



Development, Validation, and Application of a Highly Sensitive RP-HPLC Method for the Determination and Release Profile Comparison of Levonorgestrel from Silicone-Based Contraceptive Implants

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ABSTRACT

Objectives: Levonorgestrel (LNG), a synthetic progestin containing implants, has emerged as one of the most reliable, effective, and long-acting reversible contraceptive (LARC) methods for preventing unintended pregnancies. The current study aimed to develop and validate a simple, rapid, and highly sensitive reverse-phase high-performance liquid chromatography (HPLC) technique for the quantification and release profile comparison of LNG from different silicone-based LARC implants.

Materials and Methods: All the analysis was performed using HPLC equipped with UV/UV-VIS detector with the help of Waters C18 column of 250 × 4.6 mm dimension, 5 µm sized particle with mobile phase consisting of water and acetonitrile in the ratio of 30:70 (v/v%) at room temperature and 1 mL/minute flow rate, injection volume of 50 µL with the detection wavelength of 240 nm. The developed method was then validated as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and then the validated method was used successfully to quantify LNG and for a comparative release profile study of two marketed implants, Femiplant and Sino-implant (II). The obtained release data were assessed and compared using fit factors (f_1 & f_2) to compare one formulation with another.

Results: All parameters met the limits according to ICH guidelines. The total time needed for analysis was 12 minutes, having LNG eluting with a retention time of 5.8 min (± 0.2). The average LNG content was obtained to be 98.52 to 101.32% (± 0.05%). From the release kinetic study, f_1 and f_2 values of Femiplant against Sino-implant (II) determined was 10 and 62, respectively, both of which meet the acceptable limits.

Conclusion: The devolved method was straightforward and quick for any sample preparation, which could be used for routine analysis, in-process quality control analysis, and stability study analysis, among others. Moreover, Femiplant presented similar release kinetics compared to the World Health Organization prequalified implant Sino-implant (II), thereby having similar bioavailability and ensuring the consistent therapeutic effect of both implants.

Keywords: RP-HPLC, method development and validation, LNG, contraceptive implant, release profile comparison

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INTRODUCTION

Hormonal contraceptive subdermal implants are small, flexible rods about the size of a matchstick that provide a continuous release of the low-dose synthetic progestin levonorgestrel (LNG), an effective hormonal treatment intended to control menstrual complaints and endometriosis.^{1,2} LNG, similar to the natural progesterone hormone, is a potent medication used in various birth control systems, e.g., emergency oral contraceptive pills, daily combined oral contraceptives with ethinylestradiol, three-month injectable contraceptives, silicone-based long-acting reversible contraceptive (LARC) implants, and intrauterine devices for birth spacing.³⁻⁵

Various types of LNG-releasing LARC implants are available worldwide including Jadelle of Bayer Oy, Finland, and Levoplant/Sino-implant (II) of Shanghai Dahua Pharmaceuticals Company Limited, China, Jadena and Duplant of Indonesia containing LNG which is effective for up to 3-5 years of effective contraception.⁶⁻⁹ Implanon NXT, also known as Nexplanon, now replaces Implanon with a one-rod system containing etonorgestrel and is considered effective for 3 years of contraceptive action, although a new study describes its effectiveness for contraception for up to 5 years.^{10,11} Norplant, consisting of six capsules, provides 5-7 years of effectiveness, but it became obsolete in 2008 and is not valid for use now. All LNG-containing subdermal implants, consisting of two flexible rods, are placed in a V-shaped configuration, with the rods positioned at a 30-degree angle and 8 to 10 cm above the elbow in a woman's upper arm. Higher doses of LNG are released during the first 6 to 12 months after insertion, with the daily dose declining to a steady 30 to 35 μg per day throughout the shelf life of the system.¹² LNG is a synthetic progesterone hormone available as a naturally occurring female sex hormone, and its chemical formula is $\text{C}_{21}\text{H}_{28}\text{O}_2$ (d-Norgestrel)-13 β -ethyl-17 α -hydroxy-18,19-dinorpregn-4-en-20-yn-3-one (molecular weight is 312.47 g/mol) shown in Figure 1. LNG Implants primarily act by stopping ovulation (the release of eggs from the ovaries), thickening the cervical mucus, and blocking sperm from reaching the eggs.¹³⁻¹⁵

