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TRANSDERMAL DRUG DELIVERY SYSTEM USED IN INFERTILITY DRUG MANAGEMENT: A REVIEW

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ABSTRACT

Infertility is inability to conceive naturally after one year of regular unprotected intercourse. Men and women both are responsible for that equally. Female infertility 50 percent cases are due to lack of conception, stressful condition, inflammation, ovulation disorder and excess radiation. Transdermal drugs represent an attractive substitute to oral medications and are particularlyengaging when compared with hypodermic injection. From ancient times human beings are applying medicinal agents to the skin. Transdermal drug delivery is a self-contained discrete dosage form with increasing patient compliance and avoiding first pass metabolism respectively. Improved patient compliance and effectiveness are the most important aspects of a drug delivery system. For effective transdermal drug delivery system, the drug must be able to penetrate the skin so that drug can easily reach the target site. Different physical and chemical enhancers are used to improve the transdermal permeation rate by increasing drug solubility, diffusion coefficient, and reservoir effect which is not feasible and leads to toxic side effects. It has been found that drugs from herbal origin can be utilized with enhanced efficacy by incorporating in transdermal drug patches. This review focused on to the delivery of various allopathic and herbal via transdermal drug delivery system. It has been found that drugs as of herbal origin can be consumed with enhanced efficacy by incorporating in transdermal delivery and use of traditional physical and chemical enhancer like trandermal patch, nanoparticle, to improve the transdermal permeation for infertility.

Keywords: Infertility; TDDS; Herbal drug; Allophathic drug; Liposome; Nosiome; Transdermal patch; Transdermal Drug Delivery System

INTRODUCTION

Infertility is major disorder now days because of life busy schedule, frustration, demand stress and anxiety. Stress imbalances the symptoms of ovulation cycle, mensuration cycle, food intake and hormonal imbalance. Infertility is a condition that affects approximately 1 out of every 6 couples **[1]**. An infertility diagnosis is given to a couple that has been unsuccessful in efforts to conceive over the course of one full year. When the cause of infertility subsists inside the female partner, it is referred to as female infertility **[2]**.

The WHO (World Health Organization) states that the infertility is a disease of the reproductive system that manifests as a breakdown to achieve a clinical pregnancy after 12 months or more of normal unprotected sexual intercourse.

Types of female infertility

1. **Primary infertility:** It takes place if a woman cannot become pregnant and didn't have previous pregnancies and a reason is an endocrine disease cause 60-80% of primary infertility cases.
2. **Secondary infertility:** It occurs if women have biological kids from previous pregnancies. Alternatively, secondary infertility results from abortion, ectopic pregnancy, miscarriage, etc., and the woman cannot become pregnant again and reason is inflammatory condition.

According to CDC female infertility can be divided into three categories diseases of genital organs cause 80-90% of secondary infertility cases.

1. **Defective ovulation:** Endocrine and ovulation disorder, Polycystic ovarian disease, physical disorder, ovulation disorder, elevated prolactin hormone level, absence of GnRH, Premature ovarian failure.
2. **Defective Transport:** Cervical mucus problems, mechanical obstruction, pelvic inflammatory disease, age, tubal cause, inflammation of fallopian tube, clotting disorder, ovarioum failure, uterine and cervical disorder, abnormalities in cervix shape, fibroid tumour, development defects of the uterus, early menopause, scar tissue after abdominal surgery.
3. **Defective Implantation:** Immuno-logical disorders, abnormalities in cervix shape, fibroid tumour, development defects of the uterus, cervix and the uterus, hostile cervical mucus, incompetent cervix, fibroid tumour, development defects of the uterus, cervix and the uterus, hostile cervical mucus, incompetent cervix, fibroid tumor, development defects of the uterus, DES exposure, autoimmune disorder, congenital anomaly and

fibroids, hyperprolactinaemia, Kall-mann syndrome **[3, 4]**.

TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal Drugs represent an attractive substitute to oral medications and are particularly appealing when compared with hypodermic injection. Human societies have been applying medicinal agents to the skin for many years **[5]**. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect **[7, 8]** while a very major fraction of drug is transported into the systemic blood circulation but it has various limitation these can be develop by various generation. Several advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug, **[6]** estrogen patch available on market it is a transdermal delivery system for estradiol, which can be used as hormone replacement therapy to treat menopause symptoms, hypoestrogenism, and to prevent osteoporosis.

