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RECENT ADVANCEMENTS IN PROGESTERONE DELIVERY SYSTEMS

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ABSTRACT

The human body naturally secretes progesterone, a steroidal sex hormone, through the ovary, placenta, and adrenal cortex. Progesterone is necessary for the endometrium to change in the uterus during ovulation and to maintain pregnancy in humans. Progesterone is given through a variety of methods, including oral, vaginal, transdermal, topical, parental, and intranasal, when the body is unable to manufacture enough of it for a particular condition. The main obstacles to progesterone distribution are its poor solubility, limited permeability, and significant hepatic first-pass metabolism, despite the fact that it is commercially available in a variety of standard formulations. Progesterone can be effectively delivered by innovative methods such as lipid carriers, polymeric carriers, hydrogels, multiple nanocarriers, depot, and controlled release systems. Over the past 20 years, a number of research publications and patents on progesterone administration methods have been published; safety and efficacy were established through clinical investigations. The progesterone pharmacodynamic and pharmacokinetic factors, delivery limitations, and enhanced progesterone delivery technologies are the main topics of this paper.

KEYWORDS: Progesterone, Contraceptive, Novel delivery systems, Delivery constraints, Pharmacokinetic parameters.

1. INTRODUCTION

Progesterone is a naturally occurring sex steroid hormone in the human body. Progestin, progestagen, and progestogen are other names for synthetic progesterone.[1] The adrenal cortex, ovary, testes, brain, and spinal cord are the main locations in the human body where progesterone is produced and secreted. Along with other sex hormones, progesterone primarily affects the reproduction processes.[2] Because they express different enzymes, neuronal cells, glial cells, and microglial cells aid in the conversion of cholesterol to progesterone. The blood–brain barrier is easily crossed by naturally occurring progesterone produced in the human body.[3] During the menstrual cycle, the corpus luteum secretes progesterone, which increases the secretory action of the endometrium. Even after fertilisation and ovum implantation, human chorionic gonadotropin (hCG) stimulates the corpus luteum to continue secreting progesterone. In addition to preventing menstruation, the increased progesterone level fosters the ideal conditions for the embryo's development inside the uterus.[4]

After 10–12 weeks of pregnancy, luteal progesterone secretion declines as a result of decreased hCG production. Progesterone secretion, however, originates from placental trophoblasts.[5] Progesterone levels in the placenta rise until parturition. Increased progesterone levels help to keep the myometrium inactive, inhibit the immune system of the mother, stop the maturation of younger oocytes, give an implanted embryo immunological tolerance, and resist the induction of labour caused by other hormones such as oxytocin, prostaglandins, and estrogen.[6] Because of its influence on lordosis and maternal behaviour, progesterone has historically been referred to as a female hormone.[7] Progesterone is produced by steroidogenic cells, such as the corpus luteum and placenta in the human body, using a variety of enzymatic techniques, just like the majority of steroid hormones.

The primary goal of the synthesis is for cytochrome P450scc to convert cholesterol to pregnenolone through three successive hydroxylation reactions. The reaction is then completed by hydroxysteroid dehydrogenase, which turns pregnenolone into progesterone.[6]

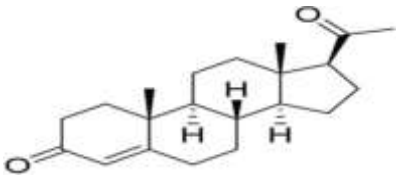

Fig. 1: The chemical structure of progesterone.[8]

The only structural difference between progesterone and testosterone (the male sex hormone) is at position C17, where progesterone has an acetyl group and testosterone has a hydroxyl group attached.[9] Progesterone is a BCS class II medication with low solubility and high permeability. It is hydrophobic, with a log P value of 3.87.[10] At room temperature, the solubility of progesterone was determined to be 16.8 µg/mL in water and 15.1 µg/mL in 0.9% saline solution.[11]

1. Mechanism of action for Progesterone

Female reproduction, from implantation to lactation, is regulated by the sex steroid hormone progesterone. The nuclear progesterone receptors are the main mechanism by which this hormone regulates transcription. Two subgroups of the progesterone receptor (PR), known as PR-A and PR-B isoforms, regulate the progesterone receptor's activity.[12] The three sites that make up PRs are the N-terminal activation and inhibition site, the C-terminating ligand binding domain (LBD), and the DNA binding domain (DBD). The PGR gene, which is found on chromosome 11q22-23, regulates these sites.[13]

PR becomes inactive for transcription when it binds to chaperones (Hsp: heat shock protein) and cochaperone. The chaperone is crucial to the maturation of PR because it aids unliganded PR in maintaining structural conformation.[14] PR becomes inactive for transcription when it binds to chaperones (Hsp: heat shock protein) and cochaperone. The chaperone is crucial to the maturation of PR and aids in the maintenance of structural conformation in unliganded PR.

Hydrophobic pockets are produced in the PR structure by conformational changes brought about by progesterone binding. By binding to PR and encouraging phosphorylation, progesterone aids in the separation of PR and the chaperone complex.

The steroid receptor complex (SRC) and activation function-2 (AF-2) are required by the gene in order to activate the DNA HRE (hormone response element) in the target's promoter region. Following its formation, SRC moves from the cytoplasm to the nucleus, where it binds to the progesterone response elements (PREs) in the target gene to activate the PRE responsive gene. The co-activators and chromatin complexes in the target PR-regulated gene facilitate the initiation of transcription. The amount of progesterone hormone that acts within a tissue is determined by the location of receptors within that tissue. Following transcription, PR separates from the DNA strand, and the 26S proteasome breaks down the receptor. This

mechanism is a part of progesterone's classical mechanism of action.[13,15]

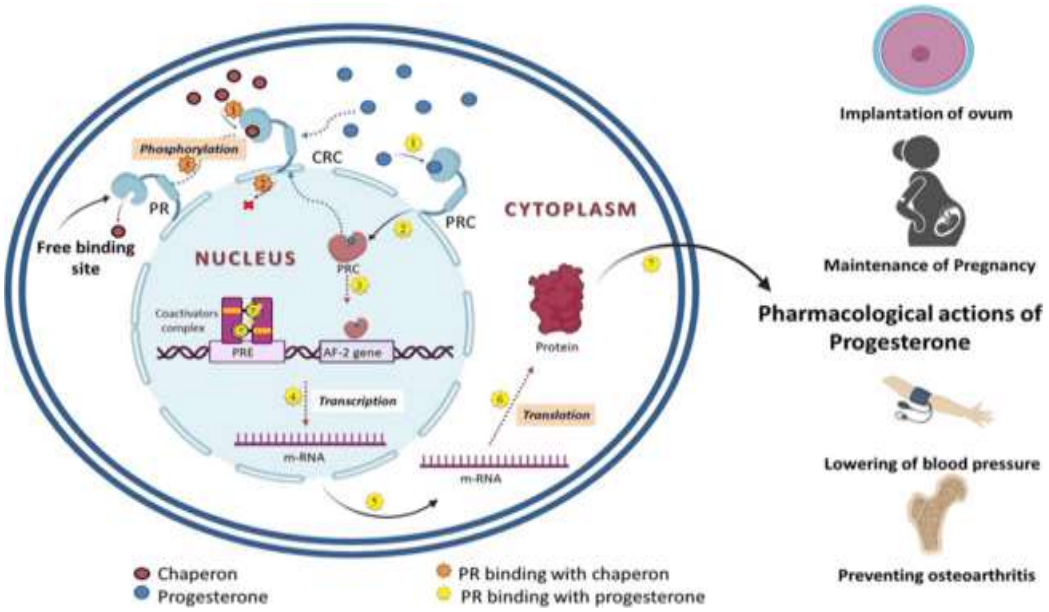

Fig. 2: The classical mechanism of action of progesterone and pharmacological activities.[8]

Rapid signaling is followed by PR on the cell membrane in the non-classical mechanism of action. Progesterone opens the Ca2+-ATPase ion channels and opens the PR that is bounded by the cell membrane. Progesterone, glucocorticoids, and mineralocorticoids are examples of steroids that bind to neurotransmitter receptors or target tissue membranes to modify the lipid fluidity and protein mobility of the tissue.[16]

2. Pharmacokinetics of progesterone

The most typical method of absorbing steroidal hormones is passive diffusion.[17] Passive diffusion is the main method of progesterone absorption facilitated by the steroidal structure and lipophilicity. Without the need for energy or transport proteins, it tracks absorption across concentration gradients.[18,19] Progesterone taken orally has a low bioavailability (less than 10%) in the intestinal tract due to its quick metabolism in the liver and intestine. Progesterone is two times more bioavailable when it is not fasting than when it is.[20]

Intramuscular and vaginal progesterone administration reduces first-pass metabolism and achieves higher concentration at the targeted site compared to the oral route.[21] When micronized progesterone was delivered vaginally, the concentration in endometrial tissue was about ten times higher than when it was administered intramuscularly.[22] Due to the high vascularity of the vaginal mucosa, progesterone is absorbed quickly when administered

vaginally.[23]

Progesterone distributes within blood and tissues after entering the systemic circulation, and its pattern of distribution is mainly determined by its binding to tissue receptors and transport proteins. Progesterone is stored in body fat and other tissues, which increases its availability and may have long-lasting effects.[24,25]

The liver and gastrointestinal tract are the sites of oral progesterone metabolism; over 50% of this metabolism takes place prior to the drug entering the bloodstream.[26] Orally administered progesterone is metabolised by two families of enzymes: 5α and 5β reductase, which are steroid-specific and non-steroid-specific, respectively. The liver is the primary site of action for 5β reductase, while multiple tissues, including the skin and brain, express 5α reductase.[27]

Pregnanolone and allopregnanolone, the main byproducts of progesterone metabolism have sedative, anaesthetic, anxiolytic, and antiepileptic properties. Pregnanolone is formed less via the vaginal route than through the oral route.[28]

Renal and biliary routes account for the majority of progesterone elimination.[29] Progesterone excretes in faeces in almost 95% of cases; 35% of the progesterone is conjugated and 65% is free progesterone. Around 14.5 percent of the residual 5% is eliminated through the urine, with the conjugated form accounting for the remaining portion.[30]

Table 1: Summary of the pharmacokinetics of progesterone administered by different routes.[8]

Route	Formulation	Study model and Dose	Half-life ($t_{1/2}$)	C_{max}	t_{max}	AUC	Key findings
Oral	Micronized progesterone	Postmenopausal women- A single dose of 20 mg and from the 2-7th day, 20 mg doses were administered BID	–	9.7 ± 2.0 nmol/l	105 ± 25 min	30 ± 2.6 nmol/l h	The oral administration of micronized progesterone showed 127% higher AUC than endogenously produced progesterone.
	Micronized progesterone capsule	Women- 200 mg	18.54 ± 24.71 h	6.50 ± 12.71 ng/mL	3.36 ± 2.76 h	15.14 ± 13.18 ng.h/mL	Oral administration shows 18 times lower AUC than vaginal administration due to metabolism
	Free Progesterone powder	Rabbits-10 mg/kg	2.4 ± 0.6 h	1.61 ± 0.04 µg/mL	6 ± 0 h	19.4 ± 0.9 µg·h/mL	The progesterone microspheres showed a 1.8-fold increased AUC than progesterone attributed to the slow release of the drug from the microsphere matrix
	Progesterone Microspheres	Rabbits-10 mg/kg	4.0 ± 0.1 h	1.37 ± 0.02 µg/mL	12 ± 0 h	34.9 ± 0.3 µg·h/mL	
Intramuscular	Nano-suspension	Sprague-Dawley Rats-6 mg/mL injection	12.7 ± 0.8 h	37.5 ± 11.8 ng/mL	0.75 ± 0.28 h.	452.75 ± 42.8 ng·h/mL	Improved bioavailability with 2.2 folds increased AUC of nanosuspension due to prolonged release from a polymer matrix
	Oily solution	Women- 100 mg/mL	22.3 ± 11. 6 h	112.9 ± 57.2 ng/mL	6.67 ± 3.79 h	2097 ± 263 ng.h/mL	Delayed onset of action and lower C_{max} due to slower release and absorption via the i.m route.
	Aqueous solution	Menopausal women – 100 mg/mL	14.27 ± 4.59 h	439.94 ± 276.17 ng/mL	0.88 ± 0.53 h	1919.39 ± 289.01 ng/mL.h	4-fold higher C_{max} than i.m. oily injection

Subcutaneous	Aqueous solution	Menopausal women –100 mg/mL	17.17 ± 11.52 h	299.53 ± 82.58 ng/mL	0.92 ± 0.19 h	1884.62 ± 289.68 ng/mL.h	3-fold improved C_{max} than i.m. oily injection
	Aqueous solution	Women –100 mg/mL	17.6 ± 5.8 h	235 ± 62.6 ng/mL	0.92 ± 0.42 h	1490 ± 213 ng.h/mL	The s.c. administration of progesterone shows higher C_{max} and shorter t_{max} than i.m. oily injection
	Silastic Implants	Women – 40 mg	–	21 ± 1.6 ng/mL	Day 1	214 µg.day/L	After an initial increase in serum progesterone level, it showed a decline due to rapid elimination and tissue deposition around silastic implant
Vaginal	Suppository with micronized progesterone	Women – 200 mg	–	54 ng/mL	12.0 h	112 ng.h/mL	Large variability in pharmacokinetic parameters
	Natural Micronized progesterone capsule	Women-200 mg	19.53 ± 23.15 h	10.07 ± 5.19 ng/mL	7.67 ± 3.51 h	272.76 ± 265.50 ng. h/mL	The vaginal administration shows higher AUC than oral administration due to oral metabolism
	Tablet	Women –100 mg	13.7 ± 1.05 h	31.61 ± 12.62 nmol/l	6.4 ± 3.35 h	247.61 ± 123.04 nmol/h/l	The vaginal tablet achieved a higher C_{max} than the capsule, indicating improved efficacy and tolerance
	Gelatin capsule	Women – 100 mg	22.08 ± 16.5 h	23.85 ± 9.57 nmol/l	6.23 ± 6.57 h	325.89 ± 167.78 nmol/h/l	
	Insert	Women – 100 mg twice a day	–	17.0 ± 2.7 ng/mL	24.0 ± 0.0 h	217 ± 46 ng.h/mL	The vaginal insert showed 2.5-fold higher C_{max} than the vaginal gel, while the vaginal gel shows prolonged progesterone concentration.
	Gel	Women – 90 mg everyday	–	6.8 ± 1.69 ng/mL	13.3 ± 2.5 h	81 ± 17.0 ng.h/mL	
	Retention suppository	Women – 400 mg	12.21 ± 3.06 h	8.80 ± 3.18 ng/mL	3.91 ± 3.25 h	209.76 ± 128.11 ng. h/mL	The retentive suppository showed better absorption rate, stability, and patient compliance than the conventional suppository
	Suppository	Women – 400 mg	11.97 ± 5.14 h	8.05 ± 3.91 ng/mL	5.42 ± 4.12 h	186.47 ± 147.34 ng. h/mL	

3. Advanced drug delivery systems of Progesterone

Fig. 3: Advanced drug delivery systems of Progesterone.[8]

4.1 Oral delivery systems

Oral progesterone formulations are recommended for a variety of therapeutic purposes during menopause, including hormone replacement therapy, because they are adaptable, simple to administer, and patient-compliant.[31]

