

Article

pH Modulation as a Key Strategy for Developing a Stable Lyotropic Liquid Crystal Formulation of Octreotide Acetate

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Abstract

Background: Lyotropic liquid crystal (LLC) systems provide sustained release and convenient administration for peptide delivery. Octreotide, a first-line somatostatin analogue, has previously been formulated into LLC systems mainly using the hydrochloride salt. Here, we investigated the acetate salt, which is widely used in marketed products, but presents unique challenges in LLC formulation due to poor stability. **Methods:** We demonstrate that pH adjustment is a critical determinant for successfully incorporating octreotide acetate into a stable LLC system. By employing 3M HCl–EtOH to adjust pH to approximately 5.7, we obtained a formulation that maintained >90% drug content after 3 months at 40 °C and >98% after 12 months at 4 °C. **Results:** Structural analyses confirmed the coexistence of cubic and hexagonal mesophases, supporting controlled release. In vivo pharmacokinetic studies in rats further demonstrated sustained-release behavior, as evidenced by prolonged systemic exposure and an extended half-life. Pharmacokinetic profiles were comparable to those of an octreotide hydrochloride LLC. **Conclusions:** These findings highlight pH modulation as an essential strategy for stabilizing octreotide acetate in LLC systems, providing a foundation for extending LLC technology to clinically relevant salt forms of peptide therapeutics.

Keywords: octreotide acetate; long-acting injectable; lyotropic liquid crystal; controlled release; subcutaneous injection



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1. Introduction

Octreotide is a first-line therapeutic agent in several major clinical indications, demonstrating significant clinical value [1–3]. As a representative somatostatin analogue, it has established a dominant position in the treatment of acromegaly [4,5], serving as primary therapy for approximately 47.23% of patients worldwide and effectively controlling growth hormone hypersecretion-related symptoms [6]. In neuroendocrine tumors, octreotide, as the standard of care for gastroenteropancreatic neuroendocrine tumors, improves flushing symptoms in 60% of patients with carcinoid syndrome and diarrhea in 48% [7]. For gastroenterological emergencies, it achieves >70% efficacy in managing acute esophageal variceal bleeding in cirrhosis, significantly reducing mortality rates [8]. Additionally, octreotide

exhibits substantial clinical benefit in postoperative complication management, providing significant improvement in over 60% of intestinal or pancreatic fistulas cases [9,10]. Owing to its broad therapeutic indications and validated clinical outcomes, octreotide retains a prominent position in the global pharmaceutical market [11,12].

Currently, globally commercialized octreotide formulations comprise three categories, covering short-acting injections, long-acting sustained-release microspheres, and novel oral preparations [13,14], thereby addressing the full spectrum of therapeutic needs from acute intervention to chronic management. However, existing octreotide formulations exhibit significant clinical limitations. Exemplified by the short-acting Sandostatin® (Basel, Switzerland) launched by Novartis in 1988, which requires multiple daily intravenous or subcutaneous (SC) administrations [15], resulting in suboptimal patient compliance. To improve dosing frequency limitations, Novartis has launched the long-acting microsphere formulation Sandostatin® LAR in 1998 which extends the injection interval to several weeks [16]. However, the clinical application of this product still faces several challenges: First, the formulation requires a complex preparation process, forming a milky suspension prone to sedimentation that requires immediate administration [17]. Second, administration mandates deep intramuscular injection via large-gauge needles [18], inducing substantial patient discomfort. Additionally, microsphere formulations face greater sterilization challenges, as sterile filtration is impractical due to their large particle size, while terminal methods such as heat or gamma irradiation can cause polymer degradation and alter drug release [19]. Consequently, microspheres must be produced under aseptic conditions, which increases manufacturing complexity and quality control demands [20]. Furthermore, its delayed onset of action necessitates concurrent short-acting SC injections during therapy initiation [21]. The novel oral preparations, taking MYCAPSSA® (Dublin, Ireland)—an oral sustained-release capsule launched by Chiasma Company in 2020 as an example although it eliminates injection-related discomfort, it still requires daily medication and entails a higher treatment cost [22].

To overcome the aforementioned limitations of existing octreotide formulations, a novel long-acting LLC formulation was developed by Camurus using FluidCrystal® (Lund, Sweden) technology, which transforms into a sustained-release depot following SC injection. LLC systems are self-assembled lipid mesophases formed by amphiphilic lipids upon hydration, giving rise to highly ordered nanostructures such as bicontinuous cubic or inverse hexagonal phases with interconnected aqueous domains. Owing to their unique bicontinuous architecture, LLC formulations are capable of accommodating both hydrophilic compounds within aqueous channels and hydrophobic compounds within lipid domains, enabling sustained drug release predominantly governed by diffusion-controlled mechanisms [23]. Moreover, the internal nanostructure and physicochemical properties of LLC systems can be rationally tuned by lipid composition, water content, and formulation conditions, providing a versatile and adaptable platform for the design of long-acting peptide delivery systems [24]. Compared to short-acting and oral products, the LLC system markedly reduces dosing frequency and improves patient adherence. Importantly, in contrast to long-acting microspheres, the LLC system does not require complex reconstitution or intramuscular injection with large-gauge needles. Instead, it is supplied as a prefilled liquid that can be administered subcutaneously, thereby simplifying preparation, reducing patient discomfort, and improving sterility assurance through filtration [25]. However, previous octreotide LLC formulations, such as Camurus' CAM2029, were developed using octreotide hydrochloride as the active pharmaceutical ingredient (API).

In this study, we sought to explore whether octreotide acetate, a salt form widely used in marketed products, could also be formulated into an LLC system. Octreotide is a small peptide composed of eight amino acids linked by peptide bonds, with the peptide backbone

cyclized through an intramolecular disulfide bond, and has a molecular weight of 1019 Da. Octreotide acetate is highly soluble in water and contains multiple ionizable functional groups, including carboxyl, amino, and imidazole moieties. Its apparent dissociation constants have been reported as $pK_a'I = 7.03 \pm 0.05$ and $pK_a'II = 10.13 \pm 0.10$ [26]. These dissociation characteristics show reasonable compatibility with the pH range required to maintain the stability of LLC formulations, and octreotide acetate also exhibits a certain intrinsic buffering capacity. Moreover, its degradation pathways are well established and can be quantitatively characterized, enabling systematic stability evaluation. Owing to its moderate molecular weight, poor lipophilicity, and limited membrane permeability, incorporation into an LLC-based delivery system can improve its apparent lipophilicity and enhance in vivo bioavailability. Collectively, these physicochemical properties make octreotide acetate a suitable and representative model drug for investigating the design of LLC-based long-acting injectable formulations.

During formulation, we observed that the acetate form exhibited pronounced instability in the lipid matrix when pH was not adjusted. This highlighted, for the first time, that the stability of octreotide LLC formulations depends critically on pH when different salt forms of the peptide are used. By applying a pH modulation strategy with 3M HCl–EtOH ($pH \approx 5.7$), we successfully stabilized the acetate-based LLC system, achieving robust storage stability and sustained release. These findings provide new mechanistic insight into the role of salt form and pH in LLC formulation, while offering a practical approach for developing stable long-acting depots of octreotide acetate.

2. Materials and Methods

2.1. Materials

Octreotide acetate and octreotide hydrochloride were obtained from Sinopep-Alisino Biopharmaceutical Co., Ltd., located in Jiangsu, China. Glyceryl dioleate was purchased from Croda International Plc, located in Staffordshire, United Kingdom. Soybean phosphatidylcholine was acquired from Lipoid GmbH, located in Ludwigshafen, Germany. Ethanol (ACS reagent grade, $\geq 99.9\%$) was obtained from Merck KGaA, located in Darmstadt, Germany. Phosphate-buffered saline (PBS, $1\times$, $pH 7.4$) was purchased from Gibco, Thermo Fisher Scientific Inc., located in Waltham, MA, USA.

2.2. Methods

2.2.1. Preparation of Octreotide Acetate LLC Formulations

The formulation was prepared by dissolving octreotide acetate in anhydrous ethanol, followed by the addition of soybean phosphatidylcholine (SPC) and glycerol dioleate (GDO) (50:50, w/w). Magnetic stirring was applied to obtain a uniform and transparent pre-formulation. To optimize the prescription, formulations were prepared with different ethanol concentrations (5–20%, w/w), different types of pH modifiers (CH_3COOH , 3M HCl–EtOH, and H_2SO_4 –EtOH), and different pH values ranging from 4.5 to 8.5. Each sample was adjusted to the target pH and sterilized via $0.22\ \mu m$ filtration, and then stored at $4\ ^\circ C$ for subsequent testing.

2.2.2. Rheological and Gelation Behavior Evaluation

We assessed the rheological properties of each formulation using a rotational rheometer equipped with a cone–plate geometry at $25 \pm 0.5\ ^\circ C$, and viscosity values were obtained under steady shear conditions. Gelation behavior was then evaluated by injecting 0.1 g of each formulation into pre-equilibrated $1\times$ PBS maintained at $37 \pm 0.5\ ^\circ C$. At predetermined time points, the resulting gels were bisected along their largest cross-section, and gelation

time was defined as the period required for the gels to maintain structural integrity without visible exudation. All experiments were conducted in triplicate to ensure reproducibility.

2.2.3. Animal Study

Local skin irritation and pharmacokinetic studies were conducted in male Sprague–Dawley (SD) rats (180–250 g).