1. **First generation transdermal delivery system:**

It has continued for delivery of small, lipophilic, low-dose drugs but first generation transdermal barrier posed by skin's outermost layer called stratum corneum, which is 10 to 20 μm thick underneath this layer is the viable epidermis, which measures 50 to 100 μm and is avascular. Drug transport across the stratum corneum typically involves diffusion through the intercellular lipids via a path that winds tortuously around corneocytes, where hydrophilic molecules travel through the lipid head group regions and lipophilic molecules travel through the lipid tails. This transport pathway is highly controlled by the structural and solubility necessities for solution and diffusion inside stratum corneum lipid bilayers **[9]**.

2. **Second generation transdermal delivery system:**

It recognizes that skin permeability enhancement is needed to expand the scope of transdermal drugs. The ideal enhancer should increase skin permeability by reversibly disrupting stratum corneum structure, provide an added driving force for transport into the skin and avoid injury to deeper, living tissues. Many successful chemical enhancers interrupt the highly ordered bilayer structures of the intracellular lipids found in stratum corneum by inserting amphiphilic molecules into these bilayers to disorganize molecular packing or by extracting lipids using solvents and surfactants to create lipid packing defects of nanometer dimensions **[10]**.

3. Third generation transdermal delivery system

Third-generation delivery systems aim their outcomes to skin's barrier layer of stratum corneum by means of microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound. Micro needles and thermal ablation are currently progressing through clinical trials for delivery of macromolecules and vaccines, such as insulin, parathyroid hormone and influenza vaccine **[11]**.

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver anexact dose of medication throughout the skin and into the bloodstream. Frequently, this promotes healing to an injured area of the body.Various other transdermal delivery used in infertility drug management system like microneedle, transferosome gel, nanoemulsion, solid lipid nano carrier, solid in oil gold nanoparticle, hydrogel, nanoparticle, microemulsion gel proniosomal gel, phytosome (for herbal drug), liposome, Mucoadhesive gel **[12]**.

VARIOUS ALLOPATHIC AND HERBAL TRANSDERMAL DRUG DELIVERY SYSTEMS

1. Liposomal gel

Liposome gel is of clomiphene citrate for treatment of polycystic ovarian syndrome. Hyperandrogenism, polycystic ovaries, and chronic anovulation along with insulin resistance, hyperinsulinemia, abdominal obesity, hypertension, and dyslipidemia as frequentas no effective single drug is identified for PCOS treatment, the treatment of PCOS is a challenging issueuniversal at present. Due to its composite pathogenesis and unrecognized etiology, there is no efficient preventive measure available for PCOS until now. Intra-Veginal route offers large surface area, rich blood supply, avoidance of first-pass metabolism, high permeability and greater **[13]**.

2. Transdermal gel to controlled ovarian stimulation

Transdermal gel to controlled ovarian stimulation is investigated the effect of transdermal testosterone gel pretreatment on controlled ovarian stimulation and IVF outcome in low responder's transdermal testosterone gel (TTG) before controlled ovarian stimulation (COS) using GnRH antagonist multiple-dose protocol (MDP) in low responders undergoing IVF/ intracytoplasmic sperm injection (ICSI) **[14]**.

3. Transdermal delivery of testosterone

This review focuses on the skin permeation characteristics of testosterone, pharmaco-kinetics following application of transdermal formulations and formulations currently available. At present, gels control the market for transdermal testosterone replacement therapy, A regulatory review

of all testosterone replacement therapies is currently underway which may have implications for future prescribing practices of transdermal testosterone products **[15]**.

4. Letrozole

Letrozole is also used to stimulate ovulation. The oral medication activates the pituitary glands to make additional FSH, to stimulate ovulation and release eggs. It works for women with PCOS, and in normal women to improve the production of eggs. Women with PCOS, particularly those with obesity, letrozole may work superior. Letrozole is also treat postmenopausal women with advanced breast cancer it is belong to Aromatase Inhibitors class of medicines. Aromatase inhibitors are a class of drugs utilized in the treatment of breast cancer in post-menopausal women and swollen breast in men. They may also be used for the prevention of cancer in high-risk women **[16]**.