Several analytical techniques, such as UV spectrophotometry, mass spectrometry, reverse-phase high-performance liquid chromatography (HPLC), and LC-MS/MS, can be used for the quantification of LNG, alone or in combination with ethinylestradiol in various dosage forms. Among them, HPLC is

one of the important techniques because of its linearity, accuracy, specificity, precision, robustness, and suitability for sample stability analysis.¹⁶⁻²³ Five years ago, Femiplant, like Jadelle and Levoplant/Sino-Implant II, a long-acting reversible sub-dermal contraceptive implant containing 150 mg of LNG, approved by the Directorate General of Drug Administration, was introduced into the national family planning program of the government of Bangladesh to provide three years of contraception; it is manufactured by a leading local pharmaceutical manufacturer, Techno Drugs Ltd.

In this study, we had an attempt for developing and validating a very simple, rapid, reliable and sensitive as well as constant RP-HPLC method as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines²⁴ to determine and quantify LNG from LARCs subdermal hormonal implants and this newly developed technique has been validated as per ICH guidelines and utilized to quantify and evaluate the comparative release characteristics and kinetic profiles of LNG from two marketed implant formulations like Femiplant of Techno Drugs Ltd, Bangladesh and Levoplant (Sino- Implant II) of Shanghai Dahua Pharmaceuticals Co., Ltd. China which is also a World Health Organization (WHO) prequalified product, both of them are effective for contraception up to 3 years that are available worldwide.

MATERIALS AND METHODS

Chemicals and apparatus with instrumentation

LNG (the active pharmaceutical ingredient) was obtained as a gift sample. Two marketed subdermal implant products, Femiplant and Sino-implant (II), which consist of two flexible, matchstick-like plastic rods, each rod containing 75 mg of LNG, were procured from the market. HPLC-grade solvents such as acetonitrile (Fischer-Scientific, UK) and chloroform (Merck, Germany), HPLC-ready water from Ultra-Pure System, 0.45 μm membrane disc filters, and 0.22 μm syringe filters were used. Moreover, for sample preparation, an electronic microbalance, a sonicator, and a planetary centrifugal mixer were utilized. The Waters RP-HPLC system, equipped with a degasser, autosampler, quaternary solvent delivery pump, column oven, and UV/UV-VIS detector, was used for the development and validation of the method. Data acquisition, processing, and evaluation were performed using LabSolutions software (version 6.40 SP1, Shimadzu).

Wavelength detection

A 0.1 mg/mL LNG stock solution was prepared using 60% acetonitrile, and serial dilution was performed to obtain a 10 μg /mL LNG concentration. This solution was then scanned between 200 nm and 400 nm using a UV spectrophotometer. The wavelength was fixed at 240 nm, and the spectra were recorded.

Chromatographic condition

All analyses were performed using a Waters RP-HPLC system equipped with a UV/UV-VIS detector. The separation of LNG

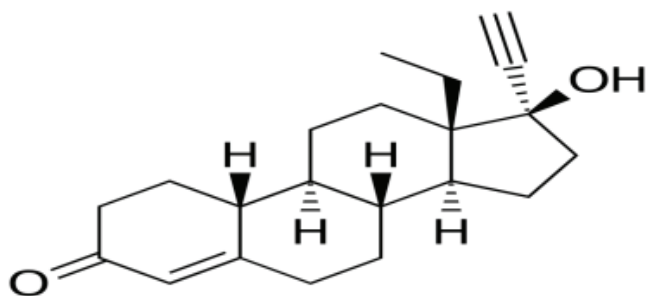


Figure 1. Chemical structure of LNG.
LNG, levonorgestrel.

had been completed with the help of C_{18} column of 250×4.6 mm dimensions, $5 \mu\text{m}$ sized particle in an isocratic mode of mobile phase composed of water and acetonitrile in the ratio of 30:70 (v/v). Drug elution was conducted at room temperature with a flow rate of one mL/minute, an injection volume of $50 \mu\text{L}$, and a total run time of 12 minutes at a detection wavelength of 240 nm. Before injecting the blank and drug solutions, the HPLC system was equilibrated for approximately one hour by degassing with the mobile phase. Then the blank solution was passed through the syringe filter ($0.22 \mu\text{m}$) and finally injected to ensure that there was no interference from the solvent.

