in over 25 min, and Formulation 3 in over 24 min. Increasing sodium croscarmellose content in Formulations 4 and 5 reduced disintegration time to 18 min, but this still did not meet pharmacopoeial requirements. This delayed disintegration is attributed to the film-forming properties of PVP in the active complex. Upon wetting, tablets swelled but did not break apart because PVP forms a dense film that prevents water penetration into the tablet matrix (Kadajji and Betageri, 2011). Thus, despite using wet granulation (a method expected to improve disintegration), the high PVP content significantly influences the physicochemical behavior of the dosage form, necessitating further formulation optimization.

The choice of PVP as the polymeric carrier for the *Levodon* complex warrants further discussion. PVP is a non-ionic, hydrophilic polymer with exceptional solubilizing and complexation properties due to its amide group, which can form hydrogen bonds with the carboxyl and keto groups of levofloxacin (Luo et al., 2021). This interaction enhances the stability of the amorphous form of levofloxacin, preventing crystallization during storage. In the context of effervescent tablets, PVP's high water solubility ensures rapid dissolution without leaving a polymeric residue, unlike HPMC or PVA, which may form gels. Moreover, PVP's film-forming properties, while beneficial for stabilizing amorphous drugs, contributed to the delayed disintegration observed in early formulations. This challenge was overcome by optimizing the balance of superdisintegrants (sodium croscarmellose and crospovidone) and compression pressure. Compared to other polymers, PVP offers an optimal balance between drug stabilization, solubility, and technological feasibility for effervescent dosage forms.

The prolonged-release behavior of levofloxacin from the *Levodon* effervescent formulation can be explained by several physicochemical mechanisms involving PVP. First, PVP forms hydrogen bonds with the carboxyl and keto groups of levofloxacin (Luo et al., 2021). These non-covalent interactions create a stable polymer drug complex that slows the diffusion of levofloxacin from the tablet matrix into the dissolution medium. Unlike immediate-release formulations, where the drug is rapidly released upon tablet disintegration, the PVP-levofloxacin complex requires additional time for dissociation, thereby extending the release period. The complexation between levofloxacin and PVP involves specific functional group interactions. Levofloxacin contains a carboxyl group (-COOH), a keto group (C=O), and a piperazine ring with a secondary amine. PVP possesses an amide group (-CONH-) in its pyrrolidone ring. The primary interaction is hydrogen bonding between the carboxyl group of levofloxacin and the amide carbonyl of PVP, as well as between the keto group of levofloxacin and the amide N-H of PVP (Luo et al., 2021). Additionally, electrostatic interactions may occur between the protonated nitrogen of the piperazine ring (at physiological pH) and the polar groups of PVP. These non-covalent interactions stabilize the amorphous polymer–drug complex, prevent crystallization of levofloxacin, and contribute to the prolonged release profile by slowing drug diffusion from the polymer matrix.

Second, PVP has a high glass transition temperature (Tg ≈ 175°C) and forms an amorphous matrix when compressed into tablets (Franco and De Marco, 2020). This amorphous matrix acts as a physical barrier, entrapping levofloxacin molecules and limiting their initial burst release. As the effervescent tablet disintegrates in aqueous medium, the PVP matrix gradually hydrates and swells, forming a gel-like layer that further retards drug diffusion. Over time, the hydrated polymer matrix erodes, releasing levofloxacin in a controlled manner. Third, the molecular weight of PVP (8.0 ± 2.0 kDa) used in the *Levodon* complex is relatively low, which facilitates rapid hydration without forming a viscous gel that would excessively delay disintegration. This balance between polymer-drug interaction and matrix hydration is critical for achieving the observed prolonged release profile (86.6% release at 28 h at pH 2.0, followed by sustained release over 48 h).

In contrast, conventional immediate-release levofloxacin tablets lack such a polymeric carrier, resulting in rapid dissolution and absorption (Tmax ≈1.3 h). Thus, the PVP-based complex not only stabilizes levofloxacin in amorphous form but also serves as the primary mechanism for extending drug release, potentially reducing peak plasma concentrations and associated adverse effects while maintaining therapeutic efficacy. To optimize disintegration characteristics, preliminary compositions for effervescent tablets were selected (Table 3). The chosen components substantially reduced disintegration time and accelerated drug dissolution in aqueous medium, promoting faster absorption of the active ingredient.

Table 3. Formulation samples for the development of effervescent tablets of the pharmaceutical product Levodon.