For the preliminary local skin irritation assessment used for formulation screening, animals were randomly assigned to five groups ($n = 8$ per group) [27]. Three groups received a single SC injection of octreotide acetate LLC formulations at a dose of 20 mg/kg in which pH was adjusted using different acidic modifiers, including CH_3COOH , 3M HCl-EtOH , or $\text{H}_2\text{SO}_4\text{-EtOH}$. The remaining two groups, namely the blank LLC group and the negative control group, each received a single SC injection at the same dose of 20 mg/kg. Injection sites were observed daily for up to 14 consecutive days to monitor local tolerability. Draize-based skin irritation scoring was performed on days 3, 7, and 10 post-injection. Four parameters at the injection site were evaluated independently, including erythema, edema, hemorrhage, and erosion/ulceration. Each parameter was scored on a scale from 0 to 4 according to the severity of the observed reaction, where higher scores indicated more severe tissue damage. For each observation time point, the total irritation score was calculated as the sum of the individual scores for erythema, edema, hemorrhage, and erosion/ulceration. Daily observations were recorded, and the irritation index was expressed as mean $\pm$ SD.

Pharmacokinetic evaluation comprised three parts with all experimental groups consisting of five animals ($n = 5$ per group) [27–29]. In the first study, formulation screening was conducted in four groups. Three groups received long-acting octreotide acetate LLC formulations containing 8%, 10%, or 15% (w/w) ethanol by single SC injection at a dose of 20 mg/kg; blood samples (0.3–0.5 mL) were collected from the retro-orbital venous plexus at predose and at 1.92, 4.08, 6.00, 24.00, 96.00, 168.00, 336.00, 384.00, 504.00, 576.00, and 672.00 h after dosing, while the fourth group received Sandostatin[®] short-acting injection by single SC administration at 0.2 mg/kg, blood samples were collected at predose and at 0.08, 0.17, 0.33, 0.50, 1.00, 2.00, 4.00, 6.00, and 24.00 h post-dose.

In the second study, a direct comparison was performed between the optimized octreotide acetate LLC formulation and the corresponding octreotide hydrochloride LLC formulation. Rats were randomly assigned to two groups. Both formulations were administered via single SC injection, the dosing regimen and blood sampling schedule followed the schedules described above for the long-acting formulation groups.

In the third study, a head-to-head comparative pharmacokinetic study was conducted in three groups. The optimized octreotide acetate LLC formulation was administered by a SC injection at a dose of 20 mg/kg, and blood samples were collected at 0.25, 1.00, 2.00, 4.00, 6.00, 24.00, 96.00, 168.00, 336.00, 384.00, 504.00, 576.00, and 672.00 h post-dose. Sandostatin[®] LAR was administered by a single intramuscular injection at the same dose of 20 mg/kg, with blood sampling performed at the same time points as the optimized LLC formulation. The short-acting formulation, Sandostatin[®] short-acting injection, was administered by a single SC injection at a dose of 0.2 mg/kg, and blood samples were collected at 0.08, 0.17, 0.33, 0.50, 1.00, 2.00, 4.00, 6.00, and 24.00 h post-dose.

Plasma octreotide concentrations were determined using LC–MS/MS in accordance with standard bioanalytical practices. Pharmacokinetic parameters, including C_{max} , T_{max} , AUC_{0-t} , and $t_{1/2}$ were calculated using non-compartmental analysis in WinNonlin software (version 8.1.0), employing the linear-up/log-down trapezoidal method.

2.2.4. Stability Evaluation of Octreotide Acetate LLC Formulations

Stability of octreotide acetate LLC formulations was assessed under both accelerated and long-term storage conditions. For accelerated testing, samples were stored at 40 °C for 3 months. For long-term testing, the optimized formulation was stored at 25 °C for 3 months and at 4 °C for 12 months.

Studies have shown that octreotide acetate has multiple degradation-related impurities, which are mainly influenced by elevated temperature and humidity, light exposure, and acid- or base-catalyzed conditions. For example, impurity B ([7-D-cysteine] octreotide) and impurity G ([2-D-cysteine] octreotide) are formed via amino-acid configurational isomerization, whereas impurity F ($O^{1,8}$ -acetyloctreotide), impurity H ($N^{6,5}$ -acetyloctreotide), and impurity I ($N^{2,1}$ -acetyloctreotide) arise from acetylation of amino or hydroxyl functional groups. In addition, impurity J (des-threoninol-8 octreotide) is generated through amide hydrolysis. Referring to existing quality standards described in the European Pharmacopoeia 11.1 and related literature [30,31], we established a total impurities determination method and applied it in the present study as a practical approach for formulation screening and preliminary quality evaluation of the optimized formulation.

Octreotide content was quantified using high-performance liquid chromatography (HPLC, RF-10AXL, Shimadzu Corp., Kyoto, Japan) equipped with a Welchrom C18 column (4.6 mm × 250 mm, 5 µm). The mobile phases consisted of 0.02% trifluoroacetic acid in water (A) and acetonitrile (B), with gradient elution, a flow rate of 1.0 mL/min, column temperature of 30 °C, and detection at 220 nm. The HPLC method for octreotide quantification was validated over a concentration range of 0.05–0.15 mg/mL, showing excellent linearity with a correlation coefficient ($r = 0.9999$). Accuracy was evaluated at 50%, 100%, and 150% of the nominal concentration, with recovery values ranging from 98.0% to 101.0%, indicating good accuracy of the method.

Total impurities were analyzed by HPLC on a Welchrom C18 column (4.6 mm × 250 mm, 5 µm). Mobile phase A contained tetramethylammonium hydroxide buffer and acetonitrile (90:10, *v/v*), and mobile phase B consisted of tetramethylammonium hydroxide buffer and acetonitrile (40:60, *v/v*), adjusted to pH 2.0 and 2.5, respectively. Gradient elution was performed at 1.0 mL/min with column temperature set to 35 °C, and UV detection at 220 nm. The method for determination of total impurities exhibited good linearity over the concentration range of 0.02–4.5 µg/mL, with a correlation coefficient of $r = 0.9999$. Accuracy was assessed at 20%, 50%, 100%, and 150% levels, and recoveries were within 90.0–115.0%. The limit of quantification (LOQ) was 0.04 µg/mL, corresponding to approximately 2.0% of the specification limit, while the limit of detection (LOD) was 0.01 µg/mL, corresponding to approximately 0.6% of the specification limit.

Glycerol monooleate and free fatty acids were quantified using size-exclusion chromatography (SEC) equipped with a styrene-divinylbenzene copolymer column (7.8 mm × 300 mm, 5 µm). The mobile phase was tetrahydrofuran at a flow rate of 1.0 mL/min. Both column and detector temperatures were maintained at 40 °C, and the injection volume was 40 µL. The SEC method for glycerol monooleate quantification showed excellent linearity over the concentration range of 0.02–4.0 mg/mL, with a correlation coefficient of $r = 1.0000$. Recoveries at 50%, 100%, and 200% levels ranged from 90.0% to 110.0%. The LOQ and LOD were 14 µg/mL and 7 µg/mL, corresponding to approximately 0.7% and 0.4% of the specification limit, respectively. For free fatty acids, the method was linear over 0.01–2.8 mg/mL ($r = 0.9998$), with recoveries between 90.0% and 110.0% at 50%, 100%, and 200% levels. The LOQ and LOD were 14 µg/mL and 7 µg/mL, corresponding to approximately 1.0% and 0.5% of the specification limit, respectively.

Lysophosphatidylcholine was determined by HPLC using an Alltima silica column (4.6 mm × 250 mm, 5 µm). Mobile phase A consisted of methanol–water–glacial acetic

acid–triethylamine (85:15:0.45:0.05, *v/v/v/v*), and mobile phase B contained n-hexane–isopropanol–mobile phase A. Detection was performed using an evaporative light scattering detector (ELSD) with a flow rate of 1.0 mL/min, column temperature of 40 °C, and 20 µL injection volume. The HPLC–ELSD method demonstrated good linearity in the range of 25–500 µg/mL, with a correlation coefficient of $r = 0.9998$. Accuracy studies conducted at 25%, 100%, and 150% levels yielded recoveries between 90.0% and 108.0%. The LOQ and LOD were 25 µg/mL and 7 µg/mL, corresponding to approximately 8.0% and 2.5% of the specification limit, respectively.

All analyses were performed monthly in triplicate. All HPLC analytical methods were developed in-house and fully validated to application. System suitability tests were conducted prior to each analytical sequence to ensure reliability.

2.2.5. Microstructural Analysis by PLM, Cryo-TEM, and SAXS

Birefringence and phase morphology were examined using a polarized light microscope (PLM) (Shanghai Caikon Optical Instrument Co., Ltd., Shanghai, China). Samples were placed between glass slides and observed under cross-polarized light at room temperature to identify characteristic textures. The internal nanostructure of the formulation was imaged using cryogenic transmission electron microscope (Cryo-TEM) (Thermo Fisher Scientific, Waltham, MA, USA). Samples were plunge-frozen in liquid ethane and transferred to a cryo-holder for visualization under low-dose conditions at $-180\text{ }^{\circ}\text{C}$. Small-angle X-ray scattering (SAXS) (Anton Paar GmbH, Graz, Austria) analysis was performed to determine the internal phase structure. Samples were loaded into capillaries and subjected to X-ray scattering. Scattering intensity was recorded as a function of scattering vector q , and peak positions were used to determine the presence of ordered mesophases based on spacing ratios.

3. Results

3.1. Screening of Octreotide Acetate LLC Formulations at Different Ethanol Concentrations

We attempted to prepare an LLC formulation using octreotide acetate as the API, guided by the formulation principles reported for Camurus' octreotide hydrochloride system. Octreotide acetate was first dissolved in ethanol, followed by the addition of SPC and GDO (50:50, *w/w*) under magnetic stirring to obtain a uniform pre-formulation.