Preparation of blank solution

The blank solution was prepared using 60% acetonitrile.

Preparation of LNG stock solution

25 mg of LNG working standard in powder form was weighed accurately and transferred to an amber-colored 100 mL volumetric flask. Then 60 mL of acetonitrile, and the mixture was sonicated for 10 minutes to dissolve completely, and the volume was made up to the mark by thorough mixing. This solution is termed the standard stock solution.

Preparation of LNG standard solution

3.0 mL of the standard stock solution was diluted with acetonitrile to prepare an LNG standard solution of $3.0 \mu\text{g/mL}$. The prepared solution was then filtered with a 0.45-micron filter.

Preparation of calibration curve of standard solutions

A stock solution of the LNG standard was used to prepare a calibration curve with concentrations ranging from 40% to 120% of the standard concentration in 60% acetonitrile. The solutions were filtered through a 0.45-micron filter, transferred to HPLC vials, and each concentration was injected in triplicate and analyzed using the proposed method.

Preparation of sample solution

LNG implants having $\approx 44 \pm 0.5$ mm of length containing total 150 mg of LNG were collected from the supplier. Average weight was determined ($\approx 228 \pm 2$ mg) and three implant rods (of each type) were taken and cut into small fragments (~ 1 mm length). The cut-piece samples equivalent to two rods were transferred to a 100 mL dried volumetric flask; 60 mL of reagent-grade chloroform was added, the mixture was sonicated for 20 minutes, allowed to stand for at least one hour, and then diluted with chloroform to a final volume of 100 mL. Then it was filtered through Whatman filter paper, and 0.5 mL of the solution was transferred into a 100 mL dried volumetric flask and evaporated to dryness. Sixty mL of acetonitrile was poured, sonicated for 10 minutes, and the final volume was obtained. Finally, this solution was filtered for analysis through a $0.2 \mu\text{m}$ syringe filter. The obtained concentration was $7.5 \mu\text{g/mL}$. Assays of all the samples were carried out by injecting them into the HPLC after system suitability testing and under the above conditions.

RP-HPLC method validation

According to ICH guidelines Q2 (R1), the method has been validated for the following parameters: specificity, linearity,

accuracy (recovery), precision, robustness, and sample solution stability.

System suitability

The suitability of the system has been evaluated by injecting a blank solution and a standard solution of LNG and measuring parameters such as tailing factor, theoretical plates, and relative standard deviation (%RSD). The acceptance limits for system suitability and the method were: RSD of peak area for LNG no more than 2%, United States Pharmacopeia (USP) tailing factor no more than 2, and theoretical plates no less than 2000 for the column.

Specificity

The method specificity was demonstrated using an HPLC system by injecting a blank solution, a placebo, and an LNG standard solution. Analysis of the obtained chromatograms showed that the blank and placebo solutions exhibited the retention time of the active pharmaceutical ingredient without interference.

Linearity

Linearity was assessed using a series of solutions prepared by quantitative dilution of the LNG stock solution over the range of 40% to 120% of the working concentration. A calibration curve has been plotted using the average peak area from triplicate injections against solution concentration. The slope, intercept, and correlation coefficient were measured from the curve to confirm the linearity of the proposed method.

Accuracy

By spiking the solution, the accuracy of the analytical technique was measured at three concentrations of LNG: 80%, 100%, and 120%. For each concentration, triplicates were prepared and evaluated for percent recovery and percent RSD.

Precision

Intra-day precision (repeatability) of the placebo solution was assessed on the same day by spiking it with six different standard solutions of LNG ($3.0 \mu\text{g/mL}$), with short intervals between measurements under similar operating conditions. The percent recovery and %RSD were determined to assess the repeatability, and inter-day precision was evaluated by comparing values obtained on two different days for separate HPLC analyses.

