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A COMPREHENSIVE REVIEW: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF UTERINE ANTIFIBRINOLYTICS BY HPLC

Rushikesh Patil, Pallavi Badhan * and Lalit Lata Jha

Department of Pharmaceutical Chemistry, School of Pharmacy, Parul University, P.O. Limda, Ta. Waghodia - 391760, Gujarat, India.

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Correspondence to Author:
Mrs. Pallavi Badhan

Research Scholar,
Department of Pharmaceutical Chemistry,
School of Pharmacy, Parul University,
P.O. Limda, Ta. Waghodia - 391760,
Gujarat, India.

E-mail: pallavi.badhan20673@paruluniversity.ac.in

ABSTRACT: The estimation of pharmaceutical and biological materials typically uses the key qualitative and quantitative technique known as high performance liquid chromatography (HPLC). It is the most adaptable, secure, trustworthy, and quick chromatographic approach for drug component quality control. Uterine fibroids are non-malignant developments that create in the uterus. They are otherwise called leiomyomas or myomas. Fibroids can be asymptomatic, however when they really do cause side effects, they can incorporate weighty feminine dying, longer or more continuous periods, pelvic strain or agony, successive pee or inconvenience peeing, developing stomach region, blockage, torment in the stomach region or lower back. This survey conveys a detail portrayal of logical ways were printed for the assessment of uterine fibroids drugs and its mix medication in prescribed drugs and natural frameworks. This evaluation incorporates scientific ways like high performance liquid chromatography (HPLC) study for the assessment of uterine fibroids drugs and with a blend combination. The purpose of this article is to evaluate the use of HPLC for chromatographic analysis of medications used to treat uterine fibroids. This survey can give a complete knowledge to specialists preceding fostering an evaluation technique and choosing a finder.

INTRODUCTION: Uterine fibroids, also known as leiomyomas and myomas, are benign neoplasms that are rich in extracellular matrix (ECM) and are made up of smooth muscle cells and fibroblasts. Between menarche and menopause, fibroids appear to form and control gene expression in response to the menstrual cyclicity of gonadal steroids, primarily oestrogen and progesterone [1].

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Uterine smooth muscle tissue, or the myometrium, is the origin of uterine fibroids, which are monoclonal tumours. Fibroids are benign neoplasms with an extensive extracellular matrix covering their disorganized smooth-muscle cells histologically. *In-vivo*, the cells multiply only moderately.

A significant amount of tumour growth is also accounted for by the formation of the extracellular matrix. Almost typically, uterine fibroids are benign [2]. Subserosal (projecting outside the uterus), intramural (inside the myometrium), and submucosal (projecting into the uterine cavity) are the three different types of uterine fibroids. The size, number, and location of the tumours have an

impact on the symptoms and available treatments. They could manifest asymptomatically or induce a variety of serious and persistent symptoms. Heavy menstrual bleeding, which can cause anaemia, exhaustion, and painful periods, is the most typical presenting symptom. Non-cyclic discomfort, abdominal protuberance, painful intercourse or pelvic pressure, and bladder or bowel malfunction leading to urine incontinence or retention, pain, or constipation are other uterine fibroids symptoms [3, 4]. Analogs of the gonadotropin-releasing hormone (GnRH), which inhibit ovarian function and lower estrogen and progesterone levels in the blood, shrink fibroids and lessen related uterine hemorrhage [2]. The most frequent neoplasm in women is uterine fibroids, and by the time menopause begins, it has been estimated that over 70% of women have them. About 25% of women with UFs are predicted to have symptoms severe enough to warrant therapy and 25% of women with UFs are estimated to have symptoms that are clinically noticeable. However, because it often goes misdiagnosed in women because it is asymptomatic or shows signs slowly over time, the condition's prevalence is probably underestimated [4, 5]. Myomectomy, thermoablative therapies, blood vessel embolization procedures, magnetic resonance guided focused ultrasounds (MRgFUSs), and symptomatic medical therapies (i.e. progesterone receptor modulators, tranexamic acid, gonadotropin releasing hormone agonists, and primarily both the oral contraceptive and the levonorgestrel intrauterine device) are additional options for fibroids management [6].