Names of the substances used	Formulation samples				
	1	**2**	**3**	**4**	**5**
Levodon, mg	1110	1110	1110	1110	1110
Magnesium stearate, mg	10	13	15	15	17
Sodium bicarbonate, mg	100	157	232	320	371
Citric acid, mg	77	120	176	242	281

Tablets of 20 mm diameter were produced by direct compression at 50, 75, 100, and 150 kgf/cm². The tablets demonstrated high mechanical strength. However, disintegration time for Formulations 1-4 exceeded 8-14 min (pharmacopoeial limit: ≤5 min). For Formulation 5, disintegration time ranged from 4-9 min depending on compression pressure. Friability was below 1%, and hardness exceeded 80 N, indicating satisfactory mechanical resistance. As shown in Figure 3, 50 kgf/cm² was optimal; higher pressures increased disintegration time beyond pharmacopoeial limits. This is explained by reduced porosity and enhanced interparticle bonding at higher compression forces, which hinders water penetration. Subsequent optimization focused on improving organoleptic properties (taste and odor).

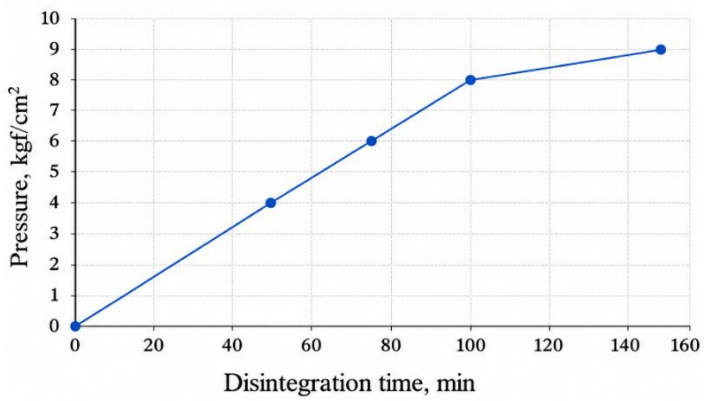

Figure 3. Effect of compression pressure (50, 75, 100, and 150 kgf/cm²) on disintegration time (min) for Formulations 1-5 (n=6, mean ± SD). The pharmacopoeial limit for effervescent tablets is ≤5 min (dashed line). The optimal compression pressure was 50 kgf/cm², as higher pressures increased disintegration time beyond acceptable limits.

Subsequent optimization focused on improving the organoleptic properties of the formulation. Five experimental compositions containing different sweeteners and flavouring agents were evaluated. The initial formulation contained sucrose, acesulfame potassium, and menthol flavouring. In subsequent formulations, sucrose was replaced with sodium saccharin at different concentrations, while lemon and orange flavourings were incorporated individually or in combination to improve palatability. Despite these modifications, several formulations retained a pronounced bitter taste characteristic of antibiotic preparations. Increasing the concentration of sodium saccharin improved sweetness but did not adequately mask bitterness. Formulations containing individual citrus flavourings provided only partial improvement in taste and aroma. The most favourable organoleptic characteristics were achieved with the formulation containing acesulfame potassium (500 mg) combined with lemon and orange flavourings (10 mg each). This composition produced a solution with a pleasant citrus taste and aroma and substantially reduced the bitterness of the active ingredient compared with the other formulations tested.

Although the sensory evaluation was qualitative and informal in nature, the consistent reduction in bitterness observed by multiple evaluators confirmed the effectiveness of the selected taste-masking system. A comprehensive sensory assessment using a trained panel and validated hedonic scales would be required for regulatory submission. Based on the obtained results, this formulation was selected as the optimal composition for the further development of *Levodon* effervescent tablets.

Based on the obtained data, a technology for producing *Levodon* effervescent tablets was developed. The process involves sequential operations ensuring high product quality, with rapid disintegration and improved organoleptic properties. The technological scheme is presented in Figure 4. Preparation of the tablet mass includes mechanical milling, sieving, blending, and incorporation of excipients to achieve mixture homogeneity and optimal compression properties (Ter Horst et al.,2021).