Robustness

The robustness of method has been carried out by changing a small and slow variation in the flow rate of ± 0.2 mL/min and mobile phase composition of $\pm 5\%$. The standard LNG solution was measured under those changed conditions, and the percentage RSD for LNG peak area, no. of theoretical plates, and the USP tailing factor for the column were then determined.

Stability of the sample solution

The stability of LNG-based implant systems was tested at regular intervals for up to 72 hours at normal temperature. During each interval, the values for LNG peak area, theoretical plates, and tailing factor were evaluated.

Application of the method

The applicability of the method for assaying LNG and evaluating its release profile from two marketed formulations of LARC implants was assessed.

Analysis of LNG implant

Assay or content determination

In this study, the developed HPLC assay was performed on the commercially available subdermal implant products Femiplant and Levoplant/Sino-Implant II, which contain 150 mg of LNG in two rods, and LNG was quantified for each implant. The quantity of drug released for each sample was measured by peak-area measurement at 240 nm, and the LNG assay per device was then performed using the following formula.

Assay (%);

$$\frac{A_{\text{Sample}} \times C_{\text{Std}} \times P_{\text{Std}}}{A_{\text{Std}} \times C_{\text{Sample}}}$$

Where,

A_{Sample} = Area of sample solution,

A_{Std} = Area of standard solution,

P_{Std} = Potency of standard LNG in percentage,

C_{Std} = Concentration of standard solution,

C_{Sample} = Concentration of sample solution.

Release study of LNG

Six sets of LNG implants (both Femiplant and Levoplant) were taken and divided into pairs. Both ends were tied up with fine threads, respectively and were suspended in a 100 mL stoppered transparent iodine bottle. The distance to the bottom of the bottle was approximately 1 cm. Then, 100 mL of purified water was added, and the iodine bottles were placed in a 37 °C constant-temperature oscillator. The round-trip speed was 60 round trips per minute. The amplitude was 3 cm. After 24 hours of constant temperature oscillation, the solution was discarded. Then, 100 mL of purified water was added, and oscillation continued for 24 hours. The above operation was repeated for 7 days. The solutions from the 3rd, 5th, and 7th days were pooled to form the test solution and then filtered through a 0.45-micron filter. The samples collected on days 3 and 7 were selected for further quantitative analysis and comparison; the remaining samples were not further analyzed. Standard and sample solutions were injected after the system suitability test. The LNG release per day from each set of implants was calculated using the following formula.

Released amount of LNG in µg per set per day;

$$\frac{A_{\text{Sample}} \times W_{\text{Std}} \times 1 \times 100 \times 1000}{A_{\text{Std}} \times 100 \times 100 \times 1} \times P_{\text{Std}}$$

Where,

A_{Sample} = Area of sample solution,

A_{Std} = Area of standard solution,

P_{Std} = Potency of standard LNG in percentage,

W_{Std} = Weight of standard LNG.

Statistical analysis

All the data were analyzed using IBM SPSS Statistics for Windows, Version 20.0.; New York, USA. The Paired Samples t-test was used for comparisons within two groups and data were expressed as mean ± standard deviation.

RESULTS

Method development and optimization by RP-HPLC

Various ratios of water: acetonitrile, such as 20:80, 30:70, 40:60, and 50:50, have been used for method optimization. The optimum mobile phase was chosen based on retention time, resolution, number of theoretical plates, and tailing factor at the maximum detection wavelength of 240 nm by UV spectrophotometry in chloroform. An appropriate separation of LNG having better resolution and less tailing factor of water and acetonitrile in ratio of 30:70 at flow rate of 1 mL/min by C_{18} (250 x 4.6 mm) column of an isocratic condition through 50 µL injection fixing as an optimized condition by HPLC.

Method validation by RP-HPLC

The system suitability results presented in the study indicate that all checked parameters met the acceptance limits for the LNG standard solution. The active drug had retained at 5.8 minutes (± 0.02) having percent RSD of 0.1 of the peak area. It indicates good repeatability in this system. There was no interference from diluents, impurities, or other excipients at the detection wavelength. The observed tailing factor was less than 1.05, indicating acceptable peak symmetry. Moreover, the no. of theoretical plates was at least 2000 in all runs on the chromatograph (Figure 2).