The current review was completed with the target of considering the different HPLC techniques created for the assurance of medications which are utilized for treatment of uterine fibroids in bulk and in various pharmaceutical forms.

High Performance Liquid Chromatography (HPLC): High performance liquid chromatography (HPLC) is an essential analytical tool in assessing drug product. The numerous pharmaceuticals and drug-related degradants that might occur during storage or production should be able to be separated, detected, and quantified by HPLC techniques. These strategies ought to likewise have the option to distinguish and evaluate any drugs and drugs related pollutants that might be added during synthesis [7, 8]. HPLC is a scientific strategy where solutes are settled by differential phases of elution as they go through a chromatographic section. The technique for partition by this instrument is represented by dispersion between the moving phase and stationary phase. The instrumentation is made-up of eight basic components, mobile phase reservoir, solvent delivery system, sample introduction device, column, detector, waste reservoir, connective tubing and computer, integrator or recorder. The fruitful utilization of HPLC for the conceivable issue requires the right blend of assortment of working circumstances, for example, the sort of segment pressing and portable stage, section length and measurement, versatile stage stream rate, section temperature and test size [9]. In modern drug industry, high-performance liquid chromatography (HPLC) is the major furthermore, essential scientific device applied in all phases of medication disclosure, improvement, and creation. HPLC is the technique for decision for really taking a look at top immaculateness of new substance elements, observing response changes is in manufactured techniques or scale up, assessing new details and completing quality control/confirmation of the last medication items [8]. HPLC is the most reliable scientific strategies generally utilized for the quantitative as well as subjective investigation of drugs and utilized for deciding drug strength. The adsorption of solute on stationary phase based on its affinity towards stationary phase is the separation principle that is used [8, 10].

Method Validation: The act of validating anything involves examining it and offering unbiased proof that it satisfies the standards for a certain intended application. A procedure for assessing a method's effectiveness and proving that it satisfies a certain condition. It basically knows what your approach can give, especially at low doses [11]. The applicant's planned and methodical gathering of the validation data to support analytical procedures is the first step in the methods validation process for analytical procedures. Validation is required for all analytical techniques intended for use with clinical material. Analytical techniques are validated in accordance with ICH parameters [7].

Validation Parameters: According to ICH Q2(R1) guidelines, these common analytical

performance traits may be evaluated during method validation [7, 12]:

1. Accuracy
2. Precision
3. Repeatability
4. Intermediate precision
5. Linearity
6. Detection of limit (LOD)
7. Quantitation of limit (LOQ)
8. Specificity
9. Range
10. Robustness

Specificity: The capacity to evaluate the analyte without a doubt in the presence of potentially present components is known as specificity. Typically, they might include pollutants, matrix, degradants, *etc*. The lack of specificity in a given analytical method can be compensated for by other supporting analytical procedures. The applications of this definition are as follows:

Identification: to confirm an analyte's identification.

Purity Tests: to make sure that every analytical technique used, such as the related substances test and the residual solvents content, allows an accurate description of the impurity content of an analyte.

Assay (content or potency): to yield a precise result that enables an exact declaration of the analyte's content or potency in the sample [14, 15].

Accuracy: The accuracy is closeness of agreement between test and standard value. It is mostly express in % recovery. Accuracy should be determined across its range [13, 16].

Precision: Precision is performed by measurement of six homogenous concentration of 100% test solution. Precision might be considered at three levels: repeatability, Intermediate Precision and reproducibility [16]. Investigations into precision should be conducted with true, uniform samples. On the other hand, artificially generated samples or a sample solution may be used for investigation if a homogenous sample cannot be obtained. A sequence of measurements' variance, standard deviation, or coefficient of variation are typically used to express an analytical procedure's precision [15, 18].

Repeatability: When an analysis is performed in a same laboratory by a same analyst with a sameinstrument over a brief period of time, repeatability is achieved [15].

Intermediate Precision: Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, *etc* [15].

Reproducibility: The precision between laboratories is expressed by reproducibility (collaborative studies, usually applied to standardization of methodology). When the analysis is performed over an uncertain period of time in different laboratories by different analyst with many types of equipment, reproducibility is achieved [15].

Linearity: The ability of an analytical method to obtain test results that are directly proportional to the concentration (amount) of analyte in the sample, within a specified range, is known as linearity [13, 15].