Oral progesterone has certain drawbacks, such as poor solubility and inconsistent absorption. It indicates oral hepatic first-pass metabolism, necessitating a greater dosage. Because oral progesterone is less soluble in water, it exhibits more intra- and inter-subject variability. Progesterone's lipidic and polymeric carrier delivery method demonstrated enhanced permeability and bioavailability.[32,33,34]

4.1.1. Lipid Nanocarriers

a) Chitosan coated Progesterone liposomes

A **liposome** is a bilayer micronized vesicular system made of cholesterol and phospholipid that is entrapped in the aqueous phase. Progesterone liposomes coated with chitosan were developed to address issues with stability and fast release brought on by gastrointestinal enzyme breakdown. Furthermore, progesterone replaced cholesterol to create cholesterol-free liposomes because the molecular structures of the two substances are similar. Progesterone solution (37.79 ± 10.03 ng/mL) and uncoated liposomes (75.94 ± 75.06 ng/mL) were less absorbable through the colon than the chitosan-coated progesterone liposomes, which demonstrated stability in the GIT. The chitosan-coated progesterone liposomes were allegedly absorbed via the lymphatic system, blocking hepatic first-pass metabolism.[35,36]

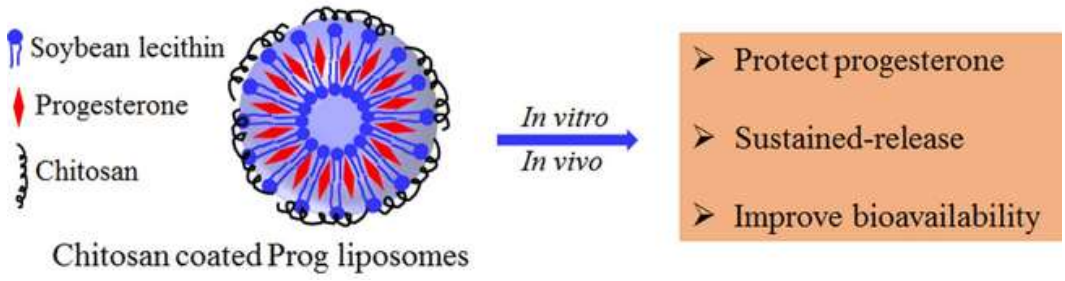

Fig. 4: Chitosan coated Progesterone liposomes.[36]

- **Method Preparation of CS-modified progesterone liposomes**

In a nutshell, a 3:1 volume ratio propylene glycol and PEG400 solution was heated to 60 °C and mixed with a mass ratio of 1:10 progesterone and soybean lecithin. Then, to create liposomes (Lipo/Prog), the solution (50 mg/ml Prog) was added to distilled water (20 times

volume). In order to create CS-Lipo/Prog by electrostatic attraction, the resultant liposomes (5 mL) were gradually put into 20 mL of chitosan solution (0.1 mg/mL) at room temperature and stirred for two hours.[36]

b) Progesterone hexosomes

Progesterone **hexosomes** were created with buccal delivery in mind to increase bioavailability. Progesterone hexosomes had an entrapment effectiveness of 98.7 ± 0.15 percent and a particle size of 257.4 ± 2.3 nm. Using confocal laser microscopy, the penetration mechanism was discovered, revealing that progesterone hexosomes go via either par-acellular or transcellular pathways. Hexosomes, as opposed to progesterone solution, enhanced progesterone's ability to penetrate the oral mucosa.[37]

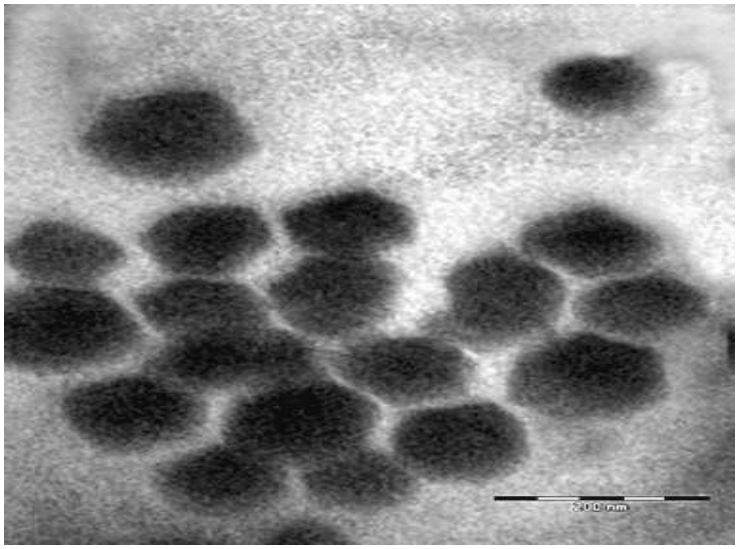

Fig. 5: Visualization of hexosomes by transmission electron microscopy (×1, 10,000). Bar 200 nm.[37]

- **Method Preparation of Progesterone hexosomes**

A colloidal dispersion of hexosomes is created by diluting of an isotropic liquid consisting of 50% lipid phase (GMO and oleic acid, 60:40 w/w) and 50% ethanol with a polymer solution (1% in water) and vortexing at 3,200 rpm for 120 seconds.

The final ratios were 1% Pluronic F-68, 5% ethanol, and 5% fat.

The dispersion was left undisturbed in the dark at room temperature for approximately two weeks in order to reach equilibrium.

Whereas the dye for the RB-loaded dispersion was dissolved in dilution solvent, the required quantity of progesterone (1% w/w w.r.t lipid) was dissolved in 100% ethanol and combined with the hydrophobic portion for the drug-loaded dispersion.[37]

c) Progesterone's nanostructured lipid carriers (NLC)

Progesterone's **nanostructured lipid carriers (NLC)** showed a 24-hour sustained release pattern that rose with the amount of liquid lipids present. When PEG-stearic acid was added to NLC, the progesterone loading capacity of the modified NLC was decreased, but the drug release rate was increased in comparison to the unmodified NLC.[38] Similar to this, progesterone NLCs were made by high shear homogenization using a 1:1 fatty alcohol mixture (cetyl and cetostearyl alcohol), which had a notable impact on the drug release, stability in stomach juice, and particle size. The ex-vivo investigation demonstrated that progesterone from NLCs was more readily absorbed and permeated in 8 hours (53%) than progesterone suspension (35%).[39]

- **Method Preparation of Progesterone NLCs**

High shear homogenization and sonication were used to produce the NLCs. The 10% w/v 93 lipid phase comprised 8% liquid lipid content, 94 sesame oil, and 2% solid lipid, stearic acid.

Sesame oil was used to dissolve the PG, which was then heated to 65°C and combined with 95°C solid lipid.

PEG combination 97 (PEG400:PEG1500:PEG400;1:1:1) was introduced to the molten lipid phase together with varying concentrations of fatty alcohols (cetyl alcohol, cetostearyl alcohol, or 96 1:1 mixture).

After heating the aqueous phase (which contained 3% Tween 80) for five minutes at 65°C, it was gradually added to the melted lipid while being continuously stirred for fifteen minutes in a water bath using a high-speed stirrer at 1300 rpm.

The EPR effect can be another method for the delivery of regular anticancer drugs, and effective bio-distribution of nanoparticles in blood would be considered to get a great level of accumulation in all solid tumors.[39]

4.1.2. Polymeric Nanocarriers

a) Progesterone-loaded nanoparticles

Encapsulating progesterone in polymers is one method for achieving continuous release of the hormone, which may also aid in boosting its solubility and bioavailability.

Using an electrospray technique, progesterone nanoparticles loaded in a polylactic-coglycolic acid (PLGA) copolymer were created.

Using scanning electron microscopy, nanoparticles with diameters ranging from 472.1 ± 54.8 to 588.0 ± 92.1 nm were shown to have a smooth and spherical shape.

Progesterone release with polymer was 79.9 ± 1.4% after 5 hours, but medication release without polymer was 57.5 ± 2.8%. This indicates that the polymeric system can control progesterone release.[40]

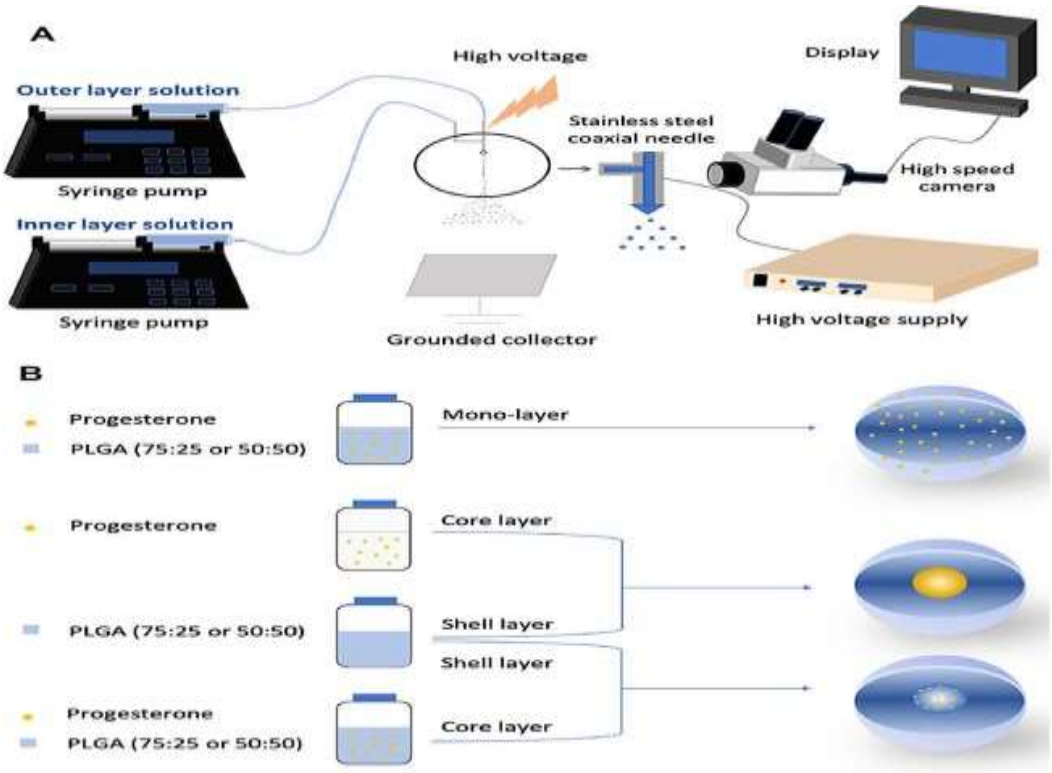

Fig. 6: Schematic illustration of (A) coaxial electrospray setup; (B) formulations of progesterone-loaded nanoparticles.[40]

- **Method of preparation progesterone-loaded nanoparticles**

Several electrospray techniques were used to create progesterone-loaded PLGA nanoparticles (Fig. 6. (A)).

DMAc and acetone were combined at a 7:3 volume ratio. To create PLGA solutions for each formulation, the polymer was dissolved in an acetone/DMAc mixture and agitated for 30 minutes (Table 2).

The inner solution for formulations 2-layer1-50 and 2-layer1-75 was progesterone in an acetone/DMAc combination.

It was then added to the polymer solution to create the inner solution for formulations 2-layer2-50 and 2-layer2-75, as well as the single solution for formulations 1-layer-50 and 1-layer-75.

The polymer to drug ratio (w:w) for each formulation was maintained at 40:1.

The relevant liquids were put into a plastic syringe measuring 10 m, and separately operated syringe pumps supplied the liquids into the capillaries at a steady flow rate of 0.18 mL h−1.

A strong positive electrical potential ranging from 12.0 to 14.0 kV was produced between the grounded collection and nozzle tip using a high voltage power supply.

The cone-jet created during particle production was observed using a Leica DMS300 camera. Following reliable cone-jet mode jetting, the particles were collected onto a grounded collector sheet that was positioned 200 mm below the needle outlet.

Every experiment was carried out with a relative humidity of 40–55% and an ambient temperature of 20°C.[40]

Table 2: Physicochemical Characteristics of the Solutions Used for Particle Formation.

Formulations	Particle Configurations	Surface Tension (mN m^{-1})	Viscosity (mPa s)	Electrical Conductivity ($\times 10^{-5}$ S m^{-1})	Density (kg L^{-1})
2-layer^{1}-50	Shell: 40 gL^{-1} PLGA (50:50) Core: 1 gL^{-1} progesterone	Shell: 30.4±0.3 Core: 27.1±0.2	Shell: 0.7 Core: 0.6	Shell: 4 Core: 3	Shell: 8.7 Core: 8.6
2-layer^{2}-50	Shell: 20 gL^{-1} PLGA (50:50) Core: 20 gL^{-1} PLGA (50:50) + 1 gL^{-1} progesterone	Shell: 28.8±0.2 Core: 27.8±0.4	Shell: 0.6 Core: 0.6	Shell: 3 Core: 3	Shell: 8.6 Core: 8.6
1-layer-50	Single: 40 gL^{-1} PLGA (50:50) + 1 gL^{-1} progesterone	30.2±0.3	0.6	4	8.7
2-layer^{1}-75	Shell: 40 gL^{-1} PLGA (75:25) Core: 1gL^{-1} progesterone	Shell: 29.8±0.4 Core: 27.1±0.2	Shell: 0.8 Core: 0.6	Shell: 4 Core: 5	Shell: 8.7 Core: 8.6
2-layer^{2}-75	Shell: 20 gL^{-1} PLGA (75:25) Core: 20 gL^{-1} PLGA (75:25) + 1 gL^{-1} progesterone	Shell: 28.9±0.5 Core: 28.1±0.3	Shell: 0.5 Core: 0.5	Shell: 3 Core: 3	Shell: 8.6 Core: 8.6
1-layer-75	Single: 40 gL^{-1} PLGA (75:25) + 1 gL^{-1} progesterone	31±0.6	0.7	4	8.5

In the Case of Viscosity, Electrical Conductivity and Density the Error was Negligible[40]

Since progesterone is a water-insoluble medication, studies have been done to improve its solubility and bioavailability by complexing it with cyclodextrin (CD).

b) SBE-β-CD–progesterone complex

Sulfobutyl ether (SBE), a cyclodextrin derivative, was utilised to create the **SBE-β-CD–progesterone complex**, which prevented progesterone displacement from the GIT and enhanced progesterone solubility by 7000 times. Rats administered the progesterone combination demonstrated a five-fold increase in bioavailability and a decrease in intestinal precipitation.[41]

- **Method Optimization of sulfobutyl-ether-β-cyclodextrin levels in oral formulations to enhance progesterone bioavailability**[41]

It would be advantageous to create a formulation that would improve progesterone's solubility in the digestive system in order to reduce variability in drug absorption and boost bioavailability.

At 400 mM sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) concentration, progesterone's solubility was approximately 7000 times higher than its inherent solubility, which was facilitated by the development of an SBE-β-CD–progesterone complex.

Nuclear magnetic resonance (NMR), Fourier-transform infrared (FTIR), and differential scanning colorimeter techniques were used to characterize the compound.

The interaction between progesterone's functional groups and SBE-β-CD's to create an inclusion complex is confirmed by FTIR and NMR examinations of the complex. Progesterone binding poses were shown by molecular modelling studies to involve four likely SBE-β-CD isomers; these results matched data from FTIR and NMR.

c) Progesterone-loaded hybrid microspheres

Using the ionotropic gelation process, **progesterone-loaded hybrid microspheres** of sodium carboxymethyl cellulose and pectin that were cross-linked with Zn2+ and Al3+ were created for colon targeting.