- *TP 1.1 Milling and Sieving of Components:* The active ingredient was milled, and all components were weighed. Raw materials were sieved through a non-vibratory stainless-steel sieve C4 (0.8 mm mesh) to remove large particles and agglomerates, ensuring uniform particle size distribution for subsequent mixing and tableting. After sieving, *Levodon*, sodium bicarbonate, anhydrous citric acid, acesulfame potassium, and flavorings (lemon and orange) proceeded to TP 1.2 (Dry blending), while magnesium stearate was directed to TP 1.3 (Lubrication) for later addition. Particles that did not pass the sieve were collected and disposed of according to environmental and sanitary regulations.
- *TP 1.2 Dry Blending:* Homogenization was performed in an M5 powder mixer to ensure uniform distribution of all ingredients. The pre-sieved components *Levodon*, sodium bicarbonate, anhydrous citric acid, acesulfame potassium, flavorings (lemon and orange), and nonconforming tablet mass, if present) were loaded into a clean, dry mixing vessel and blended for 15 min.

- *TP 1.3. Lubrication (Dusting with Magnesium Stearate):* Magnesium stearate was added to the mixer, followed by additional blending for 15 min. This excipient improves powder flowability and reduces particle adhesion to equipment surfaces during tableting. The finished blend was submitted for quality control, including identity testing and quantitative assay of the active ingredient. Upon receiving a positive conclusion from the Quality Control Department, the blend was transferred to stage TP 2.1 (Tableting).
- *TP 2.1. Tableting:* The prepared blend was compressed into tablets with specified strength, dimensions, and mass characteristics using a TP6 tablet press. The finished blend from stage TP 1.3 was loaded into the press hopper and fed into compression dies. Tableting was performed at 50 kgf/cm² using dies of 20 mm diameter. Nonconforming tablets generated during equipment setup or production were directed to stage WO1 (Waste Reprocessing). After compression, tablets proceeded to stage TP 2.2 (Dedusting).
- *TP 2.2. Dedusting:* Fine powder particles formed during compression were removed using an OT7 tablet deduster. Tablets from the loading hopper entered the rotating dedusting unit, where centrifugal forces and mechanical cleaning separated dust particles, which were collected in a filtration compartment. Cleaned tablets were discharged into a plastic container lined with a double polyethylene bag. After dedusting, tablets proceeded to filling, packaging, and final quality control. Each production batch yielded 1721 tablets (86 packs of 20 tablets). Pilot-scale manufacturing was carried out at China-Uzbekistan Medicine Technical Park LLC, a facility equipped with modern pharmaceutical equipment and compliant with occupational and sanitary standards. Quality evaluation methods were developed in accordance with the General Technical Regulation “On the Safety of Medicines” (Resolution No. 365, Cabinet of Ministers of the Republic of Uzbekistan, October 27, 2016) and the State Pharmacopoeia of the Republic of Uzbekistan (2021).

Quality assessment of pilot batches (010124, 020124, and 030124) confirmed compliance with regulatory specifications. Visual inspection met pharmacopoeial requirements (Uz. Ph 5.11; Eur. Ph.). The tablets were light yellow with slight marbling (acceptable), flat-cylindrical with clearly defined bevels on both sides, and featured a score line on one side for dose adjustment. Identity testing confirmed the presence of the active ingredient (Figure 5).