Specificity of method

The chromatograms found from blank, placebo and standard solution of LNG showed that no interference observed at the retention time of 5.8 (± 0.02) for LNG (Figure 2). Peaks were obtained for the blank solution at 2.6 minutes and for the placebo at 1.4 minutes, indicating that the peaks were pure for the analytes and confirming the specificity of the method with respect to retention time.

The close agreement among results obtained at three concentrations (80%, 100%, and 120% of the LNG solution) showed the accuracy of the proposed method. The overall percent recovery ranged from 99.75% to 100% based on 3 spiked samples. The mean percent recovery of LNG at three concentrations met the acceptance criteria shown in Table 1; hence, the method was accurate.

Precision of method

The average %RSD of LNG in the repeatability study of six replicate injections is shown in Table 2; values for intra-day and inter-day quantification were within the limits, confirming the high precision and repeatability of the developed method.

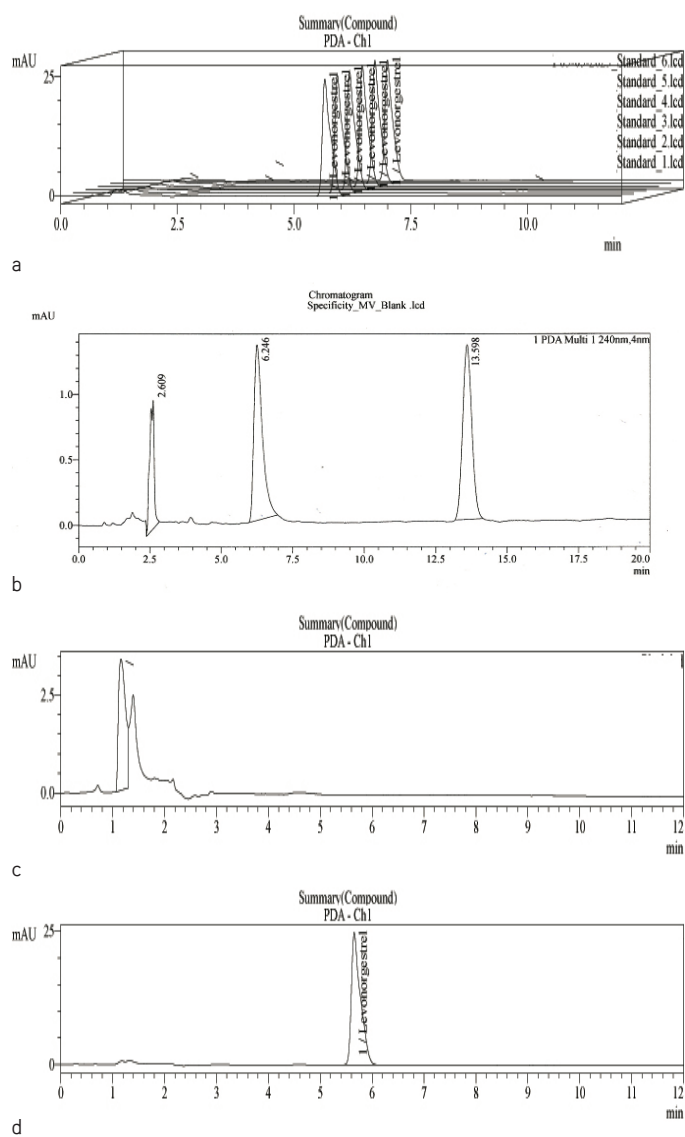


Figure 2. (a) HPLC chromatogram for method validation of LNG.

(b) HPLC chromatogram of blank solution.

(c) HPLC chromatogram of placebo.

(d) HPLC chromatogram of sample solution.

LNG, levonorgestrel; HPLC, high-performance liquid chromatography.

Linearity of method

The calibration curve obtained with the standard LNG solution was linear over various concentration ranges (shown in Figure 3), and the results indicate that the method met the limit of acceptance for linearity.