Detection of Limit: The lowest concentration of analyte in a sample that can be identified but not always quantified as an exact number is known as the detection limit of a particular analytical technique. The detection limit (DL) can be expressed as:

$$DL = 3.3\sigma / S$$ [17].

Quantitation of Limit: The lowest concentration of analyte in a sample that can be quantitatively identified with appropriate precision and accuracy is known as the quantitation limit of a particular analytical process. When determining impurities and/or degradation products, the quantitation limit is a parameter of quantitative tests for low concentrations of chemicals in sample matrices. The quantitation limit (QL) can be expressed as:

$$QL = 10\sigma / S$$ [18].

Range: The interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been shown that the analytical procedure has an appropriate degree of precision, accuracy, and linearity is known as the range of the analytical procedure [15, 17].

Robustness: An analytical procedure's robustness is an ability of the material to overcome slight but intentional changes in method parameters and gives an indicator of its reliability under typical use [13, 18].

HPLC Analysis of Leuprolide: Leuprolide belongs to a class of drugs known as gonadotropin-releasing hormone (GnRH) agonists, and it works by suppressing the production of certain hormones, including estrogen and progesterone, which can stimulate the growth of uterine fibroids.

According to a study by Foram Vandara *et al.,* (2018), Development and Validation of Stability Indicating HPLC Method for Estimation of Leuprolide Acetate in Its Parenteral Dosage Form. In this research, an RP-HPLC technique for the quantitative detection of leuprolide acetate was developed using YMC-Pack ODS-A(150mmX46mm), 3µ stationary phase. Mobile Phase A [Buffer (Triethylamine in milli Q water): Organic mixture (Acetonitrile: n-Propanol) (60:40)] was used to produce chromatographic separation. respectively, Mobile phase B (Buffer: Organic mixture) (50:50), the flow rate was maintained 1.1 ml /min and UV detection at 220 nm. Retention time was found to be 12 to 15 min. The linearity in the range of 50-150 µg/ml with a correlation coefficient (r^2) of 0.999 [19].

In an experiment by Jagdish Singh *et al.,* (2007), Quantitation of Leuprolide Acetate by High Performance Liquid Chromatography, Leuprolide acetate was analysed by high performance liquid chromatography (HPLC) using an isocratic method, which made use a C18 MICROSORB-MVTM column (4.6 mm× 15 cm), The mobile phase consisted of dibasic ammonium phosphate buffer (0.03 M, pH 6.4): acetonitrile (77:23 v/v).The flow rate was 2.0 ml/min, and the injection volume was 80 µl. The calibration curve's leuprolide acetate concentrations (5–30 g/ml) were used to determine the linearity assay's results, (r^2 =0.9999). At a signal-to-noise ratio of 3:1, it was discovered that the detection limit for leuprolide acetate using this approach was 100 ng/ml. The intra-day and inter-day method precision (%C.V.) was 0.612 and 0.26 respectively [20].

HPLC Analysis of Ulipristal Acetate: Ulipristal Acetic acid derivation is a particular progesterone receptor modulator (SPRM) that is utilized to treat uterine fibroids and as an impermanent prophylactic. Synthetically it is [(8S, 11R, 13S, 14S, 17R)- 17-acetyl-11-[4-(dimethylamino) phenyl]-13-methyl-3-oxo1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-17-yl] acetate. Ulipristal Acetic acid derivation works by obstructing ovulation and keeping progesterone from restricting to the receptor, which stops quality record and blocks the formation of proteins expected to begin and keep up with pregnancy.

Rao, A. Lakshmana, *et al.* Development and validation of stability indicating HPLC method for the determination of ulipristal acetate in pharmaceutical dosage form, a new, delicate and proficient HPLC strategy was created and approved according to ICH rules. To accomplish the best chromatographic division of Ulipristal Acetic acid derivation, a mix of 0.1 percent ortho phosphoric corrosive and acetonitrile (50:50 v/v, pH 4.0 was changed with triethyl amine) was viewed as the best portable stage utilizing a Phenoxneome C18 (150 mm x 4.6 mm, 5 µm) segment. The segment at a stream pace of 1.0 ml/min and location of frequency at 223 nm.