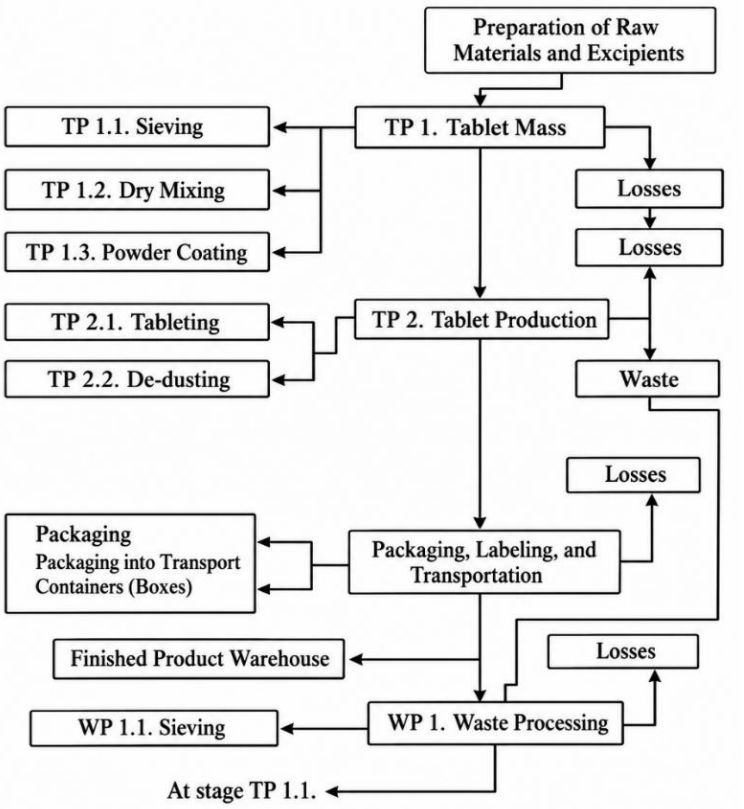

Figure 4. Technological scheme for the production of *Levodon* effervescent tablets, showing the sequential operations: TP 1.1 (milling and sieving), TP 1.2 (dry blending), TP 1.3 (lubrication), TP 2.1 (tableting), TP 2.2 (dedusting), and waste reprocessing (WO1). Quality control (QCD) is performed at intermediate stages.

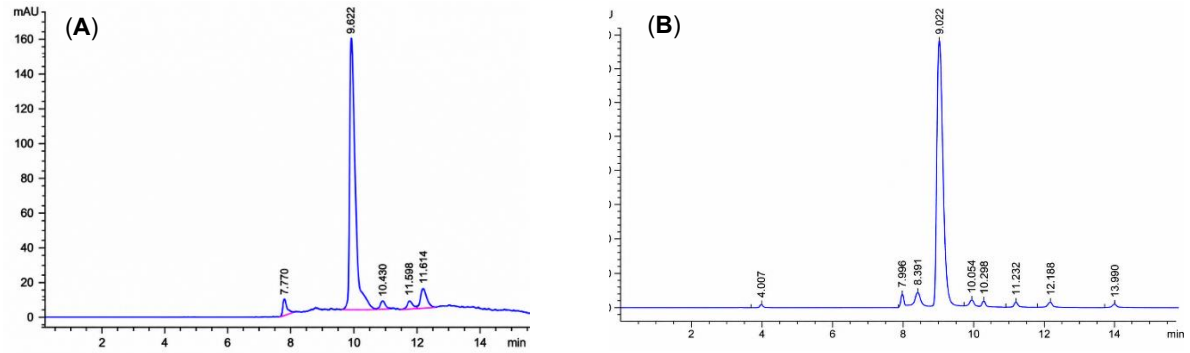

Figure 5. Representative HPLC chromatograms of levofloxacin: (**A**) levofloxacin reference standard (retention time ≈ 4.8 min); (**B**) *Levodon* effervescent tablet test sample (retention time ≈ 4.8 min). UV detection at 294 nm. The retention time and peak shape confirm the identity of the active ingredient.

The disintegration time of Levodon tablets from all three batches was less than 5 min, complying with the requirements of the State Pharmacopoeia of the Republic of Uzbekistan (2021). Tablet friability was evaluated using a CJY-300D apparatus, and the results are presented in Table 4. Impurity testing showed no additional spots on the chromatograms of test solutions from all batches. The pH values of dissolved effervescent tablets were within the acceptable range of 5.5–6.5 for all batches (Figure 6), while dissolution testing demonstrated that more than 80% of the tablets dissolved (Table 5).

Table 4. Results of the friability study of *Levodon* tablets.

Batch	Replicate (n)	Average weight of 10 tablets before friability test (g)	Average weight of 10 tablets after friability test (g)	Weight loss (g)	Weight loss (%)
010124	1	22.80	22.68	0.12	0.50
	2	23.00	22.99	0.01	0.04
	3	22.98	22.95	0.03	0.13
020124	1	23.02	22.93	0.09	0.39
	2	22.99	22.96	0.03	0.13
	3	22.98	22.93	0.05	0.21
030124	1	22.95	22.95	0	0
	2	22.93	22.90	0.03	0.13
	3	22.99	22.95	0.04	0.17

Table 5. Results of the dissolution study of *Levodon* tablets (p<0.05; n=6).