The sigmoid release pattern of the microsphere indicated pH-dependent progesterone release with almost no drug release in simulated gastric fluid and sustained release in simulated small

intestinal fluid.

The ex vivo mucoadhesion results showed that microspheres remained attached to the colon (pH 7) for more than 30 h until complete disintegration.

In vivo study confirmed colonic microflora causes the enzymatic breakdown of polymer and releases the drug from the matrix system.

The progesterone-loaded microspheres showed gradual absorption by passive diffusion across the biological membrane. Also, the microsphere had 2.3 folds more mean residual time than the free progesterone formulation, which makes it ideal for increasing the absorption of progesterone.[42]

- **Method of preparation Progesterone-loaded hybrid microspheres**

Using two cross-linking agents, the modified ionotropic gelation process was used to create hybrid Pc/NaCMC MS loaded with PG.

Under magnetic stirring, a suitable quantity of PG (1%, w/v) was distributed in a 0.3% w/v aqueous Tween® 80 solution in deionized (DI) water until a homogeneous dispersion was achieved.

The drug dispersion was then combined with a 1:1 ratio of Pc/NaCMC blend to create PG-loaded hydrogel.

The homogenous, bubble-free hydrogel was added to 25 ml of the gently stirred cross-linking solution [Zn (CH3COO)2 and Al2(SO4)3 in DI water] drop-wise at an average rate of 1 ml/min.

A disposable syringe with a 1 mm inner diameter tip and a fixed 5 cm falling distance was used to make the addition.

After 10 hours of curing in the cross-linking solution, the instantly produced MS were rinsed three times with DI water and left to dry in the air for 48 hours.

A blank was an empty MS created using the same technique but without any medication. Using a 2^3 factorial design, eight batches were created by altering the experimental settings; each batch was created in triplicate (Table 3).

Table 3: 2^3 factorial design independent parameters, studied levels and composition of the optimized formulation.[42]

Factors	Low level (−1)	Middle level (0)	High level (+1)	Optimum Level
X_1	1.5	1.75	2.0	1.5
X_2	0.05	0.06	0.07	0.07
X_3	0.025	0.088	0.15	0.15

X_1: Polymer concentration (% w/v) (Pc/NaCMC, 1:1).
X_2: $Zn(CH_3COO)_2$ concentration (M).
X_3: $Al_2(SO_4)_3$ concentration (M).

4.2. Vaginal delivery systems

Many parameters, including the vagina's surroundings, vaginal leaks, pH of the vagina (3.5–5.5), and the thickness of the endometrium during menstruation, should be taken into account while administering progesterone vaginally.

Vaginal progesterone avoids first-pass metabolism, displays greater absorption due to its vascular character, has a site-specific impact, and eases administration.[43]

The vaginal route is chosen since progesterone exhibits considerable activity in the ovary and uterus in physio- logical events such ovulation, fertilisation, and maintenance of the menstrual cycle.[44]

Due to its simplicity of delivery, lack of local pain, rapid absorption, and high bioavailability, the vaginal route is chosen over the intramuscular or sometimes oral route.

The vaginal administration of progesterone involves adverse effects such dyspareunia, local warmth of the vagina, local irritation and vaginal bleeding.[45] Progesterone delivered vaginally is less acceptable to patients due to the unpleasant discharge of the formulation caused by this route.[46]

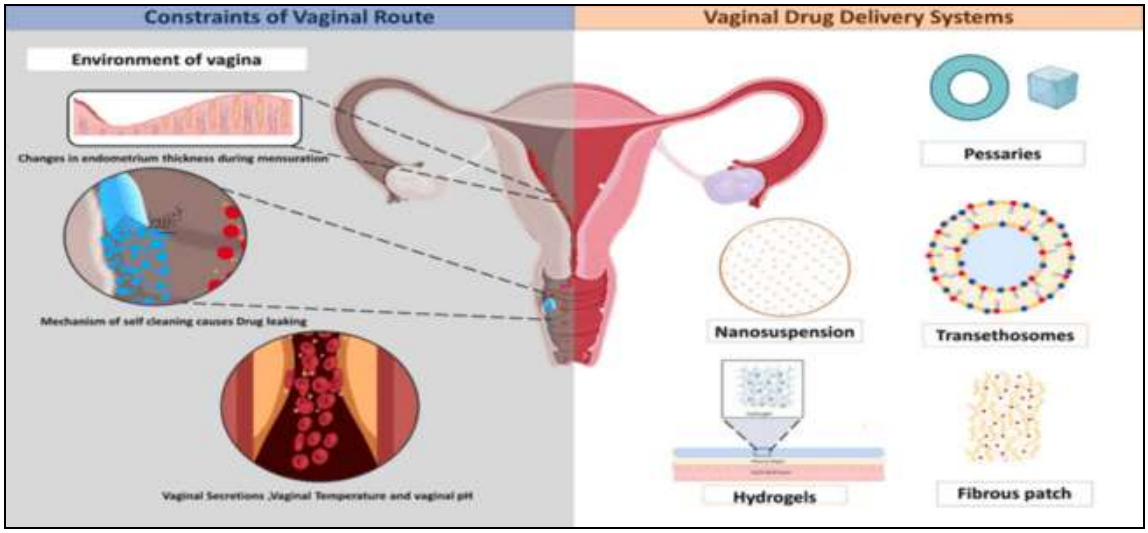

Fig. 7: Constraints of vaginal delivery and various novel systems of progesterone by vaginal route.[8]

4.2.1. Pessaries

a) Progesterone loaded pessaries

Progesterone-loaded pessaries are most frequently used for obstetric care and preterm birth control.[47]

A clinical research was carried out to assess the pharmacokinetics and endometrial histology of various progesterone dosage regimens administered via vaginal pessaries and vaginal gel. 90 mg (od) of vaginal gel and doses of 100 (bid), 200 (bid), and 400 mg (od) of vaginal pessaries were administered to the 179 healthy women volunteers, who ranged in age from 18 to 45.

For 100, 200, and 400 mg, respectively, the appropriate secretory transformation rates were 63.5%, 91.8%, and 94.0%, and for vaginal gel, the response rate was 89.8%.

Between the different dosages of pessaries and the vaginal gel, there were no appreciable differences in the endometrial histology.

The dosage-independent response was seen for the vaginal gel at 90 mg and the pessary doses of 200 and 400 mg.

The pessary dose of 100 mg was shown to be less effective than higher doses.[48]

b) Nanostructure lipid carrier (NLC) based pessaries

Pessaries based on nanostructure lipid carriers (NLC) were created to provide a progesterone release profile that was prolonged in the vagina.

The nanosize (315.60 ± 0.01 nm) NLCs possessing 96.42 ± 0.00% entrapment were biocompatible without any harmful effect on HaCaT cells. Progesterone release was sustained for up to 24 hours in NLC-based pessaries.[49]

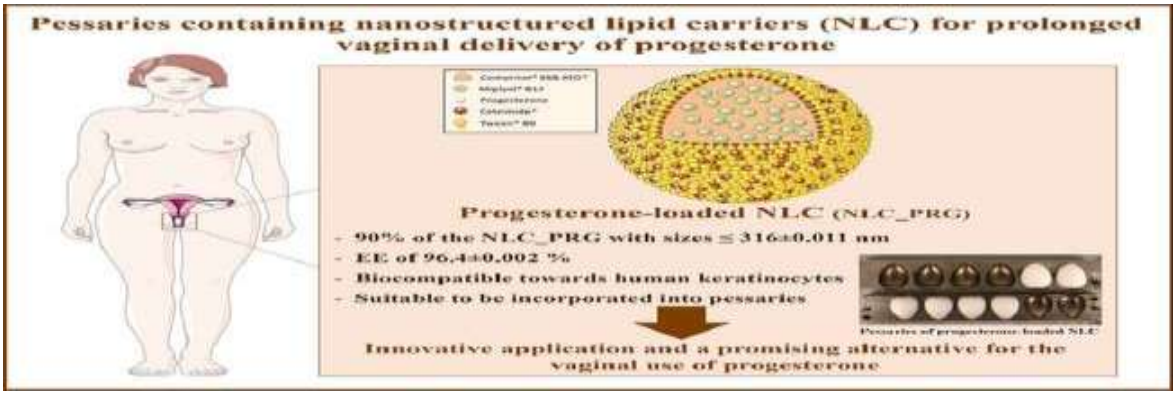

Fig. 8: Pessaries containing nanostructured lipid carriers (NLC) for prolonged vaginal delivery of progesterone.[49]

c) Vaginal retentive cream progesterone suppositories using 3D printing technology

To create vaginal retentive cream progesterone suppositories, theobroma oil o/w emulsion in hard fat was used.

Pessaries dissolve more quickly in 3-5 minutes than traditional vaginal suppositories, which take 13–15 minutes.

After utilizing these pessaries, volunteers reported excellent levels of patient satisfaction, and a pharmacokinetic analysis revealed that progesterone had a greater bioavailability than hard fat-based suppositories.[50]

With the use of 3D printing technology, pessaries in the shapes of gellhorn and donut can be created.

These extended-release progesterone pessaries were produced using 3D technology and were precisely tailored to each patient.[51]

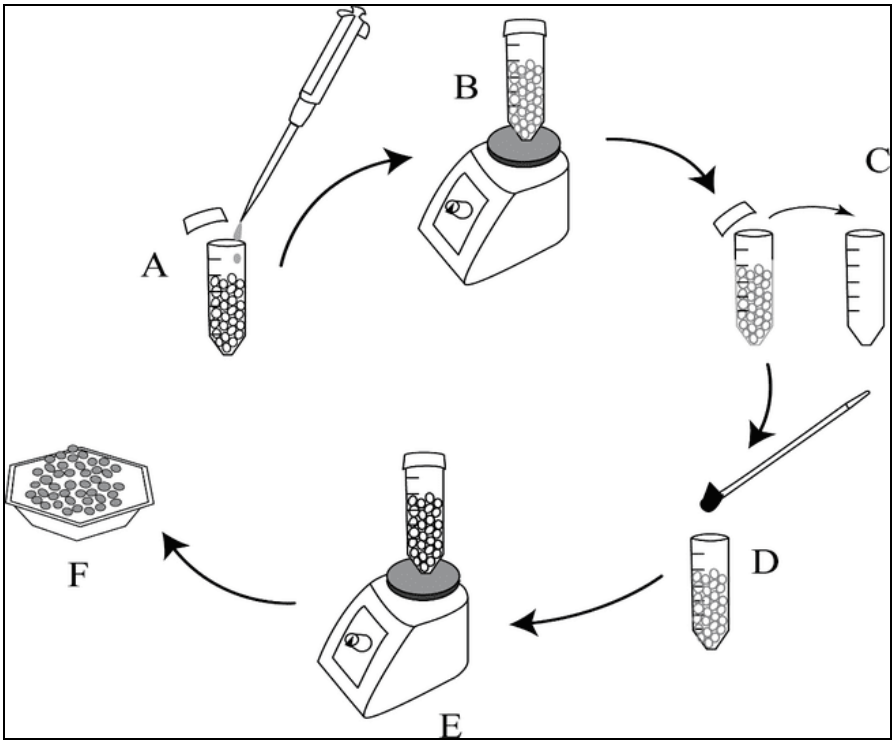

Fig. 9: The process of coating PCL pellets with hormones.

A) Coating oil is added,

B) Tube is vortexed,

C) Pellets are transferred to a new tube,

D) Hormones are added,

E) Tube is vortexed,

F) Coated pellets are removed.[51]

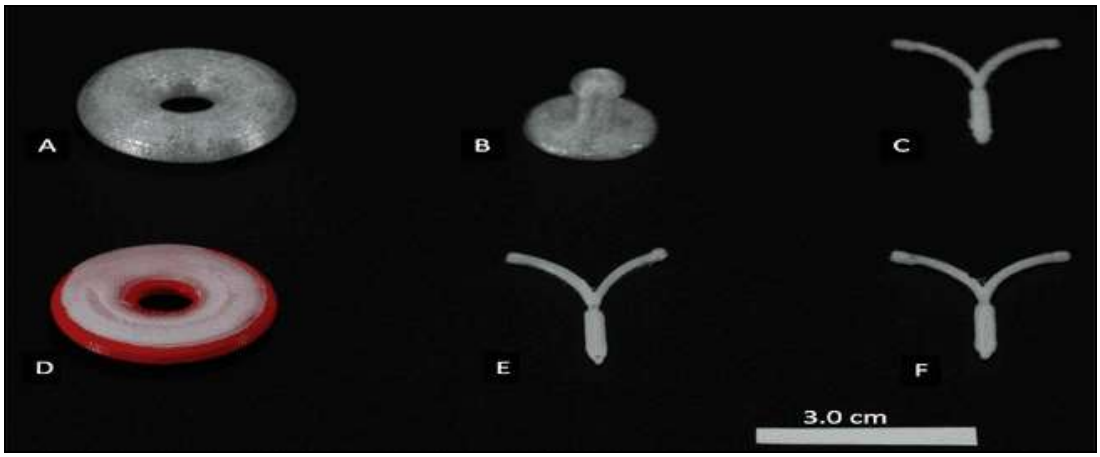

Fig. 10: 3D printed constructs A) Control donut shaped pessary, B) Control Gellhorn shaped pessary, C) Control IUD, D) Pessary printed combinations of filaments (red-PLA and white- PCL-E2), E) PCL-E1 IUD, & F) PCL-E2 IUD.[51]

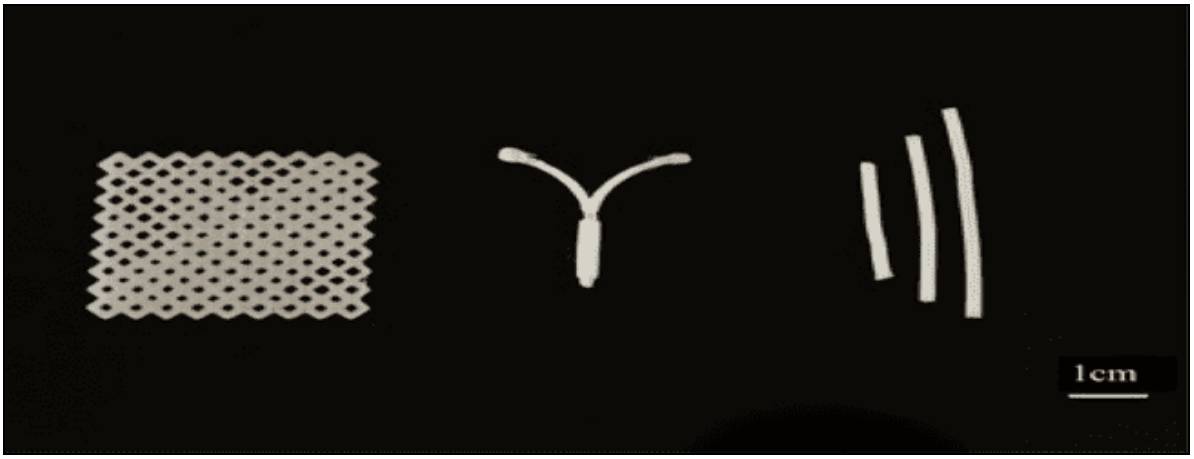

Fig 11: 3D printed PCL-Estrogen mesh, PCL-Progesterone IUD, and Subdermal implant.[51]

4.2.2 Vaginal Tablets

It was possible to get around the hepatic first-pass metabolism with vaginal progesterone pills. They absorb the vaginal secretions around them, break down into a powder that sticks to the mucosa of the vagina, and release progesterone continuously.[51]

The mucoadhesive vaginal tablet sticks to the vagina for a longer period of time by creating a covalent link with the mucous layer. For the mucoadhesive property, the tablet was made with conjugates of polyacrylic acid polymer (NaC974P) and cysteine created via the carbodiimide procedure.

