Original Article

Nano-progesterone: An improvised therapeutic approach

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Abstract

Progesterone (PG) is a natural steroid secreted during the luteal phase by the corpus luteum. It is highly required for the release of oocytes, embryo implantation and retaining and maintaining pregnancy. However, due to hydrophobic nature, its biological half-life is extremely less due to which oral delivery of PG is near to impossible. To improve its efficiency and overcome such pitfalls researchers are developing novel drug delivery system (NDDS) for sustained delivery of PG. This review highlights the major hurdles of PG administration via oral route and the application of NDDS for the delivery of progesterone.

Keywords: Progesterone, nano-progesterone, drug delivery system, hormone replacement therapy; drug delivery.

1. INTRODUCTION

Oral progesterone (PG), available as synthetic and natural PG, is used to treat various acute or chronic gynaecological conditions including menorrhagia, amenorrhea, contraception, luteal support and to pregnant woman for maintenance of pregnancy [1,2] The use of synthetic PGs for luteal support and in pregnant woman is limited owing to their inherent androgenic activity [3]. The synthetic PGs results in reduced estrogenic benefits [4], adverse effects on the lipoprotein metabolism [5] and cardiovascular system [6] and teratogenicity [7]. Conversely, natural PG, devoid of androgenic activity, has no effect on lipoprotein metabolism or cardiovascular system or induce teratogenicity [7]. In addition, several reports suggest that natural PG has a favourable effect on blood vessels [8]. The major problem with natural PG is its poor oral bioavailability due to its unfavourable physico-chemical properties [9]. It is classified as Class II drug by Biopharmaceutical Classification System (BCS) with high lipophilicity (Log P = 3.9) and very low aqueous solubility (10 mg/mL) [10]. Further, it also undergoes hepatic metabolism when given by oral route [11]. A higher dose of PG shows extensive side effects such as dizziness or somnolence. Recently, lipidic delivery systems [12], microemulsions [13], self-emulsifying delivery systems [15] and surfactants [16] have been used to enhance the solubility of PG. Although, these technologies demonstrated improved solubility of PG but there are few major concerns: (a) reduced stability of PG in lipids and of lipids themselves and (b) final product is oral softgel, which is second choice compared to tablets and (c) reduced likelihood of sustained release of PG [14,15] Presently, sustained release (SR) PG formulations are preferred due to reduce hepatic metabolism and improved patient compliance [16].

Nanotechnology has paved the path, circumventing the major hiccups in progesterone delivery. It has been long deemed the answer to conquer major issues due to its potential in analysing reams of issues, uncover potential benefits and predict effect [17–26]. The nanostructures could entrap or conjugate with the hydrophobic or hydrophilic therapeutic entities. This improves the solubility and bioavailability of the preparations. Controlled release, site specific drug delivery, ligand attachment, amelioration of drug resistance and most importantly enhanced survival and therapeutic window could be achieved upon utilization of novel drug delivery system [27–31]. We believe that novel algorithm with drugs can be translated into improved human health. Thus, the review emphasized the effective role of PG, their drawbacks and application in of novel drug delivery system in the delivery of progesterone.

2. PROBLEMS ASSOCIATED WITH ORAL PROGESTERONE

Progesterone has been included as a registered drug which is produced by ovaries, qualifies as bioidentical which is different from those considered as custom formulated bioidentical hormones [32].
Progesterone is represented as a critical tool in modern day of practice, especially in the area of reproductive medicine. Progesterone isn't a new molecule, nonetheless, considered in the stage of progression. Its pharmacological profile helps in better understanding of pharmacodynamic and pharmacokinetic parameters, while scientific evidences ascertain its implications in establishment of pregnancy, its maintenance and labor induction. Other positive effects have also been encountered with the use of progesterone such as cardiovascular protection, menopausal hormonal therapy, endometrial protection and venous thromboembolism. Progesterone modifies the level of thyroid stimulating hormone (TSH), gonadotropic hormone (GH), secretion of melatonin along with prevention of sleep disturbance [33]. Progesterone is synthesized via most cells of corpus luteum generally in two steps; a). conversion of cholesterol into pregnenolone in mitochondria, and (b). formation of progesterone from pregnenolone. PG is also produced placenta, adrenals and brain.
PG metabolises in liver by the effect of enzymes known as 3α-hydroxysteroid oxidoreductase and 5α-reductase, generally present in brain and corpus luteum. During stress, allopregnanolone (neurosteroid developed from progesterone) are synthesized by adrenal gland while some lesser extent is observed in brain [34,35]. At the time of pregnancy or during luteal phase, a significant amount of allopregnanolone is observed in brain due to excess amount of PG [36,37]. While current benefits highlight the promising role of PG, its pharmacokinetic constrains highlight a need for efficient delivery. PG possess low bioavailability and elevated clearance due to first pass metabolism. The absorption of PG is highly influenced by excipients, food intake and drug crystal diameter [38]. Significant progress in drug development influenced the development of PG derivatives which is however related to several undesirable effects such as fetal malformations and reduced level of high-density lipoprotein. Multiple synthetic progesterone has been developed including and C-19 nortestosterone derivatives (norgestrel) and C-17 progesterone derivatives (medroxyprogesterone acetate – MPA). Unfortunately, they were incapable in finely constellating the biological properties of parent compound.