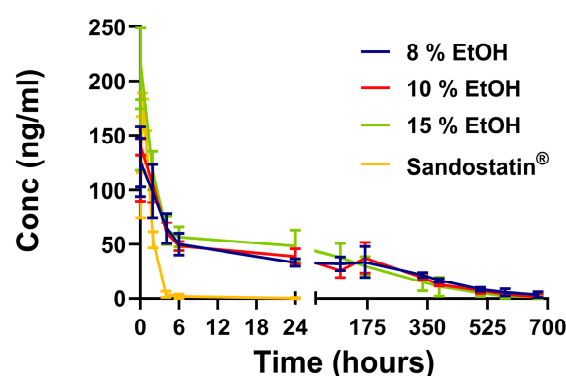
During preparation, ethanol content emerged as a critical parameter, as it directly affected drug and excipient solubility, as well as formulation viscosity and injectability [32,33]. To systematically evaluate this factor, formulations were prepared with ethanol concentrations ranging from 5.0% to 20.0% (*w/w*). At ethanol levels $\leq 7.5\%$, incomplete solubilization of octreotide acetate and lipid excipients was observed, requiring additional rotary evaporation steps and resulting in excessive viscosity ($>859\text{ mPa}\cdot\text{s}$), which made injection impractical. At higher ethanol levels, complete dissolution was achieved, and the formulations exhibited appropriate viscosity for subcutaneous injection [34] (Table 1).

Considering both preparation feasibility and formulation properties, the ethanol content range of 8.0–15.0% (*w/w*) was identified as suitable for LLC preparation. To further assess in vivo performance, pharmacokinetic studies were conducted in rats for formulations containing 8.0%, 10.0%, and 15.0% ethanol. All LLC formulations significantly prolonged half-life ($t_{1/2} = 100.8\text{--}153.2\text{ h}$) compared with conventional octreotide injection (1.7 h). As the ethanol content increased, C_{max} also increased. Among the tested groups, the 10% ethanol formulation maintained excellent sustained-release characteristics ($t_{1/2} = 153.2\text{ h}$) (Figure 1, Table 2).

Table 1. Effects of ethanol content on the performance of octreotide acetate LLC formulations.

Ethanol Content (wt %)	Processing Time (h)	Viscosity (mPa·s)	Gelation Time (h)
5.0	4.0 ± 0.2	1475 ± 68	0.3 ± 0.1
6.5	2.7 ± 0.3	972 ± 54	N/A
7.5	2.3 ± 0.2	859 ± 47	N/A
10.0	1.8 ± 0.1	392 ± 20	10.0 ± 0.5
12.5	1.1 ± 0.1	316 ± 18	N/A
15.0	0.9 ± 0.1	212 ± 15	5.0 ± 0.4
20.0	0.4 ± 0.2	79 ± 8	N/A

Note: N/A: Not applicable.

**Figure 1.** Plasma concentration–time profiles of octreotide acetate LLC formulations with different ethanol contents. Data are presented as mean ± SD, n = 5 per group.**Table 2.** Pharmacokinetic parameters of octreotide acetate LLC formulations with different ethanol contents in rats.

Sample	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h·ng/mL)
8% EtOH	132.7 ± 33.2	0.81 ± 0.38	137.3 ± 29.0	13,877 ± 1805
10% EtOH	153.2 ± 61.6	0.81 ± 0.38	139.8 ± 8.0	13,217 ± 2423
15% EtOH	100.8 ± 29.8	1.03 ± 0.13	216.0 ± 32.9	12,851 ± 2431
Sandostatin®	1.7 ± 1.9	0.42 ± 0.10	181.8 ± 13.0	327 ± 26

Note: Data are presented as mean ± SD (n = 5 per group).

Taken together, the 10% ethanol formulation was identified as the optimal octreotide acetate LLC system, balancing sustained drug release with controlled plasma concentration fluctuations.

3.2. Comparative Stability Study of Octreotide Acetate and Octreotide Hydrochloride LLC Formulations

To investigate the stability of octreotide acetate LLC formulation, a direct comparison with the corresponding hydrochloride formulation was conducted, with both formulations prepared under identical conditions (10% ethanol and the same excipient ratios), differing only in the salt form of octreotide. Accelerated testing at 40 °C revealed pronounced differences: the acetate system retained only 72.9% of drug content after 1 month and declined to 34.5% after 3 months, whereas the hydrochloride system maintained >99.3% at 1 month and 97.8% at 3 months. In parallel, total impurities in the acetate system rose from 3.8% to 11.2%, while the hydrochloride system showed slower accumulation (3.6% at 1 month and 7.4% at 3 months). Collectively, these data demonstrate that the acetate-based

LLC formulation is substantially less stable than the hydrochloride-based formulation (Figure 2).

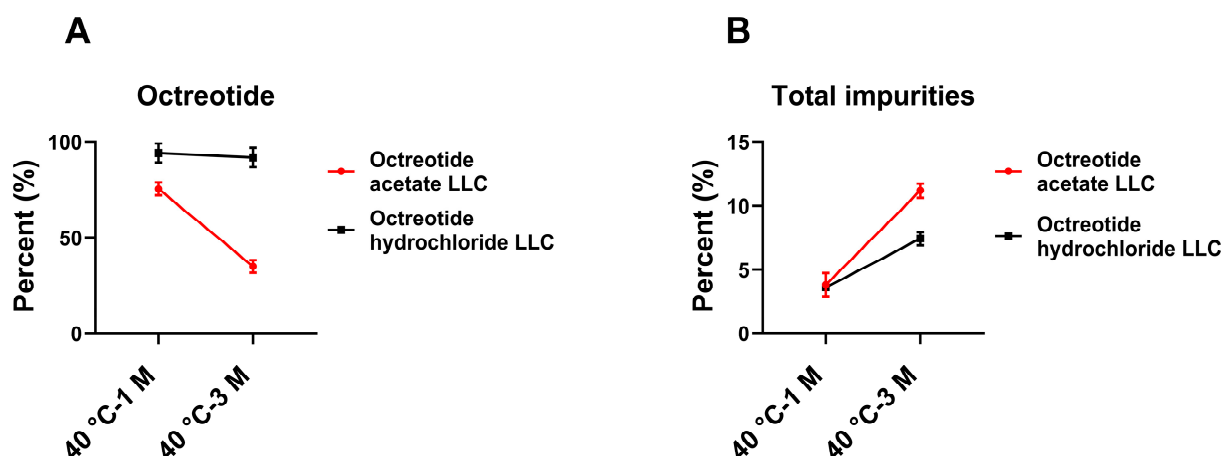


Figure 2. Comparative stability of octreotide acetate and octreotide hydrochloride LLC formulations under 40 °C. (A) Octreotide content after 1 and 3 months. (B) Total impurities content after 1 and 3 months.

Under initial conditions, the pH values of the LLC formulations were measured. The octreotide acetate LLC exhibited an alkaline pH of approximately 8.5, whereas the corresponding octreotide hydrochloride LLC showed a markedly lower pH of around 5.1.

To further explore potential factors contributing to this difference, we examined marketed octreotide products. Documentation indicates that short-acting Sandostatin® injection has a pH of 4.2 ± 0.3 , while long-acting Sandostatin® LAR maintains a pH of approximately 4.0 after reconstitution [35]. These observations suggest that pH may play a critical role in determining the stability of octreotide acetate LLC formulation.

3.3. Impact of pH Modifiers on the Stability and Skin Irritation of Octreotide Acetate LLC Formulations

Given that the physicochemical properties of pH modifiers (such as pKa and ionic strength) can significantly influence the stability and the skin irritation potential of peptide formulations [36,37], we next investigated whether adjusting pH with different acidic modifiers could improve the stability of the acetate-based LLC system. Based on preliminary screening, three acidic solvents—CH₃COOH, 3M HCl-EtOH, and H₂SO₄-EtOH—were selected to adjust the formulation pH to the same target value (pH 5.1). The resulting formulations were then subjected to accelerated stability testing at 40 °C for one month.

The type of pH modifier had a notable impact on formulation stability under accelerated conditions. After one month at 40 °C, the formulation adjusted with 3M HCl-EtOH retained 98.7% of the drug content after one month, followed by the H₂SO₄-EtOH group at 94.7% and the CH₃COOH group at 91.9%—all of which were significantly higher than the unmodified control group's retention rate of 72.4%. These findings confirm that while different [36,37]acidic modifiers enhanced formulation stability to varying degrees (3M HCl-EtOH > H₂SO₄-EtOH > CH₃COOH), all demonstrated substantial improvement compared to the original unmodified formulation at pH 8.5. Among them, the 3M HCl-EtOH group exhibited the most favorable stability performance (Figure 3).

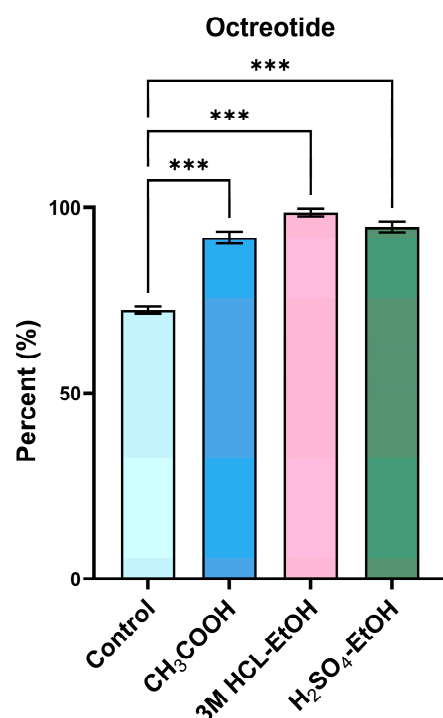


Figure 3. Octreotide content of LLC formulations adjusted with different pH modifiers after storage at 40 °C for 1 month. Data are presented as mean $\pm$ SD, $n = 3$ per group. *** $p < 0.001$. One-way ANOVA with Tukey multiple comparisons correction.