Batch	*I*	x_i, %	$\bar{x}$,%	*F*	s^2	$s_{\bar{x}}$	*t* (*P*, *f*)	Δx	ε, %
010124	1	85.3	85.2	5	0.28	0.22	2.571	0.57	0.67
	2	85.2							
	3	86.1							
	4	85.4							
	5	84.9							
	6	84.3							
020124	1	90.1	89.6	5	1.62	0,57	2.571	1.47	1.94
	2	87.3							
	3	88.9							
	4	91.3							
	5	89.5							
	6	90.5							
030124	1	89.6	90.1	5	0.68	0.34	2.571	0.87	0.97
	2	90.7							
	3	90.4							
	4	91.2							
	5	88.5							
	6	90.2							

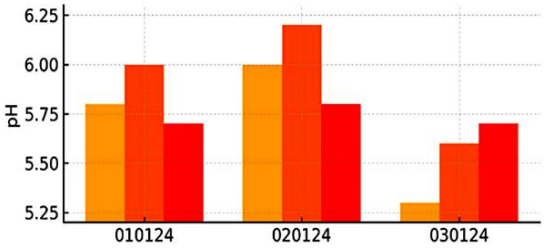

Figure 6. pH values of solutions obtained after dissolving *Levodon* effervescent tablets from three pilot batches (010124, 020124, 030124). All values fall within the acceptable range of 5.5–6.5 (dashed lines). Data are presented as mean ± SD (n=3).

Microbiological purity testing showed that Total Aerobic Microbial Count (TAMC) did not exceed 10^3 CFU/g, Total Yeast and Mold Count (TYMC) did not exceed 10^2 CFU/g, and specific microorganisms (including *Escherichia coli*) were not detected. These results complied with the State Pharmacopoeia of the Republic of Uzbekistan (2021). Quantitative determination of *Levodon* content per tablet is presented in Table 6.

Table 6. Results of the quantitative determination of *Levodon* tablets ($p<0.05$; $n=3$).

Batch	*I*	x_i, mg	$\bar{x}$, mg	*f*	s^2	$s_{\bar{x}}$	*t* (*P*, *f*)	Δx	ε, %
010124	1	1117.2	1118.9	2	4.57	1.24	4.303	5.34	0.48
	2	1121.3							
	3	1118.2							
020124	1	1145.3	1148.8	2	151.99	7.12	4.303	30.65	2.67
	2	1138.6							
	3	1162.5							
030124	1	1113.0	1107.8	2	20.44	2.61	4.303	11.23	1.01
	2	1105.6							
	3	1104.8							

Based on the obtained data, the shelf life of *Levodon* effervescent tablets is 2 years when stored in a dry place, protected from light, at a temperature not exceeding 25°C. The *in vitro* biopharmaceutical study demonstrated levofloxacin release profiles, as presented in Figure 7. At pH 2.0 (Figure 7a), rapid levofloxacin release (70.1%) occurred within the first 12 hs due to high solubility in acidic medium. Maximum concentration (86.6%) was reached by 28 h, followed by a plateau. At pH 6.8 (Figure 7b), release was more gradual, reaching 60.2-66.4% at 40-48 h, suggesting sustained therapeutic effect in the small intestine. At pH 7.4 (Figure 7c), prolonged release was also observed, reaching 50.1% (28 h), 55.4% (40 h), and 62.8% (48 h), with stable kinetics confirming activity under colonic conditions. Thus, the effervescent dosage form of *Levodon* provides prolonged, controlled levofloxacin release across a wide pH range, maintaining stable antimicrobial concentrations for up to 48 h after a single administration.