The tablet containing the cysteine-NaC974P polymer conjugate showed release in more than 10 hours, whereas the tablet lacking the polymer conjugate showed dissolution in more than 5 hours. The polymer was modified to increase its viscoelastic qualities and its ability to absorb water from the mucus layer, which reinforced the tablet's mucoadhesive qualities.[52]

Progesterone and polycaprolactone (PCL) tablets are prepared for hormonal cancer treatment with the use of selective laser sintering technology. This tablet delivery demonstrated a high flexural modulus and a homogeneous distribution of pores in the polymer matrix. The laser-printed tablet exhibited rate-controlled release by varying laser energies and uniform morphology, promoting its use as an implantable device.[53]

4.2.3. Hydrogels

To administer progesterone straight into the vagina, thermosensitive progesterone hydrogel was developed.

Because thermosensitive polymer glycol chitin is biocompatible, biodegradable, and mucoadhesive, it was chosen for the application.

The hydrogel changed into a gel at body temperature by using the sol-gel process.

Glycol chitin-containing gel's consistency was 1.5 times more robust than that of the commercially available gel (Crinone®). After being exposed to vaginal fluid, almost 50% of the progesterone was released within 4 hours.

When progesterone was applied to vaginal tissue repeatedly, it became toxic and its release remained unchanged in the presence of lactobacillus.

Both in vitro and in vivo, progesterone hydrogel was safe and did not exhibit any toxicity on the epithelial layer.[54]

4.2.4. Nanosuspension

The principal site for medication absorption in any portion of the body is the mucosal layer.

The cervicovaginal mucus layer in the vagina serves as a retention layer and regulates the distribution of drugs.

But during vaginal delivery, it's important to take into account intra-abdominal pressure, osmotic pressures, and gravitational force. A mucoinert nanosuspension of progesterone that adheres to the mucus layer was developed by Hoang et al.

The study on pregnant mice found that the nanosuspension had better vaginal absorption by seven times than the gel formulation in cervical tissue, and that the nanosuspension had a greater level of circulating progesterone by 2.3 times than the later, six-hour period.

The formation of progesterone nanosuspension (200–500 nm) involved homogenization and nanoprecipitation.

Pluronic F127 was used to cover this nanosuspension in order to effectively penetrate cervicovaginal mucus.

Progesterone nanosuspension was found to decrease the expression of oxytocin receptors.

When progesterone was given via the vagina rather than the systemic route, the concentration

of the hormone in the uterus rose. In order to avoid preterm birth, the progesterone nanosuspension formulation demonstrated enhanced absorption and bioavailability of progesterone via the vaginal route.[55]

4.2.5. Nanofibres

Longer release, fewer side effects, and focused medication delivery are just a few of the benefits that come with using nanofibers for drug delivery.

For the preparation of nanofibers, pressurised gyration is a good substitute for electrospinning.

This different approach of altering the amounts of carboxymethyl cellulose to manufacture progesterone-loaded nanofibers was proposed by Brako et al.

Progesterone nanofibers can be coiled into a tiny tampon for vaginal insertion, compacted straight into a tablet, or transformed into vaginal inserts.[56]

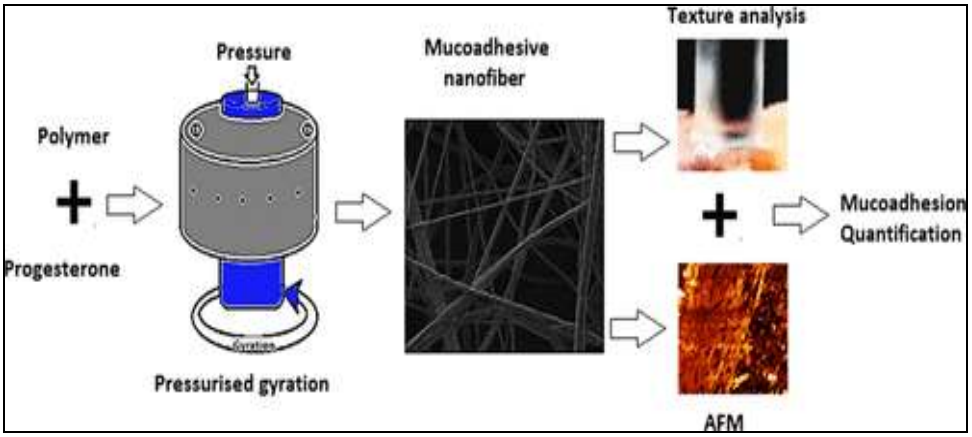

Fig. 12: Mucoadhesion of Progesterone-Loaded Drug Delivery Nanofiber Constructs.[56]

In order to avoid premature delivery, progesterone-loaded poly (lactic acid) fibrous polymeric patches were made by electrospinning and pressure gyration.

In the first four hours, the patch displayed burst release; the sustained release was seen after twenty-four hours.

While an in vivo investigation in rats revealed that a patch was placed intravaginally in the third week of pregnancy, lowering uterine contractions, the patch did not demonstrate any in vitro cytotoxicity.[57]

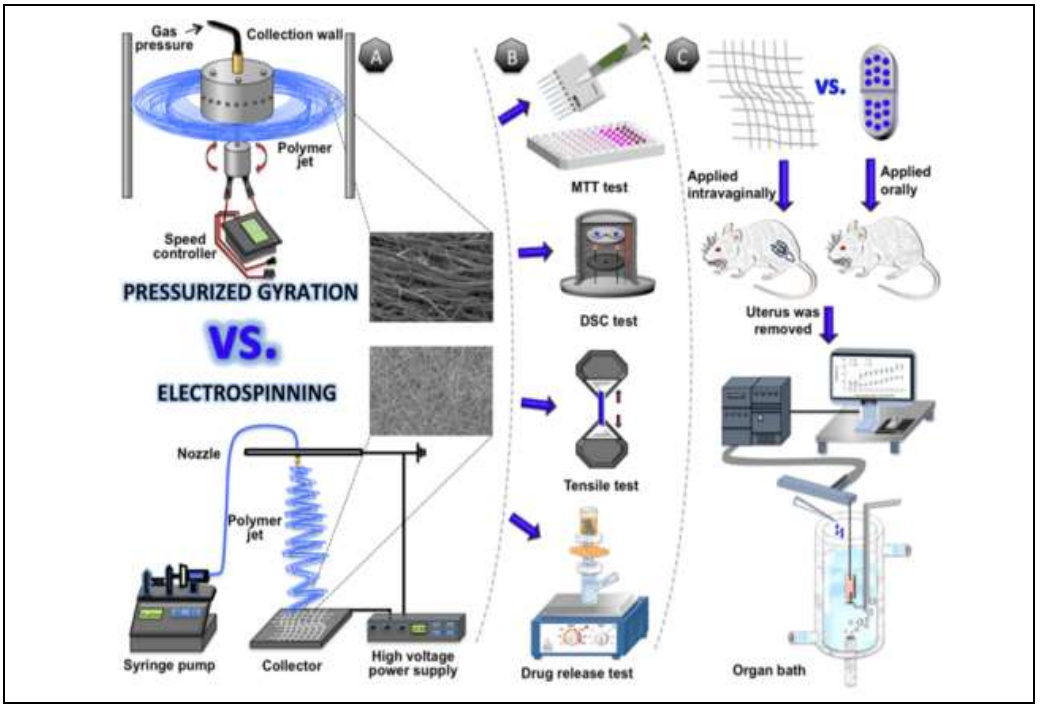

Fig. 13: Schematic illustration of the experiments.

(A) Production processes of progesterone-loaded fibrous patches of two different techniques; electrospinning and pressurized gyration,

(B) characterization of produced fibrous patches,

(C) comparisons of the tocolytic effects of progesterone-loaded fibrous patch and oral progesterone using organ bath experiments.[57]

Progesterone is a medication that is frequently used in both humans and animals. It has significant therapeutic promise for controlling female fertility and pregnancy. The full therapeutic potential of progesterone is limited by its hydrophobicity and requirement for long-term therapy.

Polymeric nanofibers have emerged as intriguing drug transporters in recent times, particularly for hydrophobic medications.

The goal of this work was to use electrospinning to encapsulate the hydrophobic medication progesterone in pullulan for regulated distribution.

Pullulan nanofibers containing progesterone were effectively integrated, with a mean fibre diameter varying between 68.68 ± 9.71 and 123.12 ± 17.41 nm.

Fourier transform infrared spectroscopy revealed the interaction of the medication with the

polymer.

Progesterone-loaded pullulan nanofibers' zeta potential ranged from 0.4 ± 0.01 to −0.5 ± 0.01, suggesting that they were suitable for transmucosal administration. Progesterone-loaded pullulan nanofibers had a considerably ($p < 0.05$) smaller hydrodynamic diameter than non-loaded pullulan nanofibers, possibly due to improved drug adsorption and penetration.

Pullulan nanofibers released progesterone for seven days, according to the cumulative drug release profile.

The drug release's kinetic modelling demonstrated progesterone's Fickian diffusion from the polymeric matrix.

The cytotoxicity assay demonstrated that progesterone-loaded pullulan nanofibers enhanced the survivability of baby hamster kidney cells, resulting in a maximum survival rate of 60.51 ± 5.81 to 72.39 ± 0.53% and ensuring biocompatibility.

The following fig. 14. describes how to successfully electro-entrap progesterone in biopolymer pullulan and optimises the method.

It also characterises the progesterone-loaded pullulan nanofibers and shows promise for regulated delivery.[58]

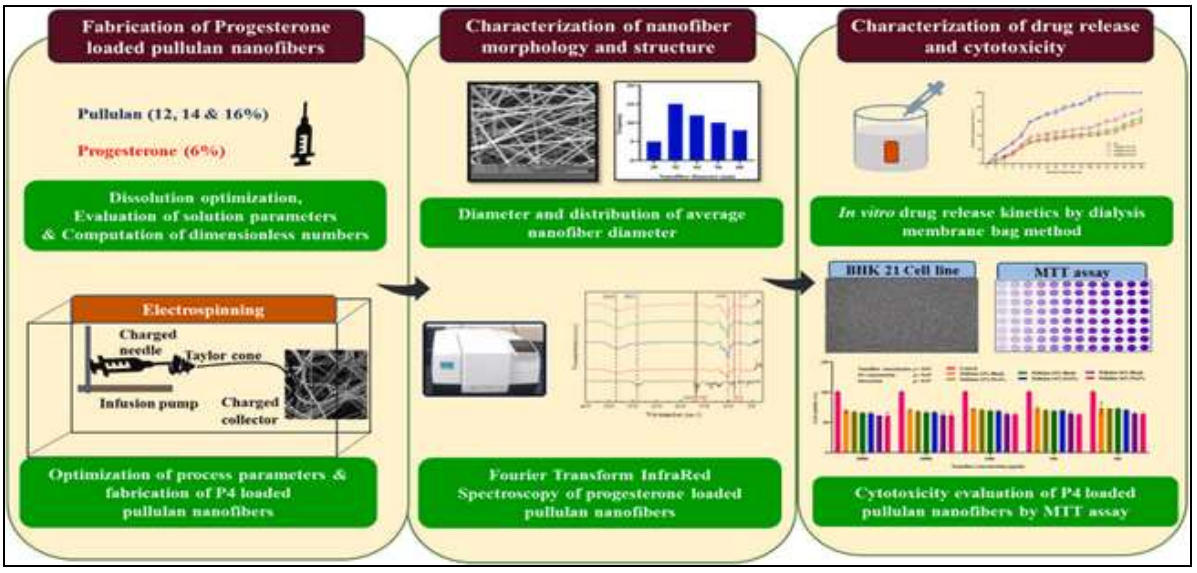

Fig. 14: Fabrication and characterization of progesterone loaded pullulan nanofibers for controlled release.[58]

4.2.6. Transethosomes

When progesterone is administered vaginally, a system of nanosized transethosomes improves permeability.

Transethosomes are composed of fifty percent ethanol, phospholipids, propylene glycol (PG) as a permeation enhancer, and cetyl trimethyl ammonium bromide as a charge inducer. Together, these components produce soft, flexible lipid vesicles.

This study used mucoadhesive polymer (Carbopol 974) to decrease vaginal clearance and lengthen residence time, therefore improving progesterone availability to uterine tissue.

After a 24-hour period, the batch of transethosomes loaded with progesterone that was optimised showed a particle size of 133.3 ± 3.42, a zeta potential of 57.2 ± 4.75 mV, and around 90.69 ± 2.07% progesterone release.

Transethosomal progesterone-loaded vaginal gel may be a useful formulation to promote the luteal phase and increase the rate of pregnancy.[59]

4.2.7. Vaginal rings

The vaginal ring is a cyclic, soft, and flexible structure made of hormones and polymers.

Progestin-containing vaginal rings are available and are used as birth control. Conventional vaginal rings have both local and systemic side effects.[60]

Helbling et al. overcame the drawbacks of the silicone used to prepare Progering® by creating intravaginal rings using an ethylene vinyl acetate copolymer.

A hot-melt extrusion mathematical simulation model was used to generate these vaginal rings. Over the course of 14 days, the in vitro progesterone from the vaginal ring showed a release rate of 12.05 ± 8.91 mg/day, which was comparable to that of Progering®.[61]

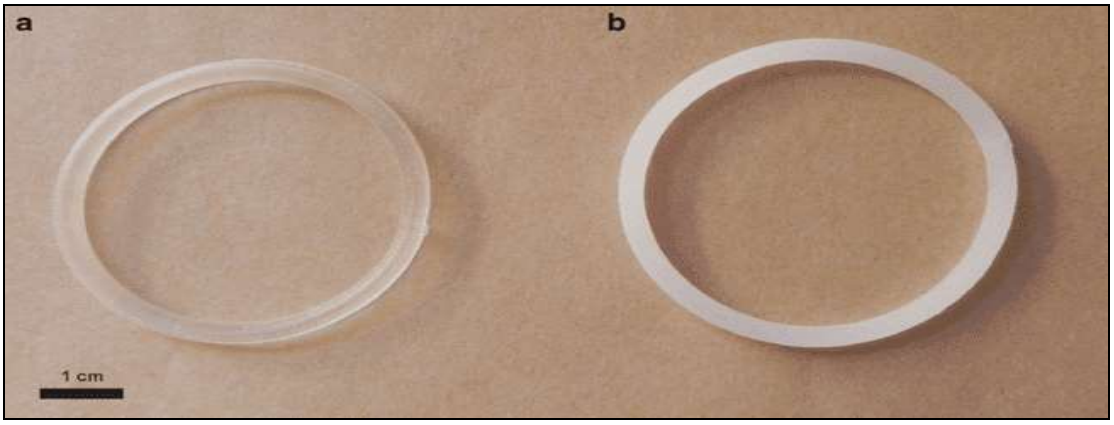

Fig. 15: EVA rings: (a) Without progesterone, (b) With progesterone.[61]

Personalised 3D-printed progesterone vaginal rings were suggested by Fu et al. as a way to counteract the negative effects of vaginal rings with predetermined size and shape. Using computer-aided design software, the **fused deposition modelling (FDM)** method of 3D printing was employed to create the progesterone vaginal rings in the shapes "M," "O," and "Y. All three rings exhibit enhanced progesterone release kinetics with customised geometries.[62]

4.3. Parenteral delivery system

An other method for giving progesterone subcutaneously or intramuscularly at a specific dose is the parenteral route. Increased effectiveness in terms of live births and the pregnancy rate has been demonstrated by parenteral progesterone administration.[63]

Progesterone injected intramuscularly demonstrated quick absorption, with a Cmax reached in as little as two to eight hours.[64]

Longer medication release, increased bioavailability, and avoidance of common oral administration side effects are all made possible via the parenteral route.