The results of the local skin irritation assessment for formulation screening are summarized in Table 3. The formulation adjusted with CH₃COOH showed an irritation score of 4.0 ± 1.1 at day 3. The score decreased to 1.8 ± 0.7 at day 7 and further decreased to 0.1 ± 0.4 by day 10. The H₂SO₄-EtOH-adjusted formulation exhibited an irritation score of 2.9 ± 0.8 at day 3, which decreased to 0.5 ± 0.5 at day 7 and reached 0 by day 10. In contrast, the formulation adjusted with 3M HCl-EtOH showed consistently low irritation scores throughout the observation period, with values of 0.6 ± 0.5 , 0.3 ± 0.5 , and 0 at days 3, 7, and 10, respectively. At day 3, the CH₃COOH and H₂SO₄-EtOH adjusted formulations showed significantly higher irritation scores compared with the 3M HCl-EtOH group and controls (* $p < 0.05$, Kruskal–Wallis test followed by Dunn’s post hoc test). No statistically significant differences were observed between the 3M HCl-EtOH group and the blank LLC or negative control groups at any time point.

Table 3. Quantitative Draize-based skin irritation scores.

Group	Day 3	Day 7	Day 10
CH ₃ COOH	4.0 ± 1.1	1.8 ± 0.7	0.1 ± 0.4
3M HCL-EtOH	0.6 ± 0.5	0.3 ± 0.5	0
H ₂ SO ₄ -EtOH	2.9 ± 0.8	0.5 ± 0.5	0
Blank LLC	0.8 ± 0.5	0.5 ± 0.5	0.1 ± 0.4
Negative control	0.3 ± 0.5	0.1 ± 0.4	0.1 ± 0.4

Note: Data are presented as mean $\pm$ SD, $n = 8$ per group.

The above findings support that 3M HCl-EtOH as the pH modifier not only ensures formulation stability effectively but also minimizes the risk of local skin irritation. Therefore, 3M HCl-EtOH was selected as the preferred pH modifier for the octreotide acetate LLC formulation.

3.4. Impact of pH on the Stability of Octreotide Acetate LLC Formulations

We next systematically investigated the effect of formulation pH on stability, as it represents a critical parameter in the development of LLC systems. Our preliminary formulation, with a pH of approximately 8.5, exhibited poor stability under accelerated storage conditions. To clarify the role of pH, we prepared formulations at values of 4.0, 5.0, 6.0, and 7.0 (adjusted with 3M HCl-EtOH) while keeping other components constant. All samples were subjected to accelerated stability testing at 40 °C for three months. The results demonstrated that pH had a significant impact on the physicochemical stability of the octreotide acetate LLC formulations. The unmodified formulation retained only 35.17% of drug content after three months, indicating poor stability. In contrast, when the pH was adjusted to a range of 5.0 to 6.0, the formulations exhibited excellent stability, with drug retention exceeding 90% (Figure 4A).

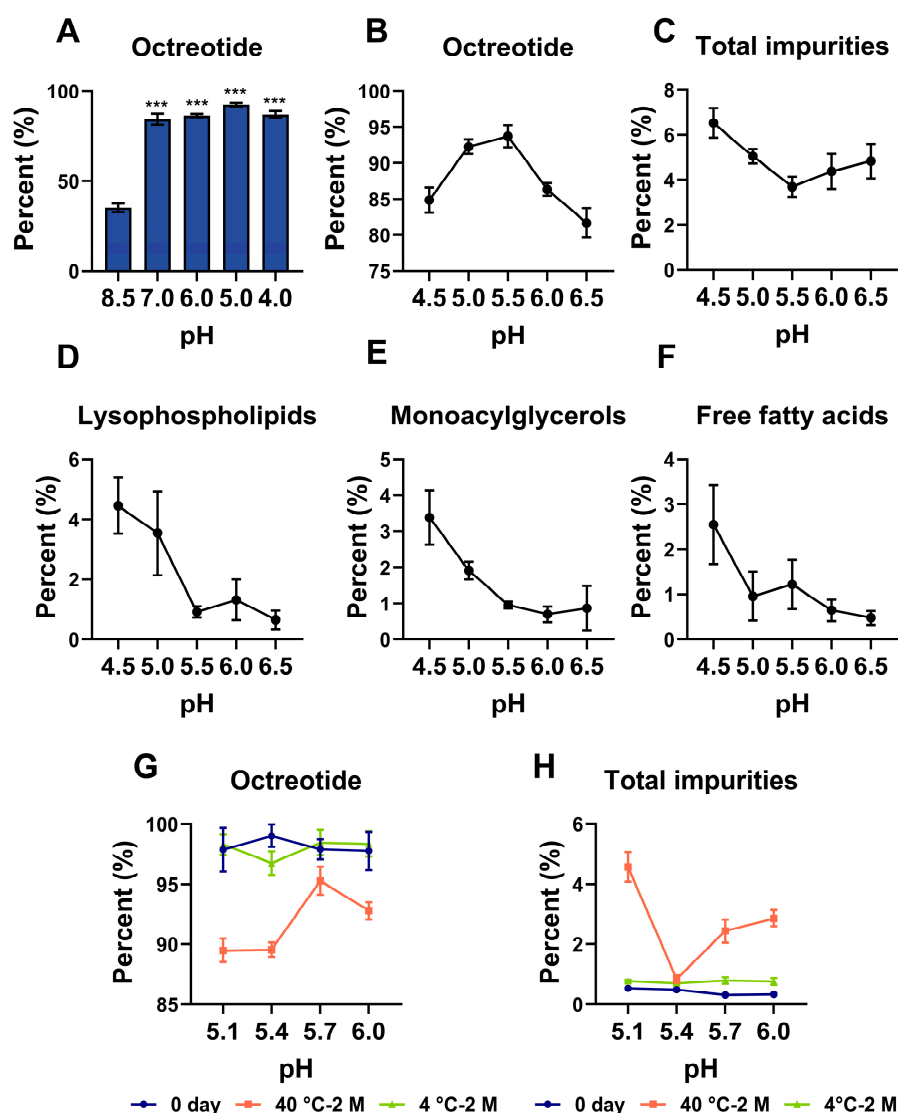


Figure 4. Stability evaluation of octreotide acetate LLC formulations at different pH values (A–F) After three months of storage at 40 °C: (A,B) Octreotide content; (C) Total impurities content; (D) Lysolecithin content; (E) Monoglycerides content; (F) Free fatty acids content. (G,H) After two months of storage at 40 °C and 4 °C: (G) Octreotide content; (H) Total impurities content. Data are presented as mean $\pm$ SD, $n = 3$ per group. *** $p < 0.001$. One-way ANOVA with Tukey multiple comparisons correction.

To further refine the optimal range, we conducted additional screening of formulations adjusted to pH 4.5–6.5. Formulations within pH 5.0–6.0 demonstrated the most favorable stability, with drug retention ranging from 86.35% to 93.72%, total impurities remaining below 5%, and lipid degradation products significantly reduced. When the pH was below 5.0, lipid degradation increased markedly—for example, lysolecithin content reached 4.45% at pH 4.5. In contrast, pH above 6.0 caused a rapid decline in drug content, with only 81.67% retention observed at pH 6.5. Based on these findings, the optimal pH range for octreotide acetate LLC formulations was defined as 5.0–6.0, which preserved drug stability and minimized degradation products (Figure 4B–F).

Finally, to confirm the robustness of this range under practical conditions, formulations with pH value of 5.1, 5.4, 5.7, and 6.0 were subjected to two-month stability testing under both accelerated (40 °C) and refrigerated (4 °C) storage. Detailed formulation compositions are provided in Table 4. At 40 °C, the pH 5.7 group performed best, retaining 95.30% of drug content with 2.43% total impurities, significantly better than the pH 5.1–5.4 groups. Under refrigerated conditions, all groups maintained excellent stability, with drug retention above 96.74% and total impurities below 0.80% (Figure 4G,H).

Table 4. Composition of octreotide acetate LLC formulations adjusted to different pH values using 3M HCl–EtOH.

pH	Composition (% <i>w/w</i>)				
	SPC	GDO	EtOH	3M HCL-EtOH	Octreotide Acetate
5.1	43.80	43.80	7.70	2.37	2.42
5.4	43.80	43.80	7.70	2.31	2.42
5.7	43.80	43.80	7.70	2.16	2.42
6.0	43.80	43.80	7.70	2.07	2.42

3.5. Comparative Evaluation of Optimized Octreotide Acetate and Octreotide Hydrochloride LLC Formulations

To further verify the stability of the optimized octreotide acetate LLC formulation, we compared its performance with an octreotide hydrochloride LLC formulation under identical experimental conditions. Both formulations were prepared with the same lipid composition and excipient ratios, differing only in the salt form of octreotide. The optimized octreotide acetate LLC formulation (pH 5.7) and the octreotide hydrochloride LLC formulation (pH 5.1) were subjected to accelerated testing at 40 °C for 3 months. Analyses of drug content, total impurities, and lipid-related degradation products revealed comparable stability profiles between the two formulations. Both retained >90% of drug content, with similar levels of impurities and degradation products. No statistically significant differences were detected, demonstrating that pH adjustment enables the acetate-based LLC formulation to achieve a stability performance equivalent to the hydrochloride-based formulation (Figure 5).