3. THE PANORAMA OF NOVEL PROGESTERONE

The drug delivery system has paved its path and shifted its paradigm towards novel drug delivery system. Encapsulation of PG into a carrier could modify its pharmacokinetic profile accelerating its therapeutic efficacy. A micronized structure of PG delivered in a soft gelatin capsule resulted in increased t1/2, reaching maximum concentration within 4 hours [39]. To avoid the hepatic first pass metabolism encountered at the time of oral delivery, intravaginal and sublingual route are also available so to achieve the higher concentration. The delivery of PG via skin also presents to cure the deficiency associated with perimenopause and menopause, diffuse fibrocystic mastopathy or mastodynia [40]. Dramatic results from the area of nanotechnology in association with drug development and delivery demonstrated great advancements. Lipid based nanocarriers has plethora of advantages over conventional preparations such as reduced toxicity by virtue of biocompatible lipids, controlled release, ability of solubilizing hydrophobic compounds and high range of routes of administration [41,42]. Lipid nanoparticles could be produced by ultra-homogenization (UH) and high-pressure homogenization (HPH) technique. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are among the lipid nanoparticles that have been extensively studied [43,44]. Esposito et al., developed PG loaded SLN and NLCs using both UH and HPH technique, while also comparing their respective effect on the morphology and characteristics of nanoparticles [12]. Hot homogenization is based on dispersion of liquid melted lipid on hot surfactant under constant stirring by a high-shearing device. The emulsion obtained were then subjected to homogenization under warm condition and the cooling to get nanoparticles developed by recrystallization of lipids. The technique of homogenization can be obtained either through UH or HPH. The mechanism of UH is based on generation of high-power ultrasound wave by a probe in a liquid media which in turn generate vacuum bubbles. Such vacuum bubbles implode causing high rate of shear forces. The major disadvantage of such system is lipid agglomeration that develops after cooling; however, its cost of instrumentation is low which accounts for its feasibility.
On the other hand, HPH under extreme pressure reduces the droplet size by the effect of piston gap homogenizer. Initially, the course emulsion under extreme pressure (up to 150 MPa) is forced through special homogenization valve at a temperature above the melting point of lipid, forming a thin emulsion. To obtain the agglomerate free lipids, several cycles in a pressure range of 50-150 MPa are required to be performed. Its noteworthy to mention that HPH at lab and pilot scale are highly costly and produce limited number of samples. However, it delivers same results at lab, pilot or scale-up level [45]. In the study, HPH method showed better performance in terms of scalability showing 20-fold increased volume of production as compared to UH.

Importantly, the developed SLN and NLCs were smaller and had uniform size than those developed by UH technique with no signs of agglomeration. The uptake of PG from PG-SLN were greater than PG-NLC, which could be due to better PG accommodation and higher affinity in the liquid phase of NLC. Thus, with respect to SLN, NLC performed better in retaining the PG. The in-vivo study, in contrast, showed higher penetration of SLN than NLC which might be due to the occlusive property of the solid nanopreparation. Some portion of nanoparticle may be retained on the surface of skin, while some fraction penetrated to the lipid layer of stratum corneum. In conclusion, both SLN and NLC showed better results when developed by HPH technique demonstrating higher encapsulation, sustained release and higher penetration. Thus, lipid-based nanoparticle could extend the delivery of PG [12].

Scientists in the field of drug development are running from pillar to post to overcome the hurdles in the delivery of poor soluble and low bioavailable compounds including progesterone. Progesterone helps in synchronizing the oestrus and relatively control the chance of abortion. Just to maintain an efficient concentration of PG, multiple runs have to be carried out which sometimes become pathetic for patients especially with irritant gastrointestinal