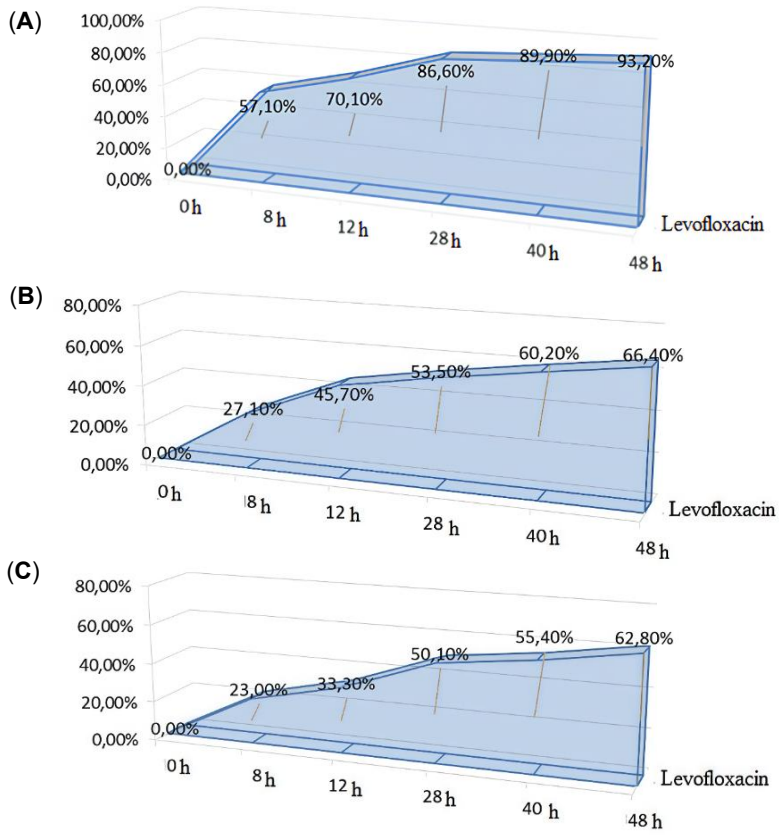

Figure 7. *In vitro* levofloxacin release profiles from *Levodon* effervescent tablets in three dissolution media: (**A**) pH 2.0 (0.1 M HCl, simulating gastric conditions); (**B**) pH 6.8 (phosphate buffer, simulating small intestinal conditions); (**C**) pH 7.4 (phosphate buffer, simulating colonic conditions). Data are presented as mean ± SD (n=6). At pH 2.0, rapid release occurred (70.1% at 12 h, 86.6% at 28 h). At pH 6.8 and 7.4, release was more gradual, reaching 66.4% and 62.8% at 48 h, respectively, indicating prolonged release across the gastrointestinal tract.

Kinetic analysis of levofloxacin release. The release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models. The calculated parameters are summarized in Table 7. At pH 2.0, the release profile was best described by the first-order model (R^2 = 0.992), indicating that the release rate is concentration-dependent. The Korsmeyer-Peppas model yielded a release exponent n = 0.42, suggesting Fickian diffusion-controlled release (n ≤ 0.45). At pH 6.8, the Higuchi model provided the best fit (R^2 = 0.986), characteristic of diffusion-controlled release from a polymeric matrix. The Korsmeyer-Peppas exponent n = 0.54 indicated anomalous (non-Fickian) transport, involving both diffusion and polymer relaxation. At pH 7.4, the release profile also followed Higuchi kinetics (R^2 = 0.981), with n = 0.51 from the Korsmeyer-Peppas model, again indicating a mixed diffusion-erosion mechanism. Overall, the kinetic analysis confirms that levofloxacin release from the *Levodon* effervescent tablets is primarily diffusion-controlled, with partial contribution from polymer matrix erosion, particularly at neutral to alkaline pH.

Table 7. Kinetic model parameters for levofloxacin release from *Levodon* effervescent tablets at different pH media.

pH	Model	R^2	k	n
2.0	First-order	0.992	0.089 h^{-1}	-
2.0	Korsmeyer-Peppas	0.981	-	0.42
6.8	Higuchi	0.986	12.4 %·$h^{-1/2}$	-
6.8	Korsmeyer-Peppas	0.973	-	0.54
7.4	Higuchi	0.981	10.8 %·$h^{-1/2}$	-
7.4	Korsmeyer-Peppas	0.965	-	0.51

n = release exponent from Korsmeyer-Peppas model; k = release rate constant

The dialysis bag method was selected for the in vitro release study due to its ability to simulate prolonged release under sink conditions while allowing direct comparison of release profiles across different pH media (Shi et al., 2010). This method is particularly suitable for effervescent formulations, as the rapid disintegration and dissolution occur outside the dialysis bag, after which the dissolved drug diffuses through the membrane, mimicking drug transport across biological barriers. However, this approach has several limitations. First, the dialysis membrane (MWCO 12-14 kDa) introduces an additional diffusion barrier that may slightly delay drug detection compared to true release in the absence of a membrane (Heigoldt et al., 2010). Second, the method does not account for gastrointestinal motility, enzymatic activity, or food effects. Third, the sink conditions maintained in the external medium (1000 mL buffer) differ from the limited fluid volume in the human stomach and small intestine. Despite these limitations, the dialysis method provides a reliable ranking of release profiles and is widely used for prolonged-release formulations during preclinical development (Bozal Palabiyik et al., 2018). The observed gradual release over 48 h across pH 2.0-7.4 strongly suggests that *Levodon* effervescent tablets would maintain therapeutic levofloxacin concentrations for an extended period after oral administration, potentially reducing peak plasma concentrations and dosing frequency. However, further pharmacokinetic studies in animals or humans are needed to establish a quantitative *in vitro-in vivo* correlation (IVIVC).