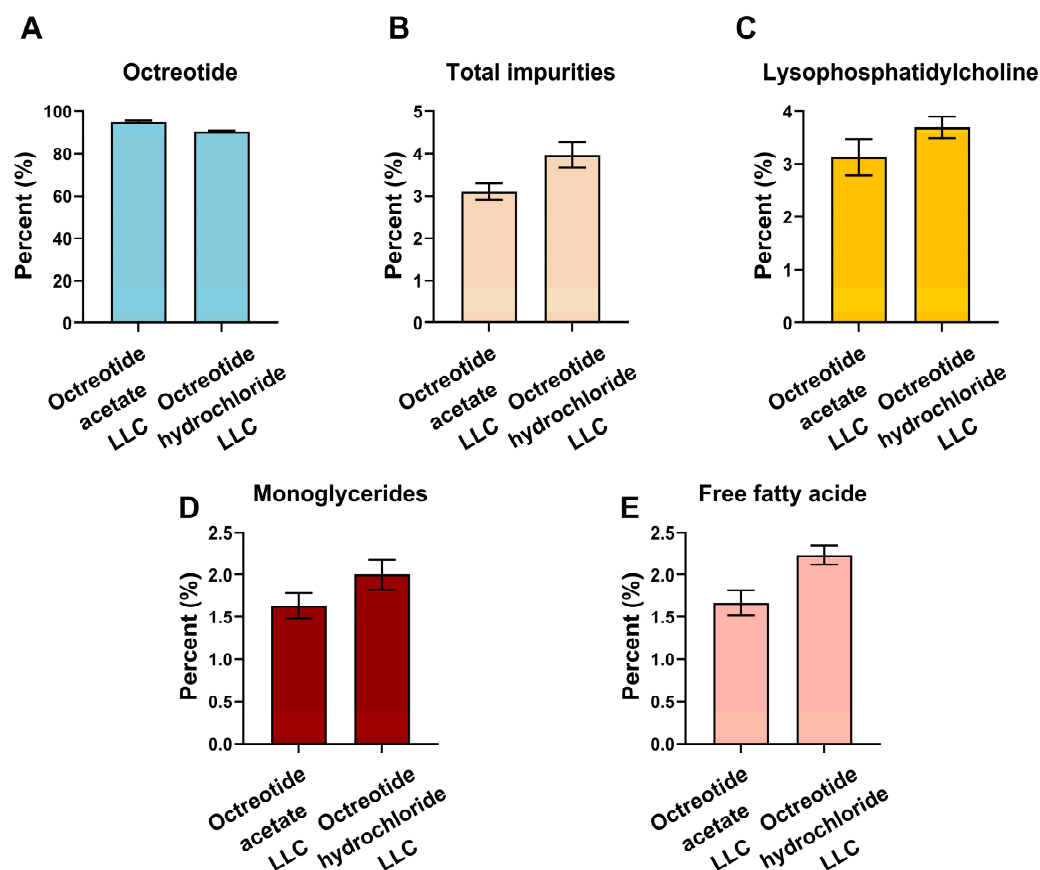


Figure 5. Comparative stability evaluation of optimized octreotide acetate LLC formulation and octreotide hydrochloride LLC formulation under 40 °C, 3 months. (A) Octreotide content. (B) Total impurities content. (C) Lysophosphatidylcholine content. (D) Monoglyceride content. (E) Free fatty acid content. Data are presented as mean $\pm$ SD, $n = 3$ per group. Statistical analysis was performed using unpaired Student's t -test.

In addition, comparative pharmacokinetic evaluation in rats showed that the two formulations provided similar overall drug exposure (AUC) and elimination half-life ($t_{1/2}$), confirming equivalent long-acting performance. The acetate-based LLC formulation exhibited slightly higher C_{max} and a greater proportion of early drug release (%AUC_{0–24h}), yet maintained a sustained release profile comparable to the hydrochloride formulation (Table 5).

Table 5. Pharmacokinetic comparison between optimized octreotide acetate and octreotide hydrochloride LLC formulations in rats.

Sample	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC _{0–t} (h·ng/mL)	AUC _{0–∞} (h·ng/mL)	%AUC _{0–24h}
Octreotide acetate LLC	123.80 $\pm$ 14.90	1.00 $\pm$ 0.26	167.00 $\pm$ 24.50	14,036.83 $\pm$ 1123.00	14,270.61 $\pm$ 1141.65	12.29 $\pm$ 3.08
Octreotide hydrochloride LLC	146.00 $\pm$ 19.60	1.00 $\pm$ 0.29	131.07 $\pm$ 19.70	13,502.16 $\pm$ 1215.20	14,230.33 $\pm$ 1278.40	7.48 $\pm$ 2.22

Note: Data are presented as mean $\pm$ SD ($n = 5$ per group).

Taken together, these results indicate that octreotide acetate—when incorporated into an LLC system with appropriate pH adjustment (pH $\approx$ 5.7 using 3M HCl–EtOH)—can achieve stability and pharmacokinetic performance comparable to an octreotide hydrochloride

ride LLC. These findings underscore that pH modulation is a critical and enabling factor for successfully formulating octreotide acetate in LLC systems.

3.6. Long-Term Stability Assessment of Optimized Octreotide Acetate LLC Formulations

We systematically evaluated the long-term stability of the finalized formulation. At 25 °C for three months, octreotide acetate content was 97.99%, total impurities 0.82%, and no notable changes were observed in key degradation products. Under 4 °C storage, the formulation maintained 98.43% drug content after 12 months, with total impurities increasing only slightly to 0.56% and degradation products remaining essentially unchanged. These findings demonstrate that the octreotide acetate LLC formulation adjusted to pH 5.7 possesses excellent long-term stability (≥ 12 months) under refrigerated conditions, with all quality attributes well controlled and within acceptable limits (Figure 6).

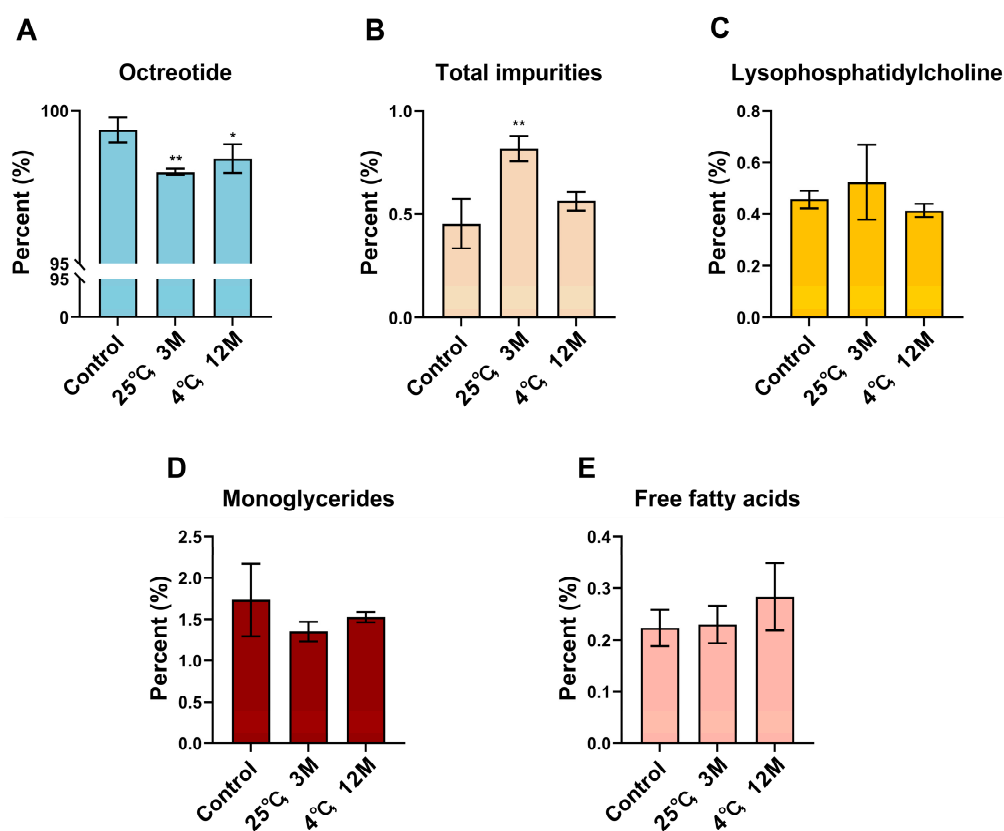


Figure 6. Stability evaluation of octreotide acetate LLC formulations under different storage conditions. (A) Octreotide content. (B) Total impurities. (C) Lysophosphatidylcholine content. (D) Monoglyceride content. (E) Free fatty acid content. Data are presented as mean $\pm$ SD, $n = 3$ per group. * $p < 0.05$, ** $p < 0.01$. One-way ANOVA with Tukey multiple comparisons correction.

3.7. Microstructural Characterization and Long-Term Structural Stability of the Optimized Octreotide Acetate LLC Formulation

To elucidate the structure–function relationship and long-term structural stability of the optimized octreotide acetate LLC formulation under relevant storage conditions, its microstructure was systematically characterized using PLM, SAXS, and Cryo-TEM.

PLM images of the freshly prepared formulation exhibited characteristic fan-like and polygonal textures (Figure 7A), which are typical of the inverse hexagonal (H_2) liquid crystalline phase [34]. PLM observations performed on the octreotide acetate LLC formulation after storage at 4 °C for 12 months showed that these textures were well preserved

(Figure 7B), with no evidence of macroscopic phase separation or structural collapse, indicating good long-term stability.