Robustness of method

Robustness was evaluated in three LNG sample solutions by introducing small variations in chromatographic parameters; the values obtained are shown in Table 3. The percent assay of three LNG standard solutions obtained met the limit of acceptance (tailing factor was less than 2 and the percent RSD was less than 2%) confirming that the method was robust with respect to small variations in flow rate of mobile phase (± 0.2 mL/min), wavelength (± 2 nm) and volume of mobile phase composition ($\pm 5\%$).

Stability of the analytical sample solution

The stability of the analytes was evaluated by analyzing LNG standard and sample solutions stored at room temperature and sampled at various time intervals. The results indicated that the analytes were stable for 72 hours, and the parameters (peak area, tailing factor, and theoretical plates) shown in Table 4 met the acceptance limits; consequently, no significant decomposition of LNG was observed.

Assay or content determination

The validated method was utilized for the analysis of LNG-releasing implants in two marketed subdermal implant preparations, such as Femiplant and Levopant/Sino-Implant, each containing 150 mg LNG (Figures 4 and 5). The average content of LNG was obtained to be 98.52% to 101.32% ($\pm 0.05\%$). The time needed for sample preparation was less than half an hour and total run time was 12 minute, enabling a quick determination of several samples in case of routine or quality control analysis of LNG from flexible silicone-based implants and the low RSD values indicating the suitability of proposed method for analysis of LNG releasing subdermal implant system available in the market.

Release profile evaluation of LNG implants

The graphs presented in Figures 6-8 show a release profile very similar to those of the two marketed LNG implant preparations, which report an extremely similar pattern of LNG release compared with the mean daily in vivo release of LNG: 100 μg daily in the first month, 40 μg daily at 24 months, and 30 μg daily after three years following subdermal insertion. This analysis did not show any indication of significant differences in behavior between the two LNG formulations and therefore

Table 1. LNG study of accuracy and recovery (n=3).

% level	Spiked conc. ($\mu\text{g/mL}$)	Obtained conc. ($\mu\text{g/mL}$)	Recovery (%)	RSD (%)
80	5.5	5.5	99.75	0.35
100	9.5	10.0	100	0.50
120	12.7	15.8	99.98	0.52

LNG, levonorgestrel; RSD (%), percent relative standard deviation.

Table 2. Intra-day and inter-day results of precision (n=6).

Precision	Peak area	RSD (%)	%Recovery factor	RSD (%) recovery
Intra-day (repeatability)	57750	0.560	1.525	0.55
Inter-day precision				
Day 1, system 1, analyst 1	55650	2.552	1.654	0.43
Day 2, system 1, analyst 1	55765	2.342	1.697	1.32
Day 2, system 2, analyst 2	66765	2.653	1.669	2.55

RSD (%), percent relative standard deviation.

Table 3. Results of robustness under various parameters (n=6).

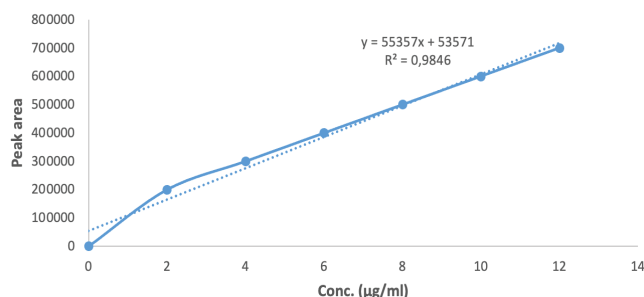
Parameters	Percent RSD	Average tailing factor	Theoretical plate
Flow rate at 1.2 mL/min	0.11	1.525	32923
Flow rate at 0.8 mL/min	0.09	1.654	32883
Water: acetonitrile, 40:60	0.07	1.697	35976
Water: acetonitrile, 20:80	0.06	1,669	33645

RSD, relative standard deviation.

Table 4. Results for stability study.