Comparison with previously reported levofloxacin prolonged-release systems. The prolonged-release profile of *Levodon* effervescent tablets (86.6% release at 28 h at pH 2.0, followed by sustained release over 48 h) compares favorably with other levofloxacin extended-release formulations reported in the literature. Awofisayo et al. (2025) developed levofloxacin-loaded nanoparticles with a release of approximately 65% over 24 h, showing faster initial release but lower cumulative release compared to our formulation. The more gradual release profile of *Levodon* suggests better potential for once-daily dosing with reduced peak plasma concentrations. Izadi et al. (2019) reviewed the pharmacokinetics of conventional levofloxacin tablets, reporting Tmax ≈ 1.3 h and rapid absorption, which is associated with dose-dependent adverse effects. In contrast, our PVP-based complex extends the release period to 48 h, potentially minimizing gastrointestinal side effects.

Kurakula and Rao (2020) discussed PVP-based delivery systems for various drugs, noting that the release mechanism depends on polymer molecular weight and drug-polymer interactions. Our results are consistent with their observations: the relatively low molecular weight of PVP (8.0 ± 2.0 kDa) used in *Levodon* facilitated rapid hydration and controlled release without excessive gel formation. Compared to other polymer-based levofloxacin formulations (e.g., using chitosan or HPMC), our effervescent tablet offers the added advantage of rapid disintegration and ease of swallowing, making it particularly suitable for patients with dysphagia or pediatric and geriatric populations. Overall, the *Levodon* effervescent tablet provides a competitive alternative to existing levofloxacin extended-release systems, combining a favorable release profile, good technological properties, and improved patient compliance. Acute toxicity of *Levodon* effervescent tablets was evaluated following single intragastric administration in mice. At a dose of 5000 mg/kg, animals exhibited grooming, eye narrowing, clustering,

and urination within 5-10 min but returned to normal condition within 2-3 h. No mortality was observed (0/5) (Table 8).

Table 8. Acute toxicity parameters of *Levodon* tablets following single intragastric administration in mice.

Sample	Animal Species / Route of Administration	Dose	Mortality (No. Dead / No. Tested)	Toxicity class (LD_{50} in mg/kg)
Levodon	Mice, males / intragastric	5000 mg/kg	0/5	>5000 (Class VI)
Control	Mice, males / intragastric	0.3 mL	0/5	-

Throughout the 14-day observation period, no abnormalities in fur or skin condition, tail position, fecal consistency, diuresis, or body weight changes were observed compared to the control group (Table 9). The acute toxicity study following single intragastric administration of Levodon tablets in mice showed that LD_{50} was >5000 mg/kg. According to OECD classification criteria, Levodon effervescent tablets are not classified as hazardous with respect to acute toxicity.

The doses used in the cumulative toxicity study are presented in Table 10. Following repeated administration of Levodon tablets, the first mortality (1/10) was observed on day 17 at a cumulative dose of 18,700 mg/kg. On day 18, a second animal died (2/10) at 21,200 mg/kg; on day 19, a third animal died (3/10) at 23,700 mg/kg; and by day 20, mortality increased to 6/10 at a cumulative dose of 26,200 mg/kg. Complete mortality was observed by day 24 at a cumulative dose of 41,200 mg/kg. Based on the calculations, the cumulative median lethal dose of the Levodon dosage form was determined to be LD_{50}n = 25,769.3 mg/kg (Schoofs et al., 1984). The cumulative coefficient (Cc) of Levodon tablets was >5, indicating weak cumulative properties, and was calculated as follows:

$$C_c = \frac{LD50_n}{LD_{50-1}} = \frac{25769{,}3\ mg/kg}{5000\ mg/kg} = 5.15 \quad (6)$$

Table 9. Body weight dynamics of mice following single intragastric administration of *Levodon* tablets (M±m, n=5).

Sample	Animal Species / Route of Administration	Dose	Body weight of mice, g		
			Outcome	Day 7	Day 14
Levodon	Mice, males / intragastric	5000 mg/kg	22.0±0.4	22.8±0.4	23.4± 0.8
Control	Mice, males / intragastric	0.3 ml/kg	21.1± 0.3	21.8± 0.3	22.9±0.4

Table 10. Investigation of the cumulative properties of *Levodon* tablets using the subchronic toxicity method in mice.