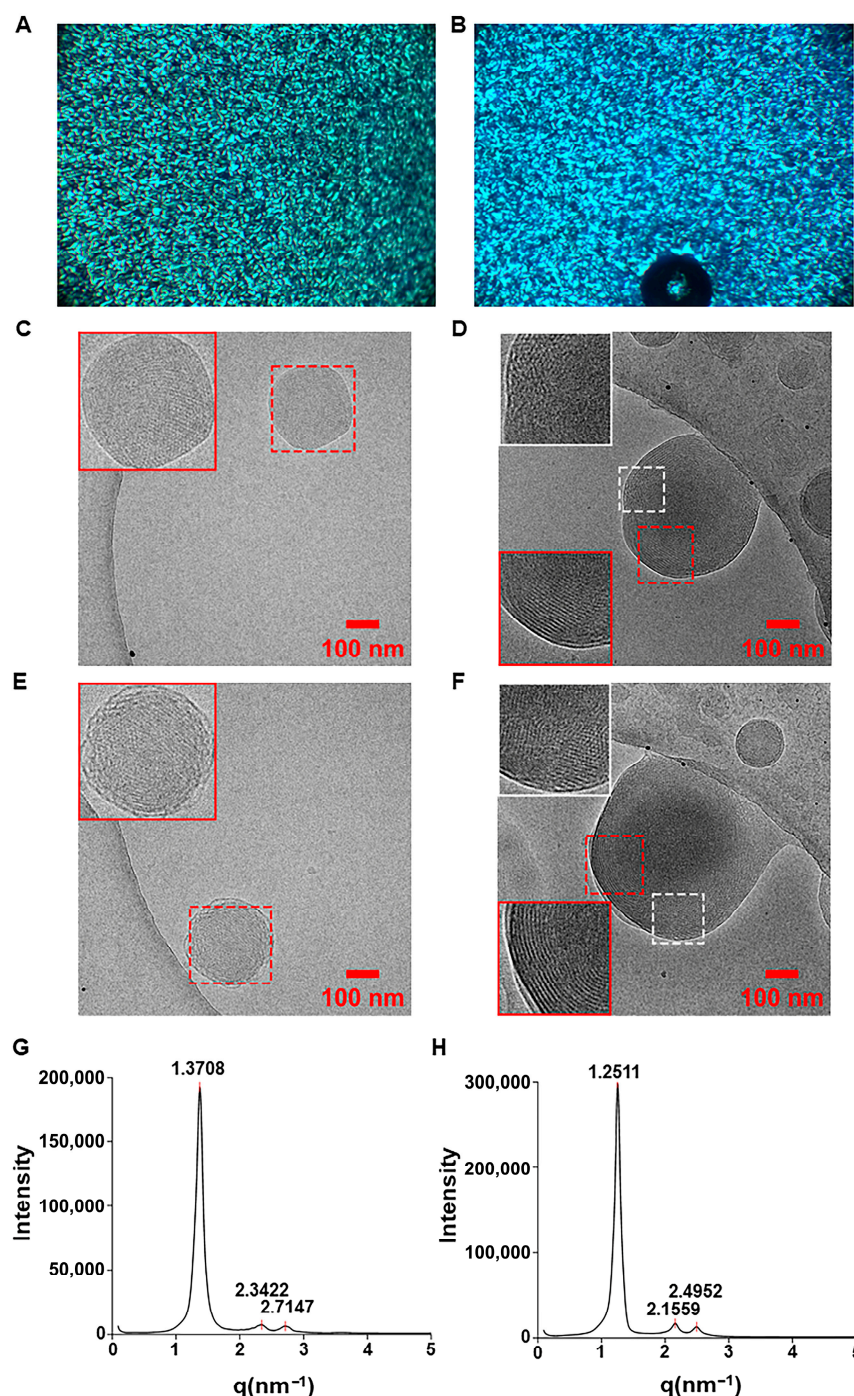


Figure 7. Microstructural characterization and long-term structural stability of the optimized octreotide acetate LLC formulation. (A) PLM image (20×) of the freshly prepared formulation. (B) PLM image (20×) after storage at 4 °C for 12 months. (C,D) Cryo-TEM image of the freshly prepared formulation. The red dashed square indicates the region with straight-line structures, while white dashed square indicates region with hexagonal structures. (E,F) Cryo-TEM image after storage at 4 °C for 12 months. The red dashed square indicates the region with straight-line structures, while white dashed square indicates region with hexagonal structures. (G) SAXS profile of the freshly prepared formulation (H) SAXS profile after storage at 4 °C for 12 months. Red and white squares indicate the magnified views of the red and white dashed squares, respectively.

Cryo-TEM imaging provided direct visualization of the internal nanostructure of the LLC matrix. As shown in Figure 7C, an interconnected network with characteristic periodic contrast was observed, forming a continuous mesh-like architecture. Such features are consistent with inverse bicontinuous cubic (Q_2) phases, reflecting the presence of interpenetrating aqueous channels embedded within the lipid matrix [38]. In addition, regions exhibiting straight-line striations (highlighted by red dashed square) as well as hexagonally arranged domains (highlighted by white dashed square) were identified in Figure 7D, which are typical morphological features of the inverse hexagonal (H_2) liquid crystalline phase [39]. After long-term storage at 4 °C, similar nanostructures were preserved, with Figure 7E showing the retained mesh-like architecture of the Q_2 phase and Figure 7F displaying both straight-line and hexagonally arranged features characteristic of the H_2 phase. No evidence of structural disruption, aggregation, or macroscopic phase separation was observed, indicating the coexistence and long-term physical stability of the Q_2 and H_2 mesophases within the optimized LLC system.

SAXS analysis further confirmed the presence of ordered liquid crystalline structures. The fresh formulation exhibited distinct diffraction peaks at $q = 1.3708, 2.3422$, and 2.7147 nm^{-1} (Figure 7G), with spacing ratios of $1:\sqrt{3}:2$, characteristic of the inverse hexagonal (H_2) phase [40,41]. Importantly, after storage at 4 °C for 12 months, the SAXS profiles retained the same peak positions and spacing ratios (Figure 7H), demonstrating that the long-range mesophase organization remained intact over prolonged storage.

The optimized formulation, containing 10% (w/w) ethanol and adjusted to pH 5.7, exhibited well-defined and persistent mesophase structures, underscoring the critical role of pH modulation and solvent composition in promoting lipid self-assembly. The coexistence of Q_2 and H_2 phases provides complementary functional advantages, wherein the bicontinuous cubic phase supports high drug-loading capacity, while the hexagonal phase offers long-range ordered diffusion pathways that contribute to controlled and sustained release kinetics [27].

3.8. Comparative Pharmacokinetics of Optimized Octreotide Acetate LLC Formulation and Marketed Products in Rats

The pharmacokinetic profiles of the optimized octreotide acetate LLC formulation were compared with those of marketed octreotide products to evaluate its release behavior and long-acting potential. As shown in Figure 8 and Table 6, the LLC formulation exhibited a sustained-release profile that was clearly distinct from the short-acting octreotide injection.

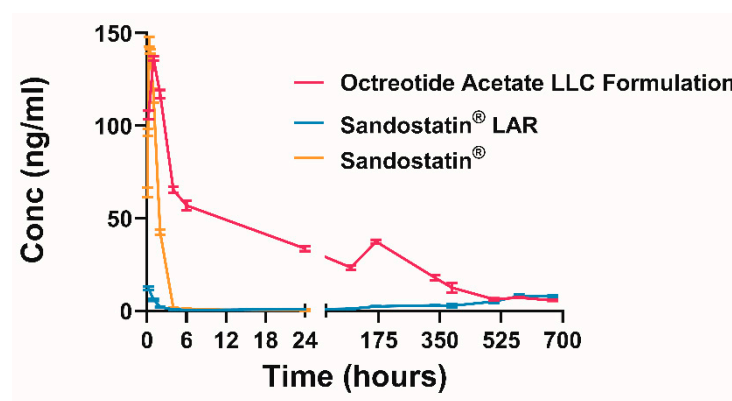


Figure 8. Plasma concentration–time profiles of the optimized octreotide acetate LLC formulation compared with marketed products in rats. Data are presented as mean $\pm$ SD, $n = 5$ per group.

Table 6. Pharmacokinetic parameters of the optimized octreotide acetate LLC formulations compared with marketed products in rats.

Sample	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)	AUC _{0–t} (h·ng/mL)
Octreotide acetate LLC formulation	136.30 ± 1.23	1.00 ± 0.00	190.12 ± 14.64	12,934.24 ± 311.71
Sandostatin [®] LAR	12.23 ± 0.95	0.25 ± 0.00	N/A	2544.19 ± 224.10
Sandostatin [®]	145.27 ± 2.76	0.33 ± 0.00	12.28 ± 9.11	226.48 ± 13.89

Note: Data are presented as mean ± SD (n = 5 per group).

Although the LLC formulation reached a peak plasma concentration (C_{max} = 136.30 ± 1.23 ng/mL) comparable to that of the short-acting formulation (145.27 ± 2.76 ng/mL), it displayed a markedly prolonged elimination half-life (t_{1/2} = 190.12 ± 14.64 h vs. 12.28 ± 9.11 h), resulting in substantially greater systemic exposure, as reflected by a significantly higher AUC_{0–t} (12,934.24 ± 311.71 vs. 226.48 ± 13.89 h·ng/mL). These results indicate that the LLC system is capable of providing sustained drug exposure while maintaining an early peak comparable to the immediate-release product.

In comparison with the marketed microsphere formulation (Sandostatin[®] LAR), the LLC formulation exhibited higher plasma drug concentrations during the early phase, and a higher C_{max} (136.30 ± 1.23 ng/mL vs. 12.23 ± 0.95 ng/mL), demonstrating pronounced initial release characteristics, followed by prolonged systemic exposure. In contrast, Sandostatin[®] LAR showed a delayed-release profile with low early plasma concentrations, consistent with its known lag-phase release characteristics. This delayed onset is associated with the clinical requirement for supplemental short-acting octreotide during treatment initiation to maintain adequate drug levels.

Overall, while both long-acting formulations provided extended drug exposure, the optimized octreotide acetate LLC formulation combined an early exposure phase with sustained release, as demonstrated by its higher initial C_{max}, prolonged half-life, and increased AUC. Together with its simple formulation strategy and ready-to-use liquid presentation, the LLC system represents a promising alternative approach for long-acting octreotide delivery.

4. Discussion

Currently reported LLC formulations of octreotide have utilized the hydrochloride salt, whereas attempts to formulate the acetate salt without pH adjustment failed due to instability. Through systematic evaluation, we found that adjusting the pH to 5.7 using an appropriate amount of 3M HCl–EtOH was critical for obtaining a stable and well-tolerated octreotide acetate LLC formulation.