Due to patient discomfort and pain, including local irritation, sterile abscesses, allergies, and inflammation at the injection site, the parenteral progesterone formulations show poor compliance.

Progesterone's limited water solubility makes it difficult to produce aqueous solutions, which makes progesterone subcutaneous administration difficult.[63]

4.3.1. Depot

Complexing progesterone with β-cyclodextrin derivatives improves its solubility for the injectable product.

A 1:2 ratio between progesterone and hydroxypropyl-β-cyclodextrin improves solubility by 48%.

The Cmax of this formulation by the intramuscular route was 400 ng/ml and the subcutaneous route was about 300 ng/ml after 2 h in humans.[65]

Hot-melt extrusion and wet milling were used to create the PLGA matrix-based progesterone microspheres, which showed improved drug loading, reduced porosity, and high density when administered intramuscularly.

Because of its internal structure, which resembles a honeycomb, the microsphere exhibited sustained releasing action for seven days.[66]

- **Method of preparation of Progesterone Microspheres (PMS)[66]**

a) Micronization of APIs

Zirconia milling beads with a diameter of 1.0 mm were placed inside the chamber and PRG was wet-milled until the particle size was approximately 1μm.

Zirconia was applied to the milling medium to enable reduced metal component contamination during the attrition process and highly energy-efficient milling.

A laser particle size analyzer was utilised to assess the particle size, and lyophilization was employed to gather the PRG particles.

b) Hot Melt Extrusion and Medium Milling

After weighing the necessary amount of PRG and polymer into a sealed polyethylene bag, the mixture was manually mixed for roughly ten minutes.

A HME (ATS ZE-16 twin-screw extruder) with a 1 mm diameter die was used to extrude the mixture, producing matrices that had a diameter of 1.1–1.2 mm.

There was a 20 rpm screw rotation speed and a roughly 10-minute residence period.

Zone 1 (40°C), Zone 2 (60°C), Zone 3 (80°C), Zone 4 (80°C), Zone 5 (80°C), Zone 6 (80°C), and die (60°C) were the temperatures specified for the extruder parts.

After the extrudate was divided into segments of 5 mm length, the microrods were broken up using a mini-type pulverizer and sieved through 100 mesh.

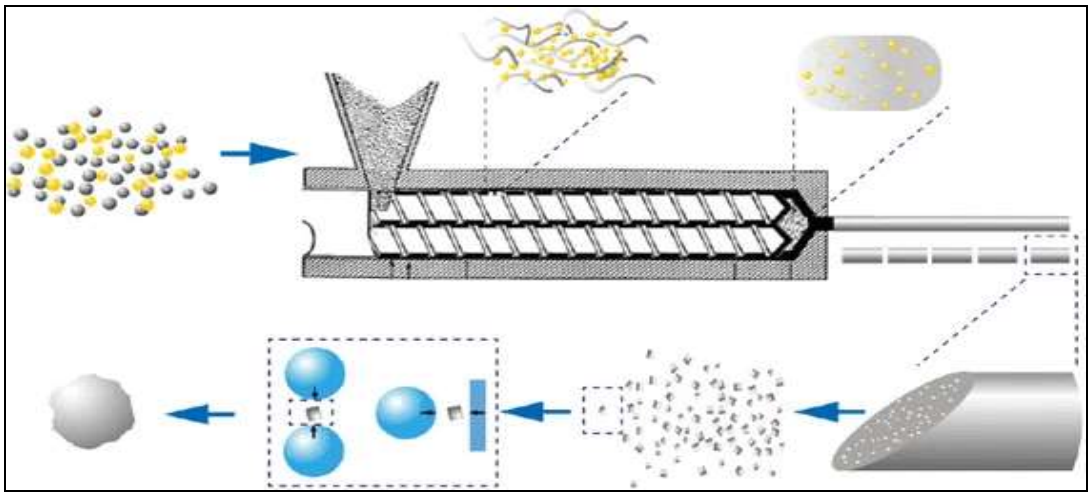

Fig. 16: Injectable Sustained-Release Depots of PLGA Microspheres for Insoluble Drugs Prepared by hot-Melt Extrusion.

The complete process and possible mechanism of formation of PMS, where PLGA is gray, PRG is yellow and Grinding beads are blue[66]

It is difficult to create a stable formulation that releases progesterone over an extended period of time at a lower dose. Progesterone nanoparticles-sucrose acetate isobutyrate (SAIB)-PLGA in situ depot system (PSPIDS) was created by Cao et al. via freeze-drying.

The pharmacokinetic analysis showed that Cmax of progesterone was obtained at 79.1 ± 3.0 µg/mL in 2.6 ± 1.3 h with AUC of 4232.2 ± 686.2 µg/L.h for PSPIDS.

The Cmax and Tmax of the commercial progesterone oil are 21.8 ± 4.5 µg/mL and 25.7 ± 39.0 h, respectively.

A particularly promising progesterone delivery method with sustained release is the PSPIDS.[67]

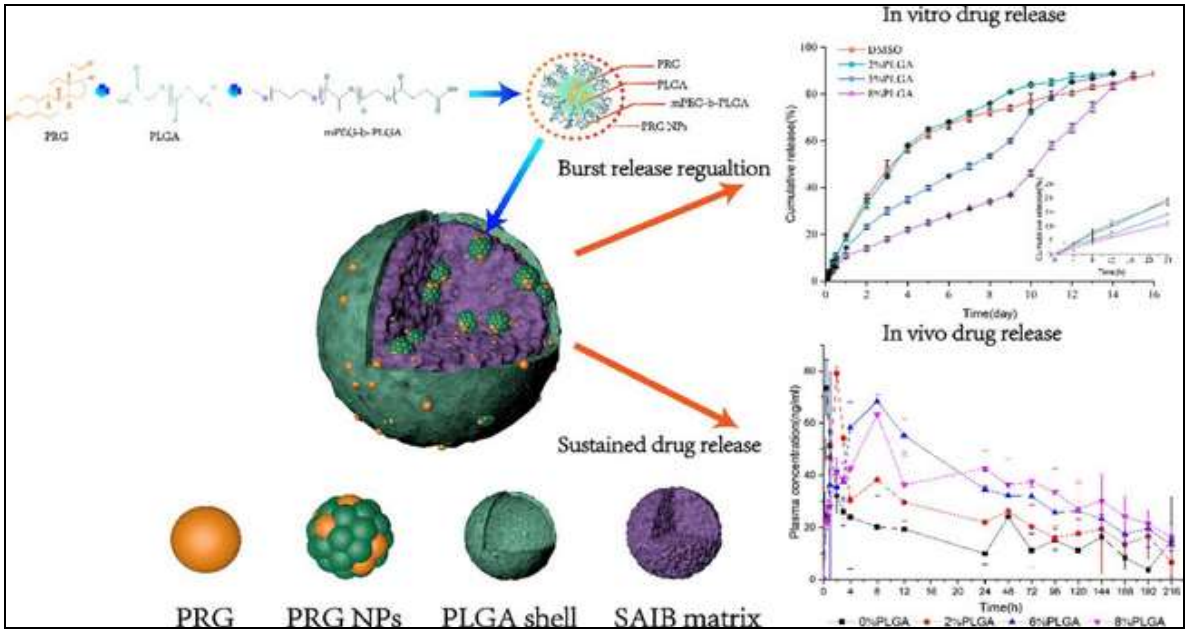

Fig. 17: Injectable Sustained-Release Depots of PLGA Microspheres for Insoluble Drugs Prepared by hot-Melt Extrusion.[67]

PEGylated nanoparticles provide sustained release for up to 120 hours and lengthen the duration of progesterone's residency in the body, whereas ordinary nanoparticles are phagocytosed by the body and have low bioavailability.

The hybrid progesterone nanoparticle pharmacokinetic research yielded the following results: a Cmax of 173.5 ± 25.8 μg/l, an AUC of 9163.867 μg/l • h^{-1}, a t1/2 of 52.7 h, and a mean residual duration of 92.3 h.

The bioavailability results indicated that the drug is released by the system over an extended period of time, allowing for a reduction in the frequency of dosing.[68]

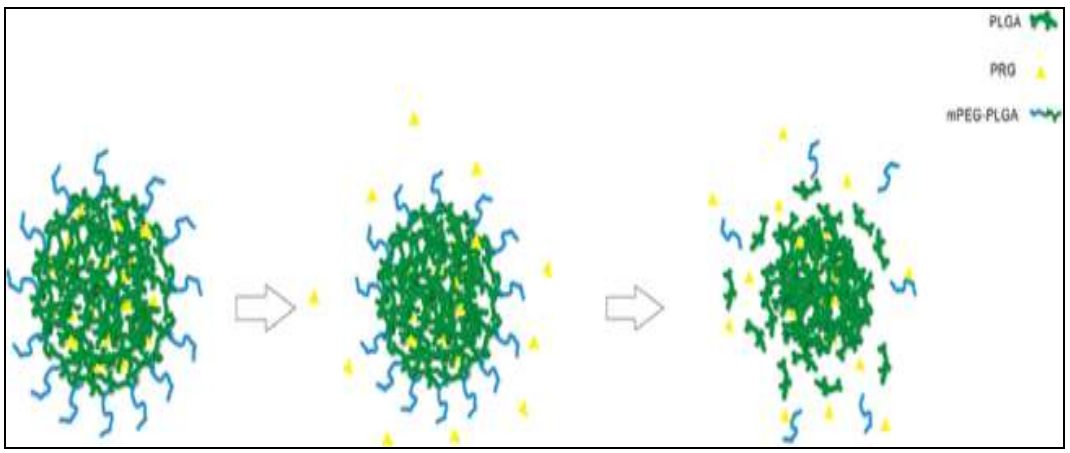

Fig. 18: The drug release process of PRG hybrid NPs (PRG H-NPs).[68]

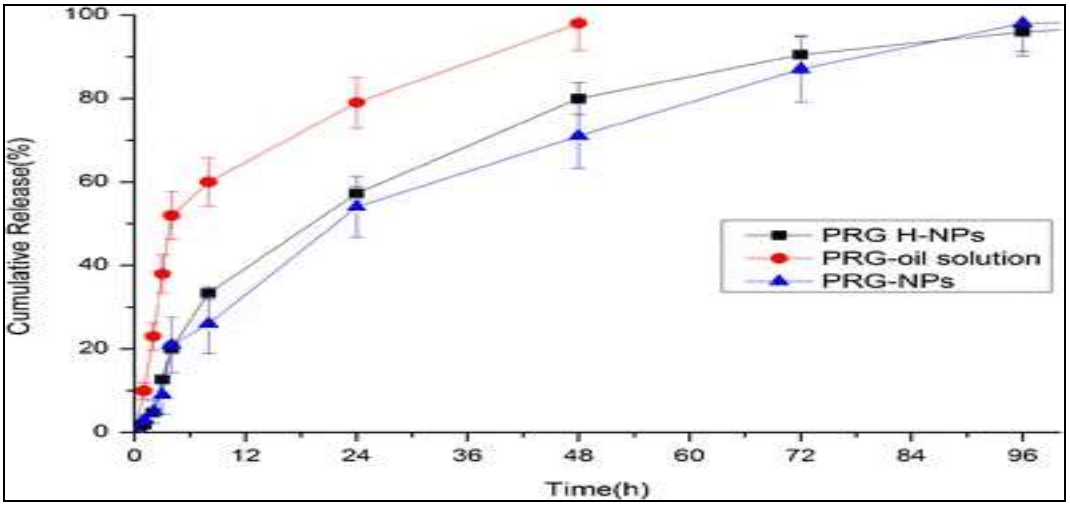

Fig. 19: *In vitro* drug release profiles of PRG from PRG oil solution, PRG PLGA NPs (PRG NPs) and PRG hybrid NPs (PRG H- NPs).[68]

4.3.2. Nanosuspension

To treat oocyte retrieval for luteal support, natural progesterone in nano- suspension form was administered intramuscularly.

A modified solvent precipitation technique was used to create the progesterone nanosuspension.

The particle size of the nanosuspension was greatly influenced by the concentration of stearic acid; as the concentration of stearic acid increased from 5 to 20 percent w/w, the particle size of the nanosuspension reduced from 680 ± 60 to 267 ± 10 nm.

Following the Higuchi method for progesterone release, the in vitro dissolution investigation of progesterone nanosuspension with 5%, 10%, and 20% stearic acid exhibited 60% ± 5.3%, 76% ± 8.2, and 88% ± 5.4 drug release, respectively, after 10 h.[69]

- **Method of preparation of Progesterone Nanosuspension[69]**

With few changes, the solvent precipitation approach was used to create the nanoparticles.

To put it briefly, progesterone (200 mg) and various concentrations of stearic acid powder (5%, 10%, and 20% w/w) were quickly mixed in ethanol (1 mL) to create nanoparticles.

Using syringe dropping under probe sonication at 60% amplitude for 20 s, this solution was added to 60 mL of cold deionized water.

After that, the resultant colloid was freeze-dried at -20°C.

For imaging and particle size measurement, a small volume of the colloid (1 mL) was held back from lyophilization.