5. Transdermal Patch:

Drug-in-adhesive (DIA) transdermal patch including letrozole, is a third generation aromatase inhibitor for the cure of breast cancer, using pressure-sensitive-adhesives (PSAs) and to evaluate the percutaneous penetration and pharmacokinetics of letrozole is compared with the oral routeafter transdermal administration. The formulation with DURO-TAK 87-4098, Azone and propylene glycol demonstrated the highest letrozole permeation. The films showed improved ex vivo skin permeation, enhanced bioavailability, and overcame the loading onto PVA-based transdermal films. The films specified enhanced ex vivo skin permeation, enhanced bioavailability, and overcame the limitations of the oral dosage form **[16]**.

6. Nanoliposome

Nanoliposomes were formulated for the treatment of breast cancer. They are preparedby using reverse-phase evaporation technique byvaried ratios of soya lecithin and cholesterol concentration. The effect of different factors was studied on size, polydispersity index, loading capacity and entrapment effectiveness of nanoliposomes. For the drug-excipients compatibility the prepared nanoliposomes were analyzed using DSC and ATR spectroscopy. The desertion of drug peak in DSC specifies the dissolution of the drug in a polymer matrix. It is accomplished that the concentration of soya lecithin and cholesterol were critical parameters that influence the encapsulation of letrozole in the formulation and optimization of nanoliposomes **[17]**.

7. Slurry based Proniosome

Slurry-based Letrozole (LTZ)-loaded proniosomes were prepared by using sucrose or sorbitol as carriers and diverse ratios of cholesterol (CH) and Tween 80 (T80) as lipid composition. Proniosomes

were hydrated and probe-sonicated to produce nano-vesicles. The proniosome powders were described in terms of morphology using scanning electron microscopy, and drug crystallinity using differential scanning calorimetry (DSC) and X-ray diffraction (XRD)., in terms of size, zeta potential, drug entrapment, storage stability, and drug release. The niosomes gave high drug entrapment and controlled biphasic release over one month **[18]**.

8. Pegylated niosome

Letrozole pegylated niosomes was described by dynamic light scattering spectroscopy (195.2nm pegylated niosome and 234.1nmletrozole pegylated niosomes), scanning electron microscopy and its entrapment effectiveness was calculated to be 66.6%. The drug released pattern (in vitro) from the pegylatedniosomes was calculated through zero order, first order, Higuchi and Hixson – Crowell kinetics models. It was found that the release pattern followed first order and Hixson Crowell models **[19]**.

9. Slurry based proniosome

Slurry-based Letrozole (LTZ)-loaded proniosomes were designed using sucrose or sorbitol as carriers and various ratios of cholesterol (CH) and Tween 80 (T80) as lipid composition. The proniosome powders were characterized in terms of morphology using scanning electron microscopy, and drug crystallinity using differential scanning calorimetry (DSC) and X-ray diffraction (XRD). Drug release showed a biphasic pattern, being fast at the first 24 h followed by a very slow release phase for duration of one month, releasing at least 95%. The release profile of niosomes fits best with the Higuchi model **[19]**.

10. PLGA nanoparticle

Letrozole (LTZ) included PLGA nanoparticles were arranged by solvent displacement technique and characterized by transmission electron microscopy, poly-dispersity index and zeta potential measurement. The labeled complex showed good in vitro stability as confirmed by DTPA challenge test. Compared to free LTZ, LTZ-loaded PLGA NPs exhibited significantly lower uptake by the organs of RES. The tumor concentration of LTZ-loaded PLGA NPs was 4.65 times higher than that of free LTZ at 4 h post-injection. This study indicates the capability of PLGA nanopartcles in enhancing the tumor uptake of letrozole **[20]**.

11. Nanoparticle

The reason of this study was to examine the therapeutic efficacy of hyaluronic acid-bound letrozole nanoparticles (HA-Letr-NPs) in restoring sensitivity to letrozole-resistant (LTLT-Ca) cells. To target letrozole to LTLT-Ca cells, hyaluronic acid-bound letrozole nanoparticles were

prepared by nanoprecipitation using biodegradable PLGA-PEG co-polymer. HA-Letr-NPs were restricted to a maximum size of 100 nm. The in vitro drug release assay showed that the highest released concentration of letrozole occurred after 23 hours at 37 degrees C in phosphate-buffered saline. HA-Letr-NPs restored and preserved a prolonged sensitivity and targeted delivery of letrozole in letrozole-resistant tumors in vivo **[21]**.