Time interval (hours)	Peak area	Tailing factor (acceptance limit, <2)	Theoretical plate (acceptance limit, NLT 2000)
0	56750	1.725	33923
24	57650	1.674	34883
48	59765	1.637	34976
72	59915	1,662	35645

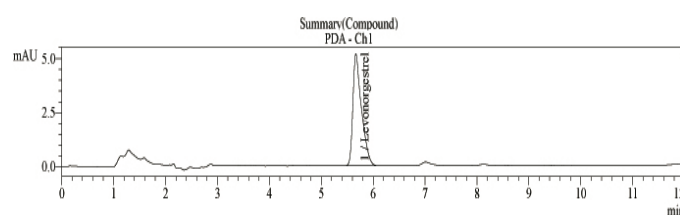
NLT, not less than.

**Figure 3.** Linearity curve of LNG. Accuracy of method.

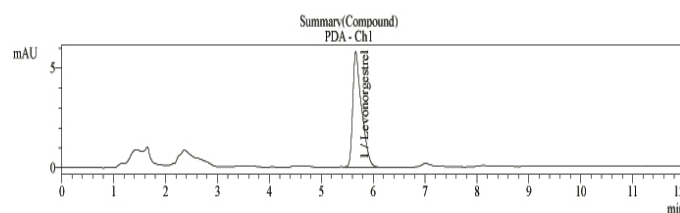
LNG, levonorgestrel.

failed to explain the unsuccessful results observed in vivo bioequivalence studies. Moreover, we determined the fit factors, such as f_1 (similarity factor) and f_2 (dissimilarity factor), by applying the following formulas to confirm whether the release profile of Femiplant is comparable to that of Levoplant/Sino-Implant-II.

In this study, the comparison of f_1 and f_2 values thus offers an opportunity to easily compare and determine pairs of release profile and it is observed that f_1 (difference factor)

**Figure 4.** Representative HPLC chromatogram for the assay of LNG from femiplant.

LNG, levonorgestrel; HPLC, high-performance liquid chromatography.

**Figure 5.** Representative HPLC chromatogram for the assay of LNG from Levoplant.

LNG, levonorgestrel; HPLC, high-performance liquid chromatography.

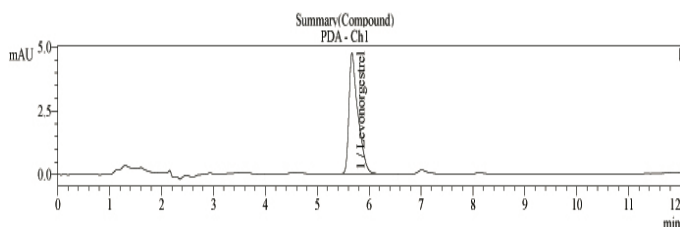


Figure 6. Representative chromatogram of release profile study of LNG from Femiplant at seventh day.

LNG, levonorgestrel; HPLC, high-performance liquid chromatography.

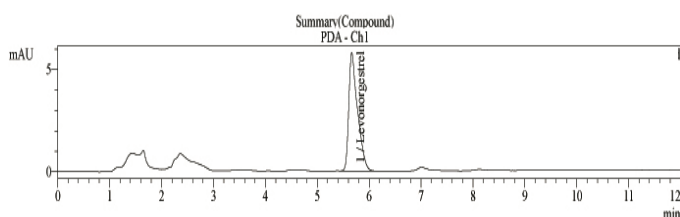


Figure 7. Representative chromatogram of release profile of LNG from Levoplant at seventh day.

LNG, levonorgestrel.

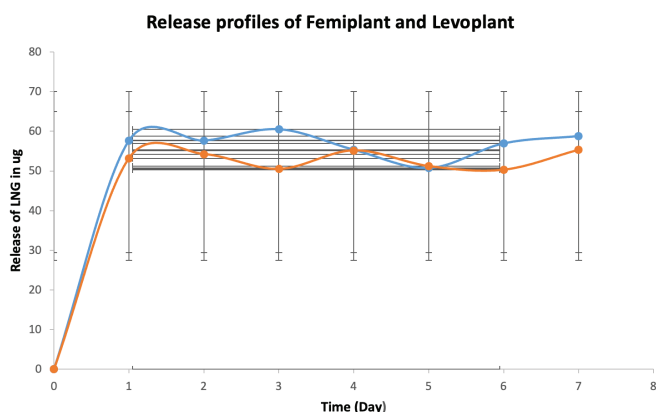


Figure 8. Release profile between Femiplant (green line) and Levoplant (pink line).