4.4. Intrauterine delivery system

To transfer the medication to the uterus, intrauterine devices (IUDs) and intrauterine systems (IUSs) are frequently utilised. IUDs include contraceptives that work by creating an adverse environment for sperm and ovum, preventing the fertilisation of embryos.[70] Progesterone is delivered intrauterine, where it avoids first pass metabolism and is more compliant. Furthermore, it lessens blood loss after menstruation and aids in reaching the maximal serum concentration in a matter of hours. Amenorrhoea, expulsion, irregular bleeding issues, hypertension, weight gain, and raised haemoglobin levels are the negative consequences of IUDs.[71] The majority of IUDs are T-shaped devices with copper surrounding the stem. Medicated intrauterine devices, or IUSs, are an improved and more efficient form of IUD than regular IUDs.[72]

The progesterone-containing IUSs that are on the market are Skyla®, Liletta®, Kyleena®, and Mirena®. Long-term usage of these IUSs is beneficial and has fewer systemic adverse effects. With an initial quick release of 20 µg/day, the first LNG-IUS, Mirena (52 mg Levonorgestrel) (LNG), demonstrated efficacy for up to 5 years. Liletta (52 mg LNG) has demonstrated prolonged efficacy for up to 7 years. It delivers a daily release of LNG and maintains plasma levels similarly to Mirena. Kyleena (19.5 mg LNG) demonstrated an average release rate of 9 µg/day, with an efficacy of 3–5 years. Skyla (13.5 mg LNG) releases 14 µg of contraceptive every day for three years. After IUSs are removed, fertility can resume.[73]

It is now simpler to insert new frameless devices into the uterus to prevent IUD side effects that usually occur, such as ejection, pain, and irregular bleeding. There are frameless LNG IUS that are commercially accessible, such as FibroPlant®, which delivers 20 µg of LNG per day for five years.[74] The IUDs that are now on the market have a set shape and occasionally cannot adjust to the shape of the body. As a result, progesterone treatment cycles, dosages, and designs might be freely altered to create personalised, 3D-printed IUDs.[51] The shape and dosage of 3D-printed IUDs could be easily and affordably customised due to their extended in vitro release, which lasted for seven days.[75]

4.5. Transdermal delivery systems

One of the secure and non-invasive ways to provide progesterone is through the transdermal method. Skin barriers, however, limit the bioavailability of transdermal delivery.[76] Progesterone's plasma concentration is not significantly altered by transdermal progesterone. Furthermore, problems with proges-terone's transdermal delivery include inconsistent pharmacokinetics and biodistribution.[77]

By using polysorbate 80 as a penetration enhancer during the electrospinning process, a transdermal polymeric progesterone fibrous patch can be prepared. Following Fig. 19. highlights the importance of surfactant in optimising drug release by showing a five-fold increase in progesterone release compared to fibres without polysorbate 80.[78]

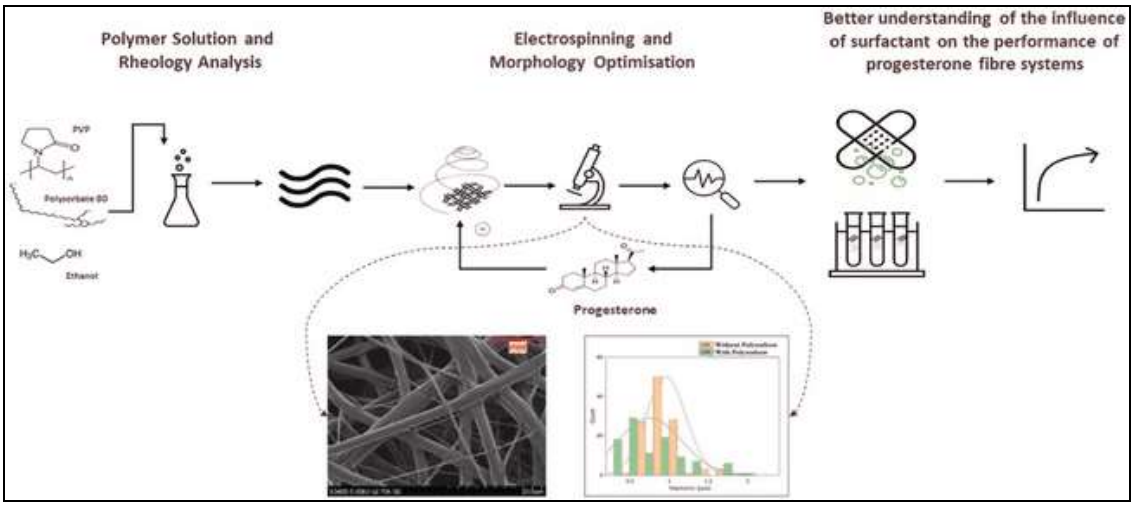

Fig. 20: Polysorbate enhanced progesterone loaded drug diffusion from macromolecular fibrous patches for applications in obstetrics and gynaecology.[78]

Waterborne poly (urethane-urea) nanocomposite films shown the ability to get past skin barriers and release progesterone under control.[79]

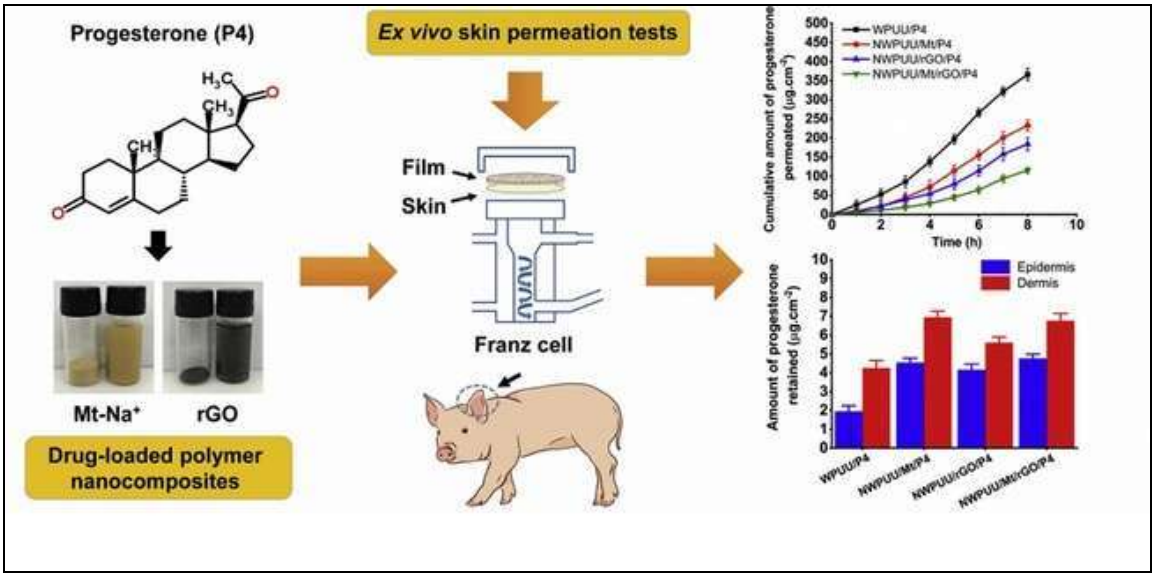

Fig. 21: Transdermal progesterone delivery study from waterborne poly(urethane-urea)s nanocomposites films based on montmorillonite clay and reduced graphene oxide.[79]

Liquid crystalline progesterone nanoparticles were created with sustained release up to 56% over the course of 24 hours. They were stable and kept their cubic shape for three months during the stability study. Progesterone in nanoparticles had a six-fold higher transdermal penetration than the aqueous suspension, according to ex vivo investigations.[80]

- **Method of preparation of progesterone loaded self-assembled liquid crystalline nanoparticles[80]**

a) Emulsification method

In a water bath with a thermostat regulated at 70°C, 4.5% w/w glyceryl monooleate (GMO) and 0.5% w/w Poloxamer 407 (PLX) were melted to form the dispersion phase. Progesterone (2% w/w) was then solubilized for 5 seconds using a vortex mixer. Subsequently, the mixture was emulsified using a rotor-stator homogenizer operating at 10,000 rpm for five minutes after being delicately injected using an insulin syringe into a heated aqueous phase at 70°C. For additional research, the final dispersion was cooled and kept at room temperature.

b) Solvent precursor dilution method

A 1% w/w aqueous solution of PLX was added to an isotropic liquid containing 5% w/w GMO phase, 2% w/w progesterone, and 5% w/w ethanol. The mixture was homogenised continuously at 10,000 rpm for five minutes, or until a colloidal dispersion of LCNPs formed. For future research, the finished dispersion was kept at room temperature.

4.6. Intranasal delivery systems

A number of benefits of intranasal distribution include its non-invasiveness, convenience of administration, and ability to avoid the hepatic first-pass effect. For postmenopausal women undergoing hormone replacement treatment, the intranasal method of progesterone administration was most recommended. Due to its high vascularization, the nasal mucosa offers a vast surface area for absorption. Nasal anatomy, its restricted volume capacity, metabolic enzymes, and other factors such nasal congestion and discharge can all affect nasal absorption.

Progesterone's intranasal lipophilic gel was created to assess its neuroprotective properties after a stroke. The gel was stable and stuck to the nasal membrane quickly. The study's findings showed that intranasal treatment of 8 mg/kg progesterone gel enhanced behavioural outcomes and survival rate 48 hours after middle cerebral artery occlusion (MCAO). Progesterone had a higher level of the neuroactive metabolite (3α,5α-THPROG) than a placebo.

Progesterone administered intranasally to mice resulted in increased sensorimotor activity, better survival, and optimal cerebroprotective function.[81]

Because progesterone has several different modes of action, it is being utilised to treat a number of neurodegenerative diseases, including Parkinson's and Alzheimer's disease.[82]

Ionotropic gelation was utilised to create progesterone nanoparticles. Trimethyl chitosan gave the resultant nanoparticles a positive surface charge, which made it easier for them to interact with the nasal mucosa's negative sialic membrane. After five hours, progesterone nasal gel's release profile showed a 50.52% release of the hormone (0.1 mg/mL). In vivo investigations done in male Sprague–Dawley rats revealed 5 folds increase in brain progesterone concentration post- intranasal treatment.[83]

4.7. Ocular delivery systems

Enhancing the drug's bioavailability at the intended site and improving patient adherence to treatment of various visual disorders are the two primary benefits of the ocular delivery system.

Less bioavailability, pain during delivery, and obscured vision were the drawbacks of progesterone administered ocularly.

The perception of foreign matter in the eye was the primary cause of the patient's discontent with the ocular formulation.

Ocular inserts are demonstrating encouraging findings with enhanced therapeutic efficacy, which could help them overcome the limitations of traditional ocular preparations.[84]

A degenerative illness of the eyes, retinitis pigmentosa (RP), involves a malfunction in the apoptotic photoreceptor, which is hereditary and ultimately in blindness.[85]

Because progesterone inhibits the loss of myelin sheets and promotes the creation of new ones, it suppresses retinal degeneration and addresses various ocular diseases. Poor aqueous solubility, which lowers progesterone's potency, is the main barrier to the hormone's ocular administration.

Soluplus and Pluronic F68 were used to create ocular progesterone micelles, which shown an impressive increase in solubility.

The chorioallantoic membrane was used to apply the formulation, demonstrating its non-irritating and ocular compatibility. Reported that these micelles enhanced the permeability of progesterone and demonstrated its increased accumulation in the sclera and cornea.[86]

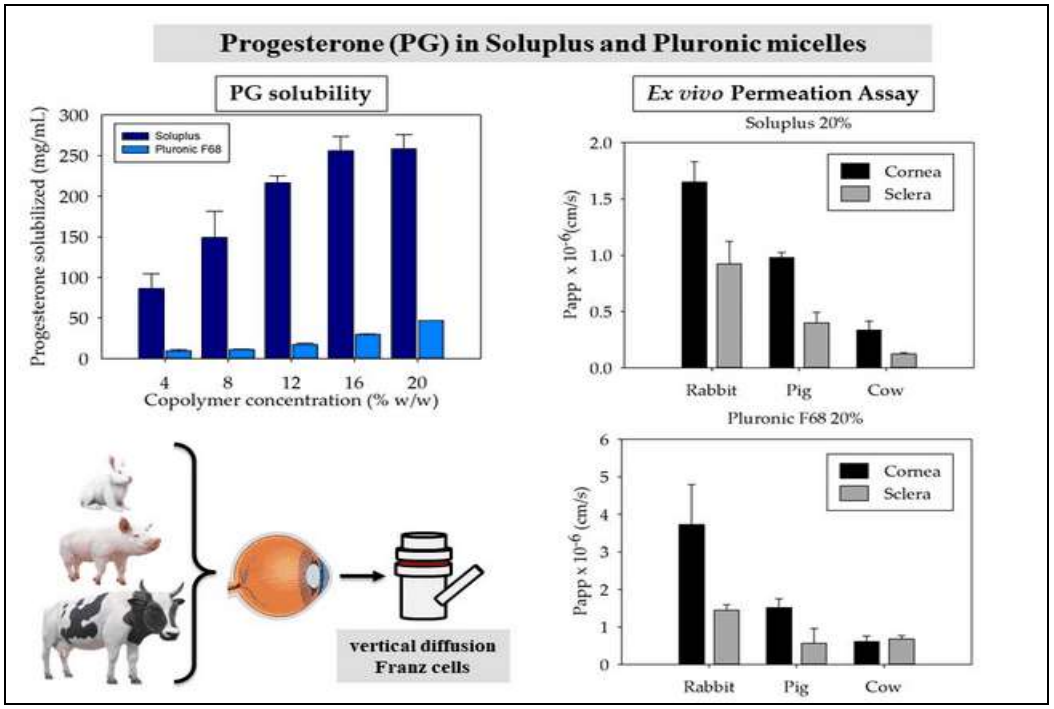

Fig. 22: Micelles of Progesterone for Topical Eye Administration: Interspecies and Intertissues Differences in Ex Vivo Ocular Permeability.[86]

Progesterone ocular implants were made using polyvinyl alcohol (PVA), PVP-K30, and PG. Within 3 hours, 80 percent of the progesterone was released in the in vitro release testing, and it continued to show regulated release for up to 21 hours. Progesterone diffused over the cornea and sclera of a rabbit eye in ex vivo diffusion investigations of ocular inserts. The ocular implant in the HET-CAM test generated no irritation.[87]

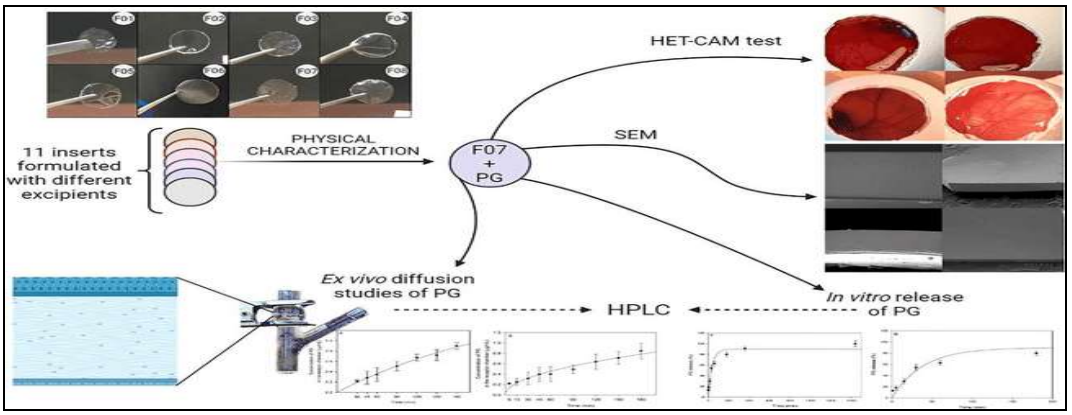

Fig. 23: Development, characterization, and ex vivo evaluation of an insert for the ocular administration of progesterone.[87]

In mice resistant to RP, progesterone combined with β-cyclodextrin inhibited retinal degeneration. Animals received the formulation for 21 days as aqueous drops in their eyes. The produced progesterone-β-cyclodextrin solution demonstrated a significant reduction in inflammation and avoided the early death of photoreceptor cells, deferring vision loss and lowering gliosis, according to findings from histological immunofluorescence tests.[88]

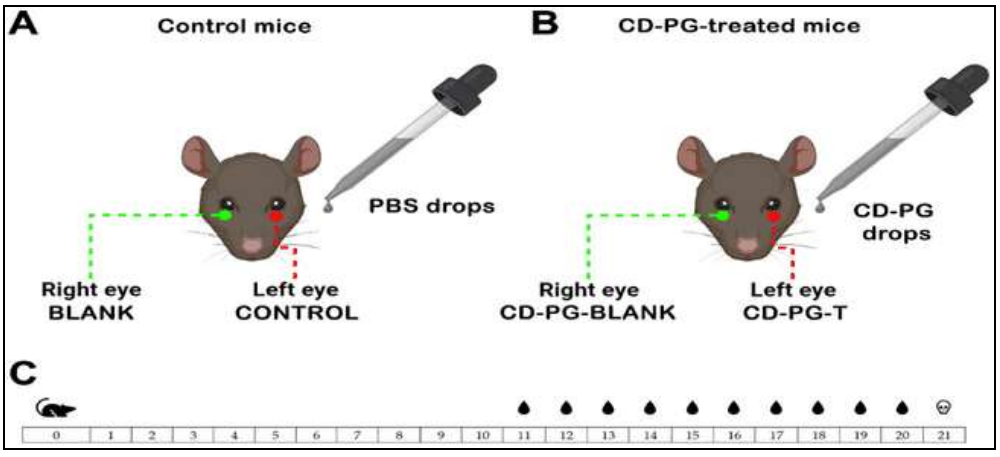

Fig. 24. Scheme of the experimental design.