The retention time of Ulipristal Acetic acid derivation was 1.895 min. With a correlation value of 0.999, the methodology was linear for ulipristal acetic acid derivation in the scope of 20-100 µg/ml. Intra-day and inter-day not entirely settled to have %RSD upsides of 1.084 and 0.906, separately. The %recoveries of Ulipristal Acetic acid derivation were viewed as in the scope of 98.15-101.45%, and the technique is accuracy since the %mean still up in the air to be 99.82%. The limit of detection and limit of quantitation were viewed as 0.064 µg/ml and 0.190 µg/ml. Ulipristal Acetic acid derivation's steadiness examinations under different pressure boundaries uncovered the accompanying corruption rate.

Acidic debasement has a 12.40 % corruption rate and the debasement item at first showed up at maintenance season of 1.858 minutes. The alkali debasement item previously displayed with a maintenance season of 1.847 min, and the corruption rate is 23.90%. On account of oxidative debasement, the item corrupted at a pace of 53.63 % after 1.833 minutes of maintenance time. The debasement item happened during neutral degradation with a maintenance season of 1.809 minutes, and the percent corruption is 5.06 %[21].

In another study conducted by Jayshreemaa Biswal *et al.,* Novel Method for Chromatographic Determination of Ulipristal Acetate in Pure Form and Formulation by Using RP-HPLC. In this work, a strategy for the exact and touchy estimation of the dynamic fixing ulipristal acetic acid derivation in the mass and business portion structure was created and approved. A 60:40 (v/v%) combination of acetonitrile and methanol was utilized as the mobile phase. An Evenness C18, ODS (250 mm x 4.6 mm, 5 µm), reverse phase column section was utilized for the examinations, with stream paces of 1 ml/min, infusion volumes of 20µl, run terms of 6 min, and wavelength detection at 275 nm. The retention time was 2.57 minutes. Intra-day and between day precisions were found to be 0.886 % RSD and 0.776 % RSD, separately. The linearity investigation of Ulipristal Acetic acid derivation was found in the focus scope of 10-50 µg/ml, with a r^2 worth of 0.999. The recognition and quantitation limits for ulipristal acetic acid derivation were 0.08 µg/ml and 0.24 µg/ml, separately.

As per the consequences of dependability tests done under different pressure circumstances, ulipristal acetic acid derivation corrupted in various ways. In essential hydrolysis, the presence of the debasement item at 2.59 min maintenance time and the convergence of the quantity of corrupted items were noticed was 16.63%. Warm weakening brought about a decayed item with a convergence of 1.08% and a maintenance term of 2.63 minutes. The decay part at first showed up during corrosive hydrolysis during a maintenance time of 2.59 minutes, and the general level of corruption items was 18.64 %. Debasement items brought about by photolytic corruption show with a maintenance time of 2.57 minutes and a centralization of 3.67. The breakdown of hydrogen peroxide occurred after 2.56 minutes of maintenance time, and the debased item had a pH of 10.59. According to the recommendations of the ICH guidelines, this work constitutes the development of a stability-indicating RP-HPLC technique for the measurement of ulipristal acetate. The suggested approach demonstrated respectable precision, selectivity, and accuracy across a broad linear concentration range. The review's discoveries showed that the method is fitting for deciding ulipristal acetic acid derivation in tablet measurement's structure and mass without obstruction from corruption items, and it is educated for routine quality control examination concerning ulipristal acetic acid derivation in pharmaceutical formulation [22].

HPLC Analysis of Relugolix: Relugolix is a drug typically used to treat uterine fibroids, although it is also effective in treating endometriosis and advanced prostate cancer. Relugolix is a member of the group of drugs known as GnRH receptor antagonists, which also includes other similar drugs. It functions by inhibiting the activity of GnRH, a hormone involved in controlling both hormone synthesis and the menstrual cycle. Relugolix is used to treat uterine fibroids' mild to severe symptoms. It can aid in easing pelvic discomfort, excessive menstrual flow, and other fibroids-related symptoms. Women with symptomatic fibroids who do not want to become pregnant are generally administered it.