Days of Administration	Mortality (No. Dead / No. Tested)	Fraction of LD_{50} (LD_{50} > 5000 mg/kg)	Administered dose (mg/kg)	Cumulative dose (mg/kg)
1-4	0/10	0,1	500	2000
5-8	0/10	0,15	750	5000
9-12	0/10	0.22	1100	9400
13-16	0/10	0.34	1700	16200
17	1/10	0.5	2500	18700
18	2/10	0.5	2500	21200
19	3/10	0.5	2500	23700
20	6/10	0.5	2500	26200
21	7/10	0.75	3750	29950
22	9/10	0.75	3750	33700
23	9/10	0.75	3750	37450
24	10/10	0.75	3750	41200

4. CONCLUSION

The present study successfully developed a novel prolonged-release effervescent formulation of Levodon based on a polymeric complex with polyvinylpyrrolidone (PVP). In a rat model of experimental polymicrobial peritonitis, Levodon demonstrated dose-dependent antibacterial activity against *S. aureus* and *E. coli*. At a dose of 95 mg/kg, its efficacy was comparable to that of pure levofloxacin ($p = 0.058$, > 0.05), while complete pathogen elimination from the peritoneal exudate was observed at 190 mg/kg. These findings confirm that complexation with PVP does not reduce the antimicrobial activity of levofloxacin. The optimized effervescent tablet (Formulation 5) contains 1110 mg of Levodon, with a total tablet weight of approximately 2305 mg. The formulation disintegrated within ≤5 min, meeting pharmacopoeial requirements, and showed acceptable taste in an informal sensory evaluation. The in vitro release study confirmed prolonged levofloxacin release across a physiologically relevant pH range (2.0–7.4), with 86.6% drug release after 28 h at pH 2.0 and sustained release for up to 48 h. Kinetic analysis indicated that drug release was primarily diffusion-controlled, with partial contribution from polymer matrix erosion under neutral to alkaline conditions. Preclinical safety assessment in mice demonstrated that Levodon effervescent tablets are not classified as hazardous in terms of acute toxicity

according to OECD classification criteria (LD_{50} > 5000 mg/kg) and exhibit weak cumulative properties (cumulative coefficient, Cc = 5.15). The predicted shelf life of the formulation is 24 months when stored at temperatures not exceeding 25°C. Overall, the developed Levodon effervescent tablet represents a promising alternative to existing levofloxacin formulations. It combines prolonged drug release, which may reduce dosing frequency and peak plasma concentrations, with improved patient compliance due to its palatable taste, rapid disintegration, and ease of swallowing, while maintaining a favorable preclinical safety profile. These findings provide a strong scientific basis for further clinical evaluation of the formulation.

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest related to this work.

AUTHOR CONTRIBUTION
Beknazarova Nuriya Seytabevna, Makhmudov Sardor Djalilovich: Writing original draft, visualisation, investigation, methodology, and data curation. Mardikulova Dilshoda Khamrokulovna, Rasulov Alisher Khayotovich, Nabiev Abdusamat Khamidovich: Conceptualisation, methodology, validation, resources, supervision, and project administration. Tagayalieva Nigora Abdunabievna, Ziyaev Khayrulla Lutfullaevich, Kholbekov Omonkul Khudoyarovich: Writing, review, editing, conceptualisation, methodology, validation, resources, supervision, and project administration. Nurmukhamedova Vazira Zaxiritdinovna, Ibragimov Abdurahmon Safievich, Sagdullaev Bakhodir Takhirovich: Writing, review, editing, conceptualisation, and project administration.

DATA AVAILABILITY
The authors confirm that the data supporting the findings of this study are available within the article.

DECLARATION OF GENERATIVE AI
During the preparation of this work, the authors used ChatGPT to assist in drafting the abstract and improving the grammar and sentence structure of the manuscript. All generated content was carefully reviewed and edited by the authors, who take full responsibility for the final content of the publication.

ETHICS
The study was conducted in accordance with Directive 2010/63/EU and institutional guidelines for the care and use of laboratory animals. According to the national regulations of the Republic of Uzbekistan, formal ethical approval was not required for this type of non-clinical pharmacological study. Nevertheless, all procedures were performed with efforts to minimize animal suffering and to reduce the number of animals used.

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