(A) Control mice: the left eye received a drop of PBS (control) every 12 h, whereas the right eye was left untreated (blank).

(B) CD-PG-treated mice received a drop of a 1 mg/mL CD-PG to the left eye (PG-T), whereas the right eye (PG-blank) was left untreated to evaluate the possible effects caused by CD-PG administered to the contralateral eye.

(C) Scheme of the treatment protocol from the time mice were born (day 0) to the time mice were sacrificed (day 21), showing the days the mice received treatment (days 11–20).

4. Recent Patents on progesterone delivery systems

Table 4: Recent patents on progesterone delivery systems[8]

Patent No	Date of Publication	Title	Applicant	Summary
US20210121480	29.04.2021	Stable pharmaceutical compositions containing estradiol and progesterone for oral administration	Slayback Pharma, United States	The salt form of progesterone consists of a surfactant and solubilizing agent.
WO2021068239A1	15.04.2021	Vaginal slow-release administration system for luteal support, a preparation method therefor and use thereof	National research institute for family planning,China	Progesterone-containing vaginal ring act as a reservoir system used in the reproduction and dysfunction of uterine bleeding
US20210008216	14.01.2021	Biodegradable drug delivery for hydrophobic compositions	Medincell, France	The present invention presents a composition for biodegradable drug delivery system comprises of a triblock copolymer and diblock copolymer
CN112156071	01.01.2021	Preparation method of Responsive amphiphilic polymer self-assembled micelle	Tianjin polytechnic university, China	The preparation method of self-assembled micelle using an amphiphilic polymer with good biocompatibility and biodegradability.
CN112022859	04.12.2020	Progesterone material based on transdermal absorption	Shenzhen chenguo material technology Co., Ltd., China	The system consists of several excipients, defoaming and dispersion agents, and diatomite converted into a solid form.
CN111529488	14.08.2020	Progesterone self-emulsifying composition and application	Zhejiang Subkom Pharmaceutical Co Ltd, Hangzhou tonghui pharmaceutical technology Co., Ltd.,China	Improved chemical stability using self-emulsion.
US20200268888	27.08.2020	Progesterone formulation has a desirable PK profile	Therapeutics MD, Inc., United States	Reduced dose of progesterone with improved therapeutic benefits.
WO2020135352	02.07.2020	Method for preparing progesterone particulate, prepared progesterone particulate, and injection thereof	Sichuan kelun pharmaceutical research institute Co., Ltd.,China	Micro-sized progesterone particulate for improved stability.
US20200230258	23.07.2020	Aqueous oral solutions of steroid hormones and hydroxypropyl-B-cyclodextrin with optimized bioavailability	Altergon S.A., Lugano (CH)	The complex of hydroxypropyl-β-cyclodextrin with progesterone with enhanced water solubility.
US20200129422	30.04.2020	Progesterone in bioadhesive formulation for buccal delivery	Viramal Ltd., London (GB)	Bioadhesive systems prevent hepatic first-pass metabolism.

5. Clinical trials of progesterone

Table 5: Clinical trials of progesterone (From 2010 to 2022)[8]

Clinical trial ID	Title	Disease	Intervention	Phase	Year of commencement - completion	Sponsor
NCT04597099	Androgen Blockade and Progesterone Augmentation of Gonadotropin Secretion	Polycystic Ovary Syndrome	Micronized progesterone	Early Phase 1	2022-ongoing	University of Virginia
NCT04143880	Progesterone in the Treatment of Acute Hemorrhagic Stroke	Stroke	Intramuscular and intranasal administration of progesterone	Phase 4	2020–2020	Zhejiang University
NCT03834883	Reducing the Risk of Drug-Induced QT Interval Lengthening in Women	Long QT syndrome	1. Oral Progesterone 400 mg daily (2 × 200 mg capsules) 2. Ibutilide	Phase 4	2019-ongoing	Indiana University
NCT03734770	Patient's Preferences About Subcutaneous or Vaginal Progesterone Administration for Luteal Phase Support (PROPER-1)	Luteal phase support, *In vitro* fertilization	Subcutaneous progesterone 25 mg once a day and micronized vaginal progesterone 200 mg TID	N/A	2019–2019	University di Verona
NCT03297216	Improving Pregnancy Outcomes with Progesterone (IPOP)	HIV Infection, Preterm Birth	Intramuscular injections of 17-alpha hydroxyprogesterone caproate (17P) 250 mg	Phase 3	2018–2020	University of North Carolina
NCT03340701	Pharmacokinetics of Progesterone in Pregnancy (PK-PiP)	Progesterone in pregnant women	Vaginal suppository of progesterone 200 mg	Phase 1	2018–2018	Thomas Jefferson University
NCT02846909	The Vaginal Progesterone and Cerclage	Abortion	Pessaries of 400 mg progesterone	Phase 2	2017–2019	Assiut University
NCT02133573	Randomized Trial of Maternal Progesterone Therapy	Congenital heart disease, neurodevelopmental disability	Vaginal gel of 90 mg progesterone, BID	Phase 2	2014–2021	Children's Hospital of Philadelphia
NCT01143064	Efficacy and Safety Study of Intravenous Progesterone in Patients With Severe Traumatic Brain Injury (SyNAPSe)	Brain Injuries	Intravenous Progesterone 0.71 mg/kg/hr and compared with lipid emulsion without progesterone	Phase 3	2010–2014	BHR Pharma, LLC

6. Global Progesterone Market

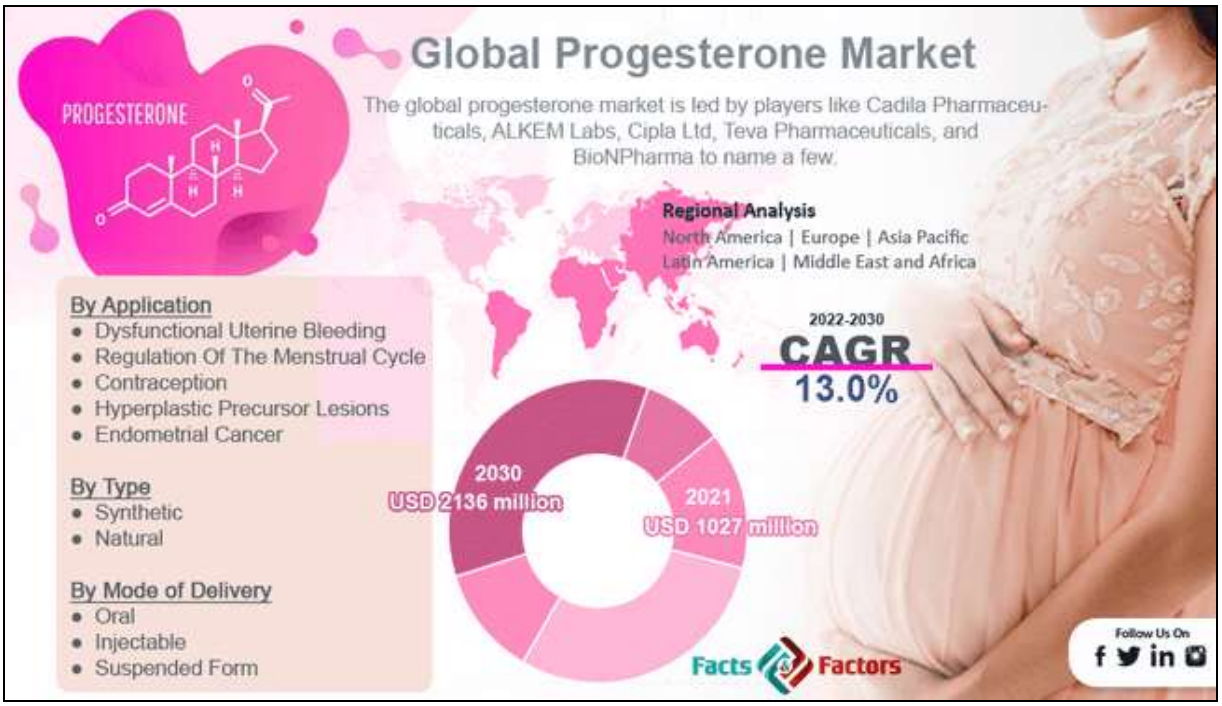

Fig. 25. Global Progesterone Market Analysis.

Ref. https://www.fnfresearch.com/progesterone-market

7.1. Marketed Products of Progesterone

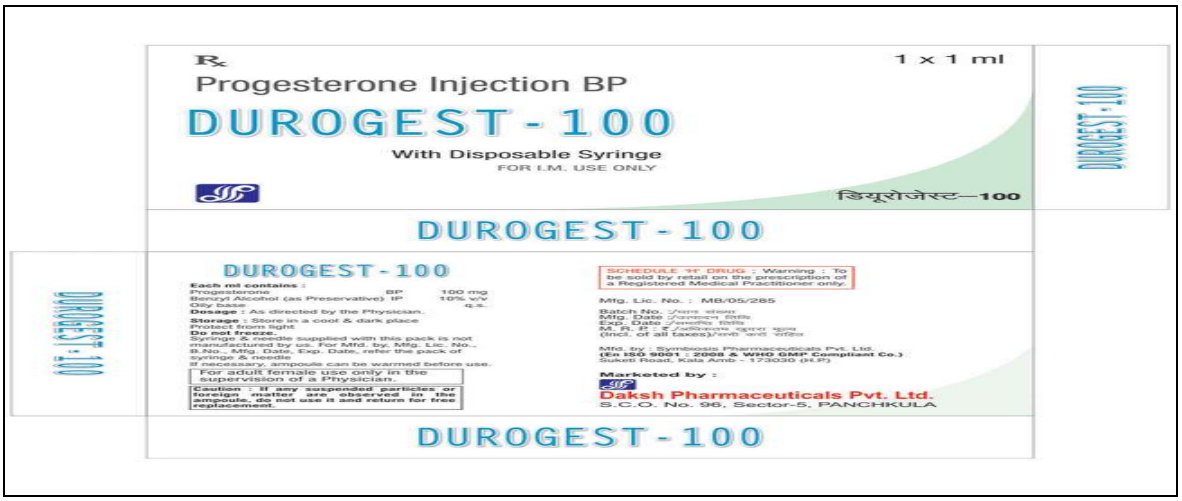

Table 6: Details of clinically available products of progesterone.[8]

Route	Type of Formulation	Product Composition	Pharmacokinetics			Indication
			Cmax	Tmax	AUC	
Oral	Capsule (Prometrium®)	Peanut oil, gelatin, glycerin, lecithin, titanium dioxide, color	17.3 ± 21.9 ng/mL	1.5 ± 0.8h	43.3 ± 30.8 ng.h/mL	Endometrial hyperplasia in postmenopausal women and for secondary amenorrhea.

Vaginal	Gel (Crinone®)	Glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, purified water	13.15 ± 6.49 ng/ mL	5.6 ± 1.84 h	288.63 ± 273.72 ng. h/mL	Used as a Progesterone supplement in Assisted Reproductive Technology (ART) and in the treatment of secondary amenorrhea.
	Vaginal ring (MilprosaTM)	Progesterone, light mineral oil and silicone elastomer	9.33 ± 2.80 ng/ mL	134.80 ± 49.17 h	1188.41 ± 374.25 ng. h/mL	For supporting embryo implantation during early pregnancy. It boosts corpus luteal activity in infertile women as ART. Helps maintain pregnancy.
	Vaginal insert (Endometrin ®)	Lactose monohydrate, polyvinylpyrrolidone, adipic acid, sodium bicarbonate, sodium lauryl sulfate, magnesium stearate, pregelatinized starch, and colloidal silicon dioxide	18.5 ± 5.5 ng/ mL	18.0 ± 9.4 h	327 ± 127 ng/h/mL	For supporting embryo implantation as part of ART.
Parenteral	Intramuscular Injection	Benzyl alcohol, sesame oil	50 ng/ mL	8 h	-	Indicated in uterine bleeding due to an imbalance of hormones and in the treatment of amenorrhea.

8. Case studies

a) Clinical use of aqueous subcutaneous progesterone compared with vaginal progesterone as luteal support in in vitro fertilization: A randomized controlled study in Taiwan[89]

Objective: In order to facilitate fresh embryo transfers during in-vitro fertilisation (IVF), this study compares the effectiveness, tolerability, and patient satisfaction with vaginal progesterone (Crinone, 90 mg/tube; Merck) and aqueous subcutaneous progesterone (Prolutex, 25 mg/vial; IBSA).

Materials & Methods: 65 IVF patients were enrolled in this prospective randomised study and randomised to receive either Prolutex (25 mg daily, n=33) or Crinone (90 mg daily, n=32) at random.

Daily luteal support regimens were administered beginning two days following oocyte pickup.

Until seven weeks of gestation, luteal support was administered if the serum pregnancy test came back positive.

The clinical pregnancy rate and serum progesterone level at 4 weeks of gestation and the mid-luteal phase were the primary outcomes.

Questionnaire-based measures of patient satisfaction and medication tolerance were secondary outcomes.

Results: Serum progesterone levels, patient satisfaction, and clinical pregnancy rates (Prolutex 25.0% versus Crinone 33.3%, p=0.699) did not differ significantly between the Prolutex and Crinone groups.

Patients who got Prolutex reported less bothersome vaginal discharges and vulvar discomforts, although complaining of increased localised pain at the injection sites.

Conclusion: Prolutex offers patients more options for progesterone administration as luteal phase support during in vitro fertilisation (IVF), and it is equally effective and patient-satisfied as Crinone.