12. Chitosan nanoparticle

Chitosan nanoparitcle is formulated using chitosan nanoparticles with the crosslinking agent sodium tripoly-phosphate. The prepared particles were described using FTIR, TGA, XRD, SEM, TEM and DLS. From the FTIR results, the formation of LTZ loaded chitosan nanoparticles. TEM images illustrates that the average particle size was in the range of 60–80 nm and 20–40 mm air dried and freeze dried samples respectively. Also the prepared formulation had been evaluated *in-vitro* for determining its hemocomp-atability, biodegradability and serum stability. Chitosan nano-particles formulation has biocom-patibility and hemocompatible properties and it can act as effective pharmaceutical excipients for letrozole **[21]**.

13. Hyaluronic acid/chitosan-coated poly (D, L lactide-co-glycolide) nanoparticle

Hyaluronic acid (HA)/chitosan (Cs)-coated poly (D, L-lactide-co-glycolide) (PLGA) nanoparticles was prepared for the delivery of LTZ to get better therapeutic efficacy, control release and reduce side effects of LTZ.PLGA nanoparticles were prepared, and the in vitro release kinetics and effect of freeze-drying process on the physicochemical characteristics of nanoparticles were also evaluated. Moreover, the in vivo acute toxicities of blank and drug-loaded nanoparticles were assessed **[22]**.

14. Letrozole and Curcumin Loaded-PLGA Nanoparticles

Curcumin (Cur) and Letrozole (Let) encapsulated in PLGA and test their effectiveness in mice induced with the disease. The nanoparticles (NPs) were synthesized using solvent evaporation method and characterization showed the spherical particles to be monodispersed, polymorphic, small in size with high encapsulation effectiveness, without having a tendency for significant aggregation or adhesion. Oxidative stress parameters, angiogenic markers, matrix degrading molecules, estrogen levels and endometriotic lesions, were assessed and compared before and after administration. Let-Cur NPs treatment in vivo, in addition to decreasing these parameters

considerably, was also successful in reducing endometrial glands and micro-vessels density in the peritoneum to a considerable extent, thereby indicating important regression of the disease **[23]**.

15. Biodegradable nanoparticle

Nanoliposomes were organized using reverse-phase evaporation method employing diverse ratios of soya lecithin and cholesterol concentration. The disappearance of drug peak in DSC specifies the dissolution of the drug in a polymer matrix. The ATR spectroscopy outcomesshow there was no interaction between components and drug is stable in the formulated nanoliposomes. It is concluded that the concentration of soya lecithin and cholesterol were critical parameters that influence the encapsulation of letrozole in the formulation and optimization of nanoliposomes **[24]**.

16. Nanoemulsion

LET loaded nanoemulsion (LET-NE) was prepared by aqueous microtitration method using Triacetin, Tween 80 and PEG-400 as the oil phase, surfactant, and co-surfactant. Nanoemulsion was studied for droplet size, polydispersity index (PDI), zeta potential, percentage transmittance, drug content, surface morphology. The study demonstrates the anticonvulsant and neuroprotective effect of LET-NE probably by inhibition of aromatization of testosterone into 17-β estradiol, proconvulsant, and diverting the pathway into the synthesis of testosterone metabolites, 3α-Diol with known anticonvulsant and neuroprotective action. Brain targeting of LET-NE showed better anticonvulsant and neuroprotective action than LET **[25]**.

17. Liposome

A dual-drug-loaded soy lecithin liposomal system was developed by coencapsulation of Letrozole (LET) with Paclitaxel (PTX) to enhance the effectiveness in breast cancer therapy. Liposomes were synthesized by the thin film layer hydration. To adequately evaluate the characteristics of these liposomes, the particle size, zeta potential, morphology, drug encapsulation, in vitro drug release, and cytotoxicity were ascertained.In addition, the in vitro cytotoxicity study on the human breast cancer cell line (MCF-7) given the dual-drug-loaded liposome showed greater inhibition of cell growth than the single drug **[26]**.