In an experiment by Meruva Sathish Kumar *et al.*, RP-HPLC method development and validation of Relugolix. In this research, an RP-HPLC technique for the quantitative detection of Relugolix was developed usingthe Zobrax, 160x5.5mm, 5 µm column coupled to the PDA detector was used to separate all contaminants and active medicines. Acetonitrile (Phase A) and Ammonium used as the mobile phases (Phase B).Proportion of mobile phase was 55:45 (v/v%) respectively. The flow rate of the mobile phase was held constant at 1.0 ml/min. The components were found using a UV detector set at 310 nm. The retention time for Relugolix were 2.79 minutes. The ICH criteria were used to verify the analytical procedure (ICH, Q2 R1), Relugolix linearity analysis revealed that it was linear between concentrations of 15µg/ml and 90 µg/ml, with an r^2 value of 0.999.Relugolix had

detection and quantitation limits of 0.4 µg/ml and 1.2µg/ml, respectively. Method Precision & intermediate precision were found to be0.5% RSD and 0.2% RSD, respectively. A straight forward and designated soundness showing slope RP-HPLC method was created in the ongoing review for the quantitative assurance of Relugolix and its connected mixtures in tablet dose structure. For deciding the medication content and portraying the corruption items under different pressure circumstances, a clear, explicit, precise, and examine strategy were deeply grounded [23].

HPLC Analysis of Estradiol: A variation of the female sex hormone oestrogen is estradiol. It is occasionally used in conjunction with hormone treatment to treat various menopause-related symptoms, including hot flashes and vaginal dryness. Heavy monthly bleeding caused by uterine fibroids in premenopausal women is a distinct medical issue that is treated with the combination of estradiol, relugolix, and norethindrone acetate. Targeting the hormonal variables that cause excessive menstrual bleeding in those with uterine fibroids is the goal of this pharmaceutical cocktail. It can assist with the management of the symptoms linked to this problem, such as heavy periods, pelvic discomfort, and anaemia brought on by blood loss, by controlling hormone levels and stifling the growth of fibroids.

According to study by Ribeiro, Ana R., *et al.*, Microbial degradation of 17β-estradiol and 17α-ethinylestradiol followed by a validated HPLC-DAD method. Following the biodegradation tests, a specially created and verified technique called High Performance Liquid Chromatography-Diode Array Detector (HPLC-DAD) was used. The reverse phase 250-4 HPLC-Cartridge LiChrospher 100 C-18 column was used for the chromatographic study. The mobile phase was acetonitrile/water (52:48, V/V) that had been acidified to pH 2 with trifluoroacetic anhydride TFAA and flowed at a rate of 1 ml/min. The eluted peaks were seen at 280 nm, and the injection volume was 20 µl. Retention time of E2, EE2 & E1 was found to be6.37 min, 7.04 min and 7.95min, respectively. The test for linearity was run at estrogens values between 0.8 and 5.6 µg/ml, with an r^2 value of E2, EE2 & E1 was 0.9945, 0.9998 and 0.9935, respectively. The detection and quantification limits for E2, EE2, and E1 were 0.105 and 0.319 µg/ml, 0.050 and 0.150 µg/ml, and 0.090 and 0.270 µg/ml, respectively. Intra-day and inter-day precisions for E2, EE2 and E1 were discovered to be 4.0 and 1.1 %RSD, 3.0 and 2.6 %RSD, and 1.5 and 5.5 %RSD, respectively. A straightforward, quick, and affordable HPLC-DAD technique was created and verified. The technique proved to be accurate, precise, and selective [24].

In another study conducted by Nováková, Lucie, *et al.* HPLC determination of estradiol, its degradation product, and preservatives in new topical formulation Estrogel HBF. On the analytical column, Supelco Discovery C18 (250 mm×3.0 mm 5µm particle), all chemicals were well separated. The mobile phase was a 23:24:53 v/v solution of acetonitrile, methanol, and water. Analytes were detected and quantitated using UV absorbance at 225 nm. Less than 12 minutes were spent on the analysis at a flow rate of 0.9 ml per minute by complying by the international ICH guidelines for validating analytical methods (Q2A and Q2B) Linearity was determined in the 20% to 150% range of concentration with correlation value of 0.9998. The precision value of estradiol and estrone was 0.39% RSD & 2.4% RSD, respectively. The detection and quantification limits for estradiol & estrone was 0.041 & 0.14 µg/ml and 1.3 & 4.0µg/ml, respectively. % recovery of estradiol and estrone is 97.19% & 97.95%, respectively. The unique analytical technique established in this study for the identification of the active component estradiol, two preservatives (methylparaben and propylparaben), and the degradation product estrone is efficient, quick, and satisfies all requirements for method validation [25].