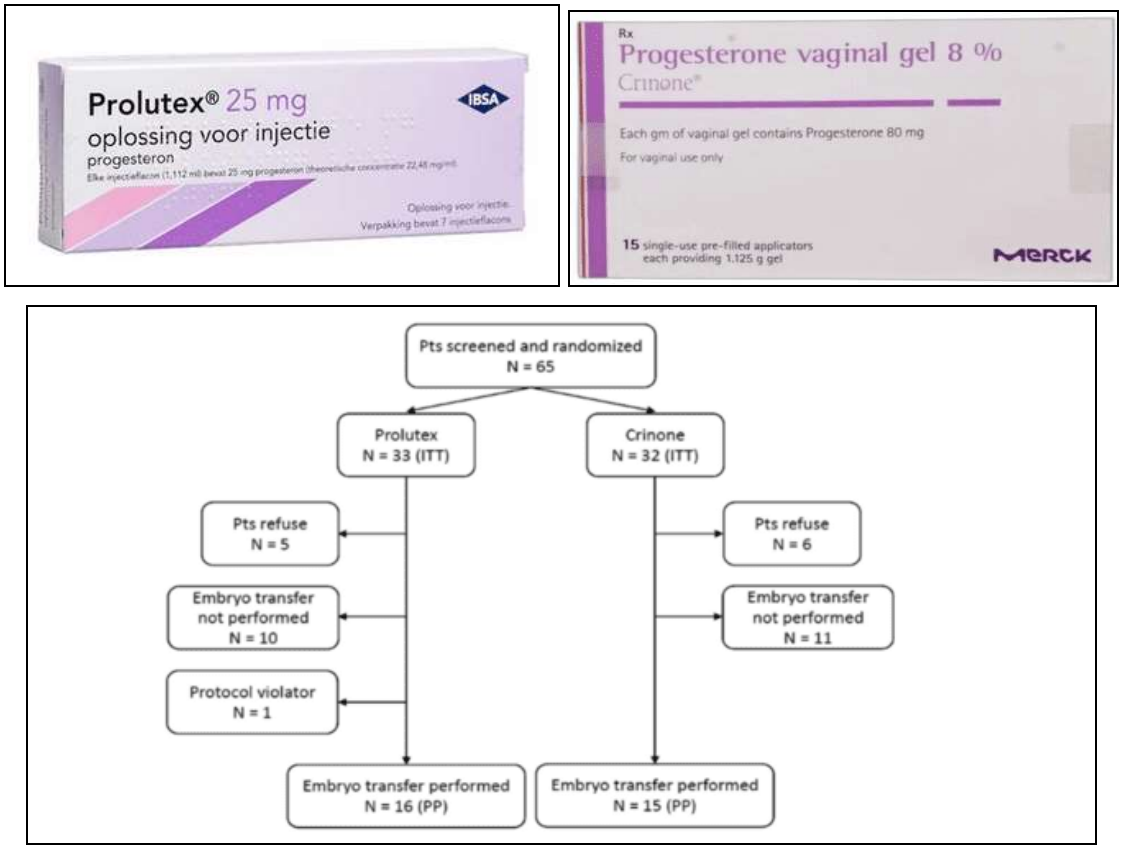

Fig. 27: Participant flow through the trial (ITT = Intention to treat; PP = per protocol).[89]

	Prolutex (n = 16)	Crinone (n = 15)	P value
Day of embryo transfer			0.172
Cleavage-stage embryo transfer	11	14	
Blastocyst transfer	5	1	
Number of embryo transfer, mean (SD)	2.6 (0.2)	2.7 (0.2)	0.752
Serum progesterone level (ng/mL)			
Mid-luteal phase, mean (SD)	21.4 (5.1)	17.6 (10.7)	0.075
4 weeks of gestation, mean (SD)	26.8 (9.6)	31.4 (13.2)	1.000
Clinical pregnancy rate (number)	25.0% (4/16)	33.3% (5/15)	0.699
Ongoing pregnancy rate (number)	12.5% (2/16)	33.3% (5/15)	0.220
Double dose for vaginal bleeding rate (number)	37.5% (6/16)	20.0% (3/15)	0.444

Table 7: Efficacy and pregnancy outcome (Per-protocol population).[89]

	Prolutex (n=16)	Crinone (n=15)	P value
Satisfaction score (0-10), mean	7.39	7.22	0.892
Adverse events (1-4), mean			
1. Breast tenderness	1.54	1.70	0.310
2. Dizziness/Tiredness	1.29	1.24	0.464
3. Nausea/Vomiting	1.12	1.22	0.264
4. Abdominal pain	1.59	1.58	0.892
5. Gastrointestinal upset	1.39	1.20	0.423
6. Administration site pain	2.32	1.02	<0.001
7. Administration site erythema	1.67	1.03	<0.001
8. Administration site itchiness	1.37	1.43	0.682
9. Injection site hematoma	1.44	1.00	0.006
10. Vaginal dryness	1.18	1.00	0.078
11. Vaginal pruritus	1.25	1.50	0.401
12. Vaginal discharge	1.56	2.03	0.011
Satisfaction score 0-10 (0 most unsatisfied, 10 most satisfied)			
Adverse events 1-4 (1 none, 2 mild, 3 moderate, 4 severe)			

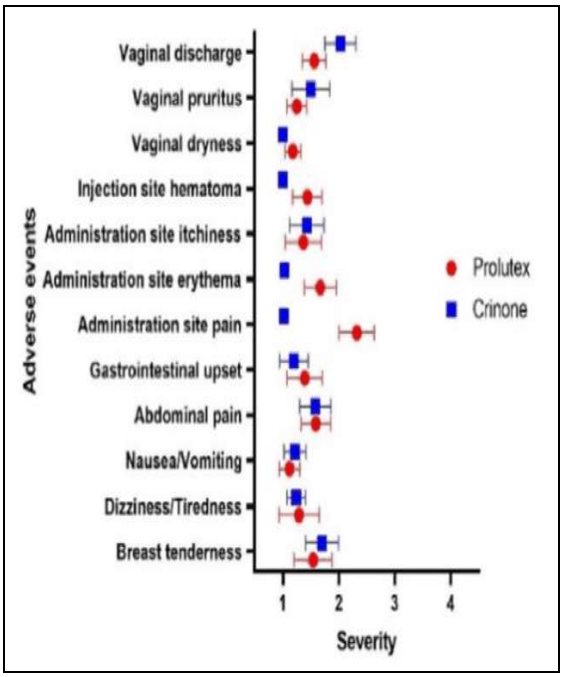

Table 7: Satisfaction and adverse effects (Per-Protocol population).[89]

b) Comparing the results of two distinct progesterone vaginal gels, Progeson™ and Crinone™, in patients who underwent frozen-thawed embryo transfer and fresh embryo transfer using a natural cycle endometrial preparation methodology, as well as pharmacokinetics research[90]

Objective: This study examined the clinical pregnancy rate and pharmacokinetic performance of two vaginal progesterone gels, Progeson™ and Crinone™.

Materials and methods: Progeson™ and Crinone™ shown comparable long-term dissolving rates in the pharmacokinetics performance. In order to compare blood progesterone levels and clinical pregnancy rates, 141 participants who had received in vitro fertilisation (IVF) procedures were enrolled in the clinical trial.

Results: Using a natural cycle endometrial preparation procedure, 78 patients underwent fresh embryo transfer and 63 underwent frozen embryo transfer. For luteal phase support, individuals in each group received either Progeson™ or Crinone™ alone, without conjunction with other progesterone medications. The research revealed that the Progeson™ group led to greater progesterone levels at mid-luteal phase and pregnancy test day in the frozen-thawed embryo transfer group, whereas the Crinone™ group led to higher oestrogen levels at mid-luteal phase in the fresh embryo transfer group.

Conclusion: In both the fresh embryo transfer and frozen-thawed embryo transfer groups, the subjects who received Crinone™ or Progeson™ had comparable rates of pregnancy, live delivery, and stillbirth.

For this reason, Progeson™ may be a good alternative to Crinone™ in assisted reproductive therapy.

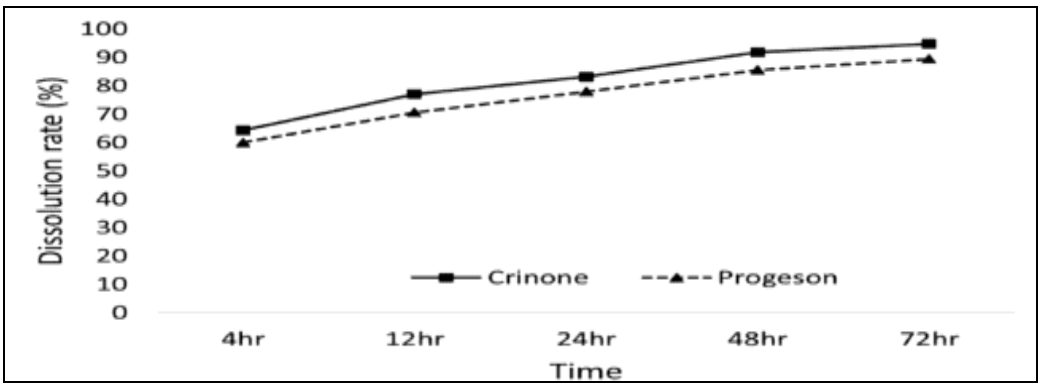

Fig. 26. Contrasting the rates at which Progeson and Crinone dissolve.

Progeson and crinone dissolution rates were calculated in accordance with USP 724. According to the findings, the rates of dissolution of Crinone and Progeson within 72 hours are comparable[90]

Table 8: The association between CrinoneTM and ProgesonTM in patients receiving fresh ET (N=78).[90]

Variable	Crinone	Progeson	p-value
Case Number	38	40	
Age	37.5 (33.0–39.0)	38.0 (34.5–40.0)	0.332[†]
BMI	21.6 (20.3–24.0)	22.7 (20.3–25.1)	0.532[†]
AMH	1.5 (1.0–2.4)	1.4 (0.8–2.4)	0.358[†]
Indication for treatment			0.352[‡]
Tubal factor	2 (5.3)	5 (12.5)	
Male factor	5 (13.2)	6 (15.0)	
Ovulatory factor	23 (60.5)	27 (67.5)	
Endometriosis	1 (2.6)	0 (0)	
More than one indication	2 (5.3)	1 (2.5)	
Unexplained	5 (13.2)	1 (2.5)	
Baseline hormone			
Day 2 FSH	8.5 (7.3–12.2)	7.8 (6.2–9.1)	0.064[†]
Day 2 E2	33.0 (23.0–42.6)	35.0 (28.5–45.8)	0.289[†]
Hormone at hCG day			
E2	1011.5 (698.0–1686.0)	1029.0 (725.0–1206.0)	0.503[†]
P4	0.6 (0.4–0.9)	0.65 (0.5–0.9)	0.631[†]
Number of extracted oocytes	4 (3.0–5.0)	3.0 (2.5–5.5)	0.267[†]
Number of transferred embryos			0.519[*]
1	16 (42.1)	14 (35.0)	
2	22 (57.9)	26 (65.0)	
Transferred embryos			0.212[‡]
Cleavage stage (days 2–3)	27 (71.1)	23 (57.5)	
Blastocyst (days 5–6)	11 (29.0)	17 (42.5)	
Mid-luteal phase hormone			
E2	1525.5 ± 807.7	1185.7 ± 586.5	**0.036***
P4	98.4 (71.4–152.0)	86.55 (60.6–118.5)	0.301[†]
Pregnancy test day P4	11.1 (7.5–98.2)	14.45 (10.0–74.0)	0.280[†]
Pregnancy rate			0.942[*]
Successful	13 (34.2)	14 (35.0)	
Fail	25 (65.8)	26 (65.0)	
Live birth rate	10 (26.3)	10 (25.0)	0.894[*]
Miscarriages rate	3 (7.9)	4 (10.0)	1.000[‡]

ET, embryo transfer; BMI, body mass index; AMH, Anti-mullerian Hormone; FSH, Follicle stimulating hormone; E2, estradiol; P4, progesterone; hCG, Human chorionic gonadotropin.
*Continuous data was performed by Student's test.
[†]Continuous data was performed by Wilcoxon rank sum test.
[‡]Categorical data was performed by y Fisher's exact test.
[*]Categorical data was performed by Chi–Square Test.
Significant result was shown in bold.

Table 9: The association between Crinone and Progeson in patients receiving frozen ET (N = 63).[90]

Variable	Crinone	Progeson	p-value
Case Number	31	32	
Age	34.0 (33.0–38.0)	37.0 (33.5–38.0)	0.594[†]
BMI	20.8 (18.8–22.2)	21.70 (20.2–23.8)	0.125[†]
AMH	2.3 (1.5–4.2)	3.8 (2.1–4.8)	0.080[†]
Indication for treatment			0.310[‡]
Tubal factor	7 (22.6)	4 (12.5)	
Male factor	10 (32.3)	10 (31.3)	
Ovulatory factor	9 (29.0)	16 (50.0)	
Endometriosis	1 (3.2)	1 (3.1)	
Others	0 (0.0)	0 (0.0)	
Unexplained	4 (12.9)	1 (3.1)	
Baseline hormone			
Day 2 FSH	7.8 (6.6–9.7)	7.0 (6.1–8.7)	0.090[†]
Day 2 E2	31.0 (26.0–38.7)	30.8 (23.6–47.1)	0.804[†]
Hormone at hCG day			
E2	2253.9 (1468.0–2747.0)	2677.5 (1602.5–3250.5)	0.364[†]
P4	0.9 (0.5–1.1)	1.05 (0.7–1.4)	0.071[†]
Number of extracted oocytes	7.0 (5.0–10.0)	8.0 (5.0–11.5)	0.503
Number of transferred embryos			0.291[‡]
1	13 (41.9)	9 (28.1)	
2	17 (54.8)	22 (68.8)	
3	0 (0.0)	1 (3.1)	
4	1 (3.2)	0 (0.0)	
Transferred embryos			1.000[‡]
Cleavage stage (days 2–3)	4 (12.9)	4 (12.5)	
Blastocyst (days 5–6)	27 (87.1)	28 (87.5)	
Mid-luteal phase hormone			
E2	251.0 (174.0–288.0)	246.5 (182.0–284.5)	0.951[†]
P4	24.1 (15.0–33.5)	31.85 (23.8–41.6)	**0.049**[†]
Pregnancy test day P4	15.2 (7.0–22.9)	24.55 (12.1–32.7)	**0.030**[†]
Pregnancy rate			0.932[*]
Successful	21 (67.7)	22 (68.8)	
Fail	10 (32.3)	10 (31.3)	
Live birth rate	17 (54.8)	17 (53.1)	0.892[*]
Miscarriages rate	4 (12.9)	5 (15.6)	1.000[‡]

ET, embryo transfer; BMI, body mass index; AMH, Anti-mullerian Hormone; FSH, Follicle stimulating hormone; E2, estradiol; P4, progesterone; hCG, Human chorionic gonadotropin.
[†]Continuous data was performed by Wilcoxon rank sum test.
[‡]Categorical data was performed by Fisher's exact test.
[*]Categorical data performed by Chi–Square Test.
Significant result was shown in bold.

9. Future Perspectives

Many wearables and smart gadgets with enhanced progesterone delivery have been developed recently using cutting-edge technology that can self-monitor.

The wireless fertility tracking gadgets track hormone levels and aid in ovulation prediction. There is still room for research into the integration of digital technology for progesterone monitoring in order to improve accuracy and efficiency in health monitoring.

One potential application for 3D printing in pharmaceutical and medical device technologies is customised progesterone therapy.

Furthermore, the sensors may be used in conjunction with a microelectromechanical system and electrochemical impedance spectroscopy to detect and measure progesterone.[91]

Future developments in progesterone therapy could also concentrate on creating customised treatments, combining progesterone with other hormones to create combination therapies, and optimising delivery methods or device designs with cutting-edge medical technologies.[8]

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