18. Transdermal organo gel

Pluronic lecithin organogel is a micro emulsion-based gel that has been efficiently utilized by physicians and pharmacists to transport hydrophilic and lipophilic drugs topically and transdermally diagonally the stratum corneum. It is thermodynamically stable, viscoelastic, and biocompatible gel composed of phospholi pids (lecithin), organic solvent, and polar solvent. PLO enhances the topical administration of drug

mostly due to desired drug partitioning, biphasic drug solubility, and the alteration of skin barrier system by organogel components. Beside this, it shows low skin irritation, increases patient compliance, reduces side effects, avoids first pass metabolism, and increases efficiency of drug. In addition, PLO has been shown in vivo and in vitro to modulate the release and permeation of drugs applied transdermally.The pH of all the formulations was around the skin pH and found to be in the range of 5.81 to 6.65. All the formulations were smooth in feel and free from grittiness which increases the patient compliance **[27]**.

19. Transdermal patch

Metformin hydrochloride is anti- diabetic drug in transdermal patch required less dose. The prepared transdermal patch consists of the ethyl cellulose and HPMC as a polymer, this combination of polymer was found to maintain the sustained release effect of the transdermal. PEG 400 used as plasticizer in the patch it produces good flexibility. It may improve compliance of patient those unable to take drug orally **[28]**.

20. Hydrogel-forming microneedles

Patches (two layers) were assembled from a lyophilised drug reservoir layer, with the MN layer made from aqueous blend of 20% w/w poly (methylvinylether-co-maleic acid) cross linked by esterification with 7.5% w/w poly (ethylene glycol) 10,000 Da. >90% of metformin was recovered from homogeneous drug reservoirs. Drug reservoir dissolution time in PBS (pH 7.4) was <10 min. MN penetrated a validated skin model Parafilm® M consistently. The combined MN and metformin HCl reservoir patch respectively **[29]**.

21. Transferosome

Metformin, a prominently prescribed antihyperglycemic agent has been established to increase life span of both diabetic and nondiabetic individuals.The use of transfersomes in transdermal patch offers the potential The post treatment glucose level of hyperglycemia-induced rabbits applied with metformin transfersome patch (p=0.002) showed significant decrease in glucose level relative to untreated alloxan-induced hyperglycemic rabbits **[29]**.

22. Vitex Nirgundo Nanoparticle

Zinc oxide nanoparticles are widely used as an important kind of biomaterials. The biocompatibility of nanoparticles is important for specific biomedical applications. In this present investigation, using *Vitex negundo* L. extract and characterized by XRD, UV-DRS and DLS analysis. The UV–visible absorption and fluorescence spectroscopic studies were performed to investigate the binding interaction between HSA and ZnO NPs. The Stern–Volmer constants (*KSV*),

quenching rate constants (*kq*), number of binding sites and binding constants were calculated from relevant fluorescence quenching data. Moreover, circular dichroism (CD) spectroscopy used to study the conformational changes of protein in the presence of ZnO NPs [**30]**.

CONCLUSION

Infertility is a common problem affecting one couple in six. It is incapacity to fulfill pregnancy after reasonable time of sexual intercourse with no contraceptive measures taken. The evidence for changes in the prevalence of infertility is difficult to establish. In in-vitro fertilization doctors try to completely control the women's menstrual cycle in order to produce more mature oocytes. A number of different drugs are used in the treatment cycles. Because each woman is unique, the drugs may vary even from cycle to cycle. The most common drugs used as fertility drug can treat many issues, increasing the chances of conceiving and carrying. various drug to improving the function of pituitary gland, regulate the hormone of FSH and LH therefore stimulating of the ovary and preventing premature ovulation and also improving the ovarian stimulation , insulin sensitization, control the level of prolactina better drug bioavailability and patient compliance and less dosing frequency achieved by transdermal drug delivery system including permeation of drug can be influence by various nano technology like nanosuspension nano emulsion, transdermal patch. Nano gel, technologies used to develop the transdermal patch. This all are desirable advantageous improving drug bio-availability, reducing dosing frequency, prevent the risk of side effect and providing painless and easy administration thus leading to improved patient compliance. More dedicated work in developing transdermal system for infertility drug.

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