Table 5. Release profile comparison of femiplant and sino-implant.

LNG-implants	Difference factor of Femiplant compared to Levoplant (f_1)	Similarity factor of Femiplant compared to levoplant (f_2)
Femiplant	10	62
Acceptance criteria	0-15	50-100

LNG, levonorgestrel.

and f_2 (similarity factor) value between Femiplant against Sino-Implant (Levoplant) is 10 and 62 respectively, shown in Table 5, both of them met the acceptance criteria indicating a very similar release profile for both of the silicone-based implants thereby having similar bioavailability and ensuring the consistent therapeutic effect of these two products.

DISCUSSION

In our study, a specific and robust HPLC method was developed and optimized for the quantification of LNG from contraceptive subdermal implants. Among several mobile phase compositions examined, a combination of water: acetonitrile (30:70 v/v) at a 1.0 mL/min flow rate utilizing a C_{18} reverse phase column of 250×4.6 mm under isocratic conditions formed sharp and symmetric peaks with an acceptable retention time and resolution, detecting at 240 nm provided optimal sensitivity for LNG determination.

System suitability results established the suitability of the system, with a retention time of 5.8 ± 0.02 minute, tailing factor <1.05 , and theoretical plates >2000 , demonstrating outstanding effectiveness and repeatability. The absence of interference from blank or placebo samples confirmed method specificity, and the method demonstrated excellent linearity over the concentration range, meeting ICH criteria. In addition, the method demonstrated high precision, with mean recovery values of 99.75% and 100%, and outstanding accuracy, with %RSD values $<2\%$ for both intra- and inter-day analyses. Minor variations in chromatographic factors did not significantly affect the results, confirming the robustness of the technique. LNG remained stable for up to 72 hours, demonstrating the system's suitability for routine analysis.

The validated method was used for LNG assay and for comparing release profiles of two marketed formulations, Femiplant and Levoplant/Sino-Implant, yielding values between 98.52% and 101.32% and meeting the content uniformity standard. The release profiles of both types of implants were comparable, with $f_1 = 10$ and $f_2 = 62$, meeting the similarity criteria and indicating equivalent release profiles and bioavailability performance.

Overall, the developed RP-HPLC method proved to be simple, precise, accurate, specific, and robust, making it appropriate for routine QC analysis and release-rate studies in subdermal contraceptive implant dosage forms.

Study limitations

The current study may be limited by the number and variety of samples analysed, as well as the degree of method validation across the various implant dosage forms. Moreover, this comparative analysis between two types of silicone-based contraceptive implant formulations limited the generalizability of the results to other formulations, such as polymer-based implants. In addition, similar *in vitro* release profiles of Levonorgestrel do not necessarily ensure equivalence with *in vivo* findings under physiological conditions for contraceptive effectiveness and therefore require suitable pharmacokinetic or bioequivalence studies in a clinical setting.

CONCLUSION

The developed HPLC method demonstrated simple, rapid, and efficient sample preparation, making it appropriate for routine analysis, in-process quality control, and stability studies of LNG in subdermal implants. Method validation confirmed that specificity, linearity, accuracy, precision, and robustness met the acceptance criteria as per ICH guidelines, ensuring that the method was consistent and reproducible. Importantly, this method was used effectively to assess the release-kinetic profiles of marketed formulations without interference. With a total run time of 12 minutes (less than 30 minutes), the method enables high-throughput analysis, allowing rapid quantification of a large number of samples for routine or quality-control laboratory analyses. Application of this method to commercially available implants showed that Femiplant had a release profile comparable to Sino-implant (II), a WHO-prequalified subdermal implant. Such similarity in release kinetics offers strong evidence of bioequivalence between the two types of implants.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: A.K.L.K., E.H., M.M., Design: A.K.L.K., M.M., Data Collection or Processing: A.K.L.K., E.H., M.M., Analysis or Interpretation: A.K.L.K., E.H., Literature Search: A.K.L.K., E.H., Writing: A.K.L.K., E.H., S.C.B., M.M.

Conflict of Interest: The authors declare no conflicts of interest.

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