For peptide drugs such as octreotide acetate, changes in pH directly affect chemical stability [42,43]. Under alkaline conditions, peptides are prone to hydrolysis and acetylation, whereas they remain relatively stable under mildly acidic to near-neutral environments [43]. Moreover, pH can influence the ionization state of lipid excipients, potentially affecting the structural integrity of the LLC system [44]. From a biocompatibility perspective, excessively high or low pH may also cause injection-site irritation, making pH optimization essential [45]. In contrast, octreotide acetate adjusted with CH₃COOH or H₂SO₄ failed to reach the same balance, suggesting that the physicochemical properties of counter-anions, beyond pH alone, may play an important role in stabilizing peptide–lipid systems. Previous studies have shown that peptide degradation and aggregation behaviors are highly sensitive to ionizable microenvironments [46,47]. Moreover, anion valence and hydration strength influence the degree of specific ion–lipid binding and mesophase

stability according to Hofmeister-type effect [48,49]. Monovalent anions such as acetate typically provide weak buffering capacity and insufficient protection from alkaline-driven degradation, whereas divalent sulfate can induce strong ionic cross-linking with peptide side chains and disrupt lipid packing, potentially leading to defects in the liquid-crystal lattice and irritation upon administration [50]. By contrast, chloride—characterized as a weakly coordinating anion—exhibits minimal interference with peptide conformation and lipid self-assembly [51], which likely explains the superior stabilization obtained with HCl–EtOH adjustment.

Upon addition of 3M HCl–EtOH to the octreotide acetate LLC formulation, one to three acetate anions associated with the peptide may be partially or completely replaced by chloride ions. However, owing to steric constraints imposed by the peptide conformation and the capacity of octreotide to associate with one to three chloride ions, the exact number of acetate anions displaced or chloride ions bound to the peptide may vary. Consequently, free acetate and multiple ionic species may coexist within the lyotropic liquid crystal. As the primary focus of this study was to identify strategies for constructing a stable octreotide acetate LLC formulation, quantitative determination of acetate and chloride ions was not performed. In subsequent, more in-depth studies, systematic quantitative analysis of acetate and chloride ions will be conducted to further elucidate the ionic composition and microenvironmental characteristics of the LLC system.

Extensive prior work has demonstrated that peptide salt form, local pH, and ionic environment critically influence peptide–carrier interactions, aggregation propensity, and long-term stability in depot formulations. For example, long-acting insulin analogs and in situ forming insulin depots rely on precise pH control to maintain structural integrity, regulate self-association behavior, and ensure predictable release kinetics [52,53]. These parallels support the broader relevance of microenvironmental pH and counter-ion selection as general determinants of peptide stability in sustained-release delivery systems. In this context, the pH modulation strategy described in the present study may not be limited to octreotide acetate alone. Peptide drugs containing ionizable residues and formulated as organic acid salts may similarly experience destabilization within lipid matrices if the microenvironmental pH and ionic composition are not appropriately controlled. Therefore, adjusting local pH to optimize peptide–lipid compatibility could potentially be extended to other therapeutic peptides formulated in LLC or related non-aqueous lipid depot systems.

5. Conclusions

In this study, we developed a long-acting octreotide acetate LLC formulation by introducing a pH modulation strategy with 3M HCl–EtOH. We found that without pH adjustment, acetate-based formulations were unstable, whereas adjustment to pH $\approx$ 5.7 enabled long-term stability, with >90% drug retention after 3 months at 40 °C and >98% after 12 months at 4 °C. Structural characterization confirmed the coexistence of inverse cubic (Q_2) and hexagonal (H_2) mesophases, providing an ordered nanostructure for sustained release. Pharmacokinetic studies in rats demonstrated prolonged drug exposure with a half-life of up to 190.12 h, markedly longer than conventional injections. Collectively, these findings highlight that pH modulation is a critical enabling factor for stabilizing octreotide acetate in LLC systems, thereby offering a clinically relevant and industrially practical platform for long-acting octreotide therapy.

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Abbreviations

The following abbreviations are used in this manuscript:

LLC	lyotropic liquid crystal
SC	subcutaneous
API	active pharmaceutical ingredient
PBS	phosphate-buffered saline
SPC	soybean phosphatidylcholine
GDO	glycerol dioleate
HPLC	high-performance liquid chromatography
LOQ	limit of quantification
LOD	limit of detection
SEC	size-exclusion chromatography
ELSD	evaporative light scattering detector
SD	Sprague Dawley
LC-MS/MS	liquid chromatography-tandem mass spectrometry
PLM	polarized light microscope
Cryo-TEM	cryogenic transmission electron microscope
SAXS	small-angle X-ray scattering

References

1. Butturini, G.; Bettini, R.; Missiaglia, E.; Mantovani, W.; Dalai, I.; Capelli, P.; Ferdeghini, M.; Pederzoli, P.; Scarpa, A.; Falconi, M. Predictive factors of efficacy of the somatostatin analogue octreotide as first line therapy for advanced pancreatic endocrine carcinoma. *Endocr. Relat. Cancer* **2006**, *13*, 1213–1221. [\[CrossRef\]](#)
2. Jann, H.; Denecke, T.; Koch, M.; Pape, U.F.; Wiedenmann, B.; Pavel, M. Impact of octreotide long-acting release on tumour growth control as a first-line treatment in neuroendocrine tumours of pancreatic origin. *Neuroendocrinology* **2013**, *98*, 137–143. [\[CrossRef\]](#)
3. Daniel, C.P.; Wagner, M.J.; Borne, G.E.; Plaisance, C.J.; Ahmadzadeh, S.; Aquino, A.; Shekoohi, S.; Kaye, A.M.; Cornett, E.M.; Kaye, A.D. Acromegaly: Pathophysiological considerations and treatment options including the evolving role of oral somatostatin analogs. *Pathophysiology* **2023**, *30*, 377–388. [\[CrossRef\]](#)

4. Newman, C.B.; Melmed, S.; George, A.; Torigian, D.; Duhaney, M.; Snyder, P.; Young, W.; Klibanski, A.; Molitch, M.E.; Gagel, R.; et al. Octreotide as primary therapy for acromegaly. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 3034–3040. [CrossRef]
5. Corica, G.; Ceraudo, M.; Campana, C.; Nista, F.; Cocchiara, F.; Boschetti, M.; Zona, G.; Criminelli, D.; Ferone, D.; Gatto, F. Octreotide-resistant acromegaly: Challenges and solutions. *Ther. Clin. Risk Manag.* **2020**, *16*, 379–391. [CrossRef] [PubMed]
6. Somatostatin Analogs Market Size & Share Analysis-Growth, Trends, and Forecast (2025–2030). Available online: <https://www.mordorintelligence.com/industry-reports/somastostatin-analogs-market> (accessed on 26 April 2025).
7. Alexandraki, K.I.; Angelousi, A.; Chatzellis, E.; Chrisoulidou, A.; Kalogeris, N.; Kanakis, G.; Savvidis, C.; Vassiliadi, D.; Spyroglou, A.; Kostopoulos, G.; et al. The role of somatostatin analogues in the control of diarrhea and flushing as markers of carcinoid syndrome: A systematic review and meta-analysis. *J. Pers. Med.* **2023**, *13*, 304. [CrossRef]
8. Garbuzenko, D.V. Current approaches to the management of patients with liver cirrhosis who have acute esophageal variceal bleeding. *Curr. Med. Res. Opin.* **2016**, *32*, 467–475. [CrossRef]
9. Bassi, C.; Falconi, M.; Lombardi, D.; Briani, G.; Vesentini, S.; Camboni, M.G.; Pederzoli, P. Prophylaxis of complications after pancreatic surgery: Results of a multicenter trial in Italy. Italian study group. *Digestion* **1994**, *55*, 41–47. [CrossRef] [PubMed]
10. Büchler, M.; Friess, H.; Klempa, I.; Hermanek, P.; Sulkowski, U.; Becker, H.; Schafmayer, A.; Baca, I.; Lorenz, D.; Meister, R.; et al. Role of octreotide in the prevention of postoperative complications following pancreatic resection. *Am. J. Surg.* **1992**, *163*, 125–131. [CrossRef]
11. Sabatino, G.; Guryanov, I.; Rombecchi, A.; Zanon, J.; Ricci, A.; Cabri, W.; Papini, A.M.; Rovero, P. Production of peptides as generic drugs: A patent landscape of octreotide. *Expert. Opin. Ther. Pat.* **2016**, *26*, 485–495. [CrossRef] [PubMed]
12. Fan, M.; Huang, Y.; Zhu, X.; Zheng, J.; Du, M. Octreotide and octreotide-derived delivery systems. *J. Drug Target.* **2023**, *31*, 569–584. [CrossRef]
13. Dogliotti, L.; Tampellini, M.; Stivanello, M.; Gorzegno, G.; Fabiani, L. The clinical management of neuroendocrine tumors with long-acting repeatable (lar) octreotide: Comparison with standard subcutaneous octreotide therapy. *Ann. Oncol.* **2001**, *12*, S105–S109. [CrossRef] [PubMed]
14. Remba-Shapiro, I.; Nachtigall, L.B. Treatment of acromegaly with oral octreotide. *Best. Pract. Res. Clin. Endocrinol. Metab.* **2024**, *38*, 101888. [CrossRef]
15. Shprakh, Z. Somatostatin analogues for the treatment of neuroendocrine tumours. Dosage forms and routes of administration (review). *Int. J. Appl. Pharm.* **2020**, *12*, 6–11. [CrossRef]
16. Lancranjan, I.; Bruns, C.; Grass, P.; Jaquet, P.; Jervell, J.; Kendall-Taylor, P.; Lamberts, S.W.J.; Marbach, P.; Ørskov, H.; Pagani, G.; et al. Sandostatin lar®: Pharmacokinetics, pharmacodynamics, efficacy, and tolerability in acromegalic patients. *Metabolism* **1995**, *44*, 18–26. [CrossRef]
17. Sandostatin® lar depot. Novartis Pharmaceuticals Corporation. Available online: https://www.novartis.us/sites/novartis_us/files/sandostatin_lar.pdf (accessed on 26 April 2025).
18. Gonella, A.; Grizot, S.; Liu, F.; López Noriega, A.; Richard, J. Long-acting injectable formulation technologies: Challenges and opportunities for the delivery of fragile molecules. *Expert. Opin. Drug Deliv.* **2022**, *19*, 927–944. [CrossRef]
19. Qi, F.; Wu, J.; Li, H.; Ma, G. Recent research and development of PLGA/PLA microspheres/nanoparticles: A review in scientific and industrial aspects. *Front. Chem. Sci. Eng.* **2019**, *13*, 14–27. [CrossRef]
20. Kumar, R.; Palmieri, M.J., Jr. Points to consider when establishing drug product specifications for parenteral microspheres. *Aaps J.* **2010**, *12*, 27–32. [CrossRef]
21. Chung, C. Management of neuroendocrine tumors. *Am. J. Health Syst. Pharm.* **2016**, *73*, 1729–1744. [CrossRef] [PubMed]
22. Kim, J.C.; Park, E.J.; Na, D.H. Gastrointestinal permeation enhancers for the development of oral peptide pharmaceuticals. *Pharmaceutics* **2022**, *15*, 1585. [CrossRef]
23. Guo, C.; Wang, J.; Cao, F.; Lee, R.J.; Zhai, G. Lyotropic liquid crystal systems in drug delivery. *Drug Discov. Today* **2010**, *15*, 1032–1040. [CrossRef]
24. Silvestrini, A.V.P.; Caron, A.L.; Viegas, J.; Praça, F.G.; Bentley, M. Advances in lyotropic liquid crystal systems for skin drug delivery. *Expert. Opin. Drug Deliv.* **2020**, *17*, 1781–1805. [CrossRef] [PubMed]
25. Melmed, S. New therapeutic agents for acromegaly. *Nat. Rev. Endocrinol.* **2016**, *12*, 90–98. [CrossRef] [PubMed]
26. Novartis Pharma, K.K. Interview form: Sandostatin® Injection (Octreotide Acetate). Available online: https://www.pro.novartis.com/sites/pro_novartis_com_jp/files/2024-08/if_sas_h_202008.pdf (accessed on 30 January 2026).
27. Chen, Y.; Ma, P.; Gui, S. Cubic and hexagonal liquid crystals as drug delivery systems. *Biomed. Res. Int.* **2014**, *2014*, 815981. [CrossRef]
28. Yang, B.C.; Chu, Z.F.; Zhu, S.; Wang, L.J.; Feng, Y.H.; Li, F.H.; Liu, C.S.; Yuan, Y. Study of pharmacokinetics and tissue distribution of liposomal brucine for dermal administration. *Int. J. Nanomed.* **2011**, *6*, 1109–1116. [CrossRef]
29. Kamali, H.; Karimi, M.; Abbaspour, M.; Nadim, A.; Hadizadeh, F.; Khodaverdi, E.; Eisvand, F. Comparison of lipid liquid crystal formulation and vivitrol® for sustained release of naltrexone: In vitro evaluation and pharmacokinetics in rats. *Int. J. Pharm.* **2022**, *611*, 121275. [CrossRef] [PubMed]