Under investigation by Aydoğmuş, Zeynep, *et al.*, Development of simultaneous derivative spectrophotometric and HPLC methods for determination of 17-beta-estradiol and drospirenone in combined dosage form. The mobile phase of the chromatographic technique, which included acetonitrile and water in the ratio of 70:30 by volume, was used to separate the two analytes on aa Waters Symmetry C18 column (4.6 mm × 250 mm, in diameter 5 μm). A UV-photodiode array detector operating at 279 nm was used for the detection process flow rate was 1 ml/min.

The EST and DRS had typical retention times of around 3.54 and 4.55 minutes, respectively. For DRS, the linear range was 0.8-2.5μg/ml, while for EST, it was 0.23-7.5μg/ml, with Correlation coefficient (r^2) was 1.0 & 0.999, respectively. For EST and DRS, the limits of detection (LOD) were 0.05µg/ml and 0.02 µg/ml, and the limits of quantification (LOQ) were 0.15µg/ml and 0.05 µg/ml, respectively.

In this investigation, two different methods RP-HPLC approach with a shorter analytical run and a first derivative spectrophotometric method were developed and validated for the simultaneous detection of ESR and DRS in their tablet form. The techniques created may be utilised successfully in quality control laboratories for regular examination of substances in both pure form and pharmaceutical forms without prior preparation [26].

According to study by Havlíková Lucie, *et al.,* Determination of estradiol and its degradation products by liquid chromatography. A brand-new HPLC technique was created to measure estradiol and all seven of its breakdown products in topical gel simultaneously. The chromatographic separation employing UV detection at 225 nm was performed using a Zorbax SB-CN (150 mm×4.6 mm, 5 m) analytical column and mobile phase made of acetonitrile, phosphoric acid (0.085 percent), and tetrahydrofurane (27:63:10, v/v/v) at a flow rate of 1.0 ml per min linearity analysis revealed that it was linear between concentrations of 6 µg/ml to 21 µg/ml with correlation coefficient (r^2) was 0.99903. Precision of estradiol was 0.17 %RSD. In method validation Accuracy recovery was 100.69% [27].

HPLC Analysis of Norethindrone Acetate: Hisham hashem, *et al.,* a rapid stability indicating HPLC method for determination of norethisterone acetate in plasma, tablets and in a mixture with other steroids. Using an isocratic binary mobile phase with an acetonitrile/water ratio of 55:45, a flow rate of 1 ml/min, chromatographic separation is performed. At 240 nm, a diode array detector is employed for detection. An analytical reversed phase C-18 column of 150mm x 3.0 mm I. D. (Bridge column XBridgeTM, Waters) was used to produce the separations. The linearity in the range of 0.125-50µg/ml with a correlation coefficient (r^2) of 0.9998. Norethisterone acetate's limits of detection and quantitation were 0.0625 µg/ml and 0.125 µg/ml, respectively. This method's recovery value is 101.90 %. Intra-day and inter-day precisions of norethisterone acetate were discovered to be0.24 %RSD and 1.11 % RSD, respectively.

The suggested approach works well for separating Norethisterone Acetate from several other steroids that can be used with it to form a contraceptive pill. This approach provides a significant decrease in analysis time when compared to the existing HPLC-methods and is regarded as a stability indicating method [28].

CONCLUSION: Leuprolide, Ulipristal acetate, Relugolix, estradiol, and norethindrone acetate are the specific drugs used treating uterine fibroids, and sensitive and accurate HPLC and LC-MS/MS methods have been developed to evaluate them in pharmaceutical formulations. Both the ICH and the FDA published guidelines for these approaches, encompassing Specificity, Linearity, Accuracy, Precision, Ruggedness, and Robustness. The findings of this study support the viability of developing unique, highly accurate, and sensitive procedures using HPLC, UPLC, and LC-MS/MS for the analysis of drugs used to treat uterine fibroids.

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