30. *European Pharmacopoeia*, 11.1st ed.; Council of Europe: Strasbourg, France, 2023.
31. Li, Q.; Liu, Y. Determination of related substances in octreotide acetate and its preparation by hplc. *West China J. Pharm. Sci.* **2023**, *38*, 323–328. [[CrossRef](#)]
32. Han, K.; Pan, X.; Chen, M.; Wang, R.; Xu, Y.; Feng, M.; Li, G.; Huang, M.; Wu, C. Phytantriol-based inverted type bicontinuous cubic phase for vascular embolization and drug sustained release. *Eur. J. Pharm. Sci.* **2010**, *41*, 692–699. [[CrossRef](#)]
33. Chen, Y.; Liang, X.; Ma, P.; Tao, Y.; Wu, X.; Wu, X.; Chu, X.; Gui, S. Phytantriol-based in situ liquid crystals with long-term release for intra-articular administration. *AAPS PharmSciTech* **2015**, *16*, 846–854. [[CrossRef](#)]
34. Saklani, R.; Yadav, P.K.; Nengroo, M.A.; Gawali, S.L.; Hassan, P.A.; Datta, D.; Mishra, D.P.; Dierking, I.; Chourasia, M.K. An injectable in situ depot-forming lipidic lyotropic liquid crystal system for localized intratumoral drug delivery. *Mol. Pharm.* **2022**, *19*, 831–842. [[CrossRef](#)]
35. Rhee, Y.S.; Sohn, M.; Woo, B.H.; Thanoo, B.C.; DeLuca, P.P.; Mansour, H.M. Sustained-release delivery of octreotide from biodegradable polymeric microspheres. *AAPS PharmSciTech* **2011**, *12*, 1293–1301. [[CrossRef](#)]
36. Negrini, R.; Mezzenga, R. Ph-responsive lyotropic liquid crystals for controlled drug delivery. *Langmuir* **2011**, *27*, 5296–5303. [[CrossRef](#)]
37. Shi, M.; McHugh, K.J. Strategies for overcoming protein and peptide instability in biodegradable drug delivery systems. *Adv. Drug Deliv. Rev.* **2023**, *199*, 114904. [[CrossRef](#)]
38. Demurtas, D.; Guichard, P.; Martiel, I.; Mezzenga, R.; Hébert, C.; Sagalowicz, L. Direct visualization of dispersed lipid bicontinuous cubic phases by cryo-electron tomography. *Nat. Commun.* **2015**, *6*, 8915. [[CrossRef](#)] [[PubMed](#)]
39. Pattipeiluhu, R.; Zeng, Y.; Hendrix, M.; Voets, I.K.; Kros, A.; Sharp, T.H. Liquid crystalline inverted lipid phases encapsulating sirna enhance lipid nanoparticle mediated transfection. *Nat. Commun.* **2024**, *15*, 1303. [[CrossRef](#)] [[PubMed](#)]
40. Huang, Y.; Gui, S. Factors affecting the structure of lyotropic liquid crystals and the correlation between structure and drug diffusion. *RSC Adv.* **2018**, *8*, 6978–6987. [[CrossRef](#)]
41. Jones, B.E.; Greenfield, J.L.; Cowieson, N.; Fuchter, M.J.; Evans, R.C. Light-driven hexagonal-to-cubic phase switching in arylazopyrazole lyotropic liquid crystals. *J. Am. Chem. Soc.* **2024**, *146*, 12315–12319. [[CrossRef](#)] [[PubMed](#)]
42. Takasu, Y.; Yoshida, M.; Shimizu, K.; Asahara, K.; Tange, M.; Uchida, T. Prediction of the stability of octreotide in a mixed infusion. *Chem. Pharm. Bull.* **2014**, *62*, 316–321. [[CrossRef](#)]
43. Nugrahi, P.P.; Hinrichs, W.L.J.; Frijlink, H.W.; Schöneich, C.; Avanti, C. Designing formulation strategies for enhanced stability of therapeutic peptides in aqueous solutions: A review. *Pharmaceutics* **2023**, *15*, 935. [[CrossRef](#)]
44. Philipp, J.; Dabkowska, A.; Reiser, A.; Frank, K.; Krzysztoń, R.; Brummer, C.; Nickel, B.; Blanchet, C.E.; Sudarsan, A.; Ibrahim, M.; et al. Ph-dependent structural transitions in cationic ionizable lipid mesophases are critical for lipid nanoparticle function. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2310491120. [[CrossRef](#)]
45. Bak, A.; Leung, D.; Barrett, S.E.; Forster, S.; Minnihan, E.C.; Leithead, A.W.; Cunningham, J.; Toussaint, N.; Crocker, L.S. Physicochemical and formulation developability assessment for therapeutic peptide delivery—A primer. *Aaps J.* **2015**, *17*, 144–155. [[CrossRef](#)]
46. Manning, M.C.; Chou, D.K.; Murphy, B.M.; Payne, R.W.; Katayama, D.S. Stability of protein pharmaceuticals: An update. *Pharm. Res.* **2010**, *27*, 544–575. [[CrossRef](#)]
47. Roberts, C.J. Protein aggregation and its impact on product quality. *Curr. Opin. Biotechnol.* **2014**, *30*, 211–217. [[CrossRef](#)]
48. Zhang, Y.; Cremer, P.S. Interactions between macromolecules and ions: The hofmeister series. *Curr. Opin. Chem. Biol.* **2006**, *10*, 658–663. [[CrossRef](#)]
49. Collins, K.D.; Washabaugh, M.W. The hofmeister effect and the behaviour of water at interfaces. *Q. Rev. Biophys.* **1985**, *18*, 323–422. [[CrossRef](#)] [[PubMed](#)]
50. Zhang, Z.; Ai, S.; Yang, Z.; Li, X. Peptide-based supramolecular hydrogels for local drug delivery. *Adv. Drug Deliv. Rev.* **2021**, *174*, 482–503. [[CrossRef](#)]
51. Salis, A.; Ninham, B.W. Models and mechanisms of hofmeister effects in electrolyte solutions, and colloid and protein systems revisited. *Chem. Soc. Rev.* **2014**, *43*, 7358–7377. [[CrossRef](#)] [[PubMed](#)]
52. Zhang, T.; Luo, J.; Peng, Q.; Dong, J.; Wang, Y.; Gong, T.; Zhang, Z. Injectable and biodegradable phospholipid-based phase separation gel for sustained delivery of insulin. *Colloids Surf. B Biointerfaces* **2019**, *176*, 194–201. [[CrossRef](#)]
53. Fontana, G.; Innamorati, G.; Giacomello, L. Nanoparticle-based oral insulin delivery: Challenges, advances, and future directions. *Pharmaceutics* **2025**, *17*, 1563. [[CrossRef](#)] [[PubMed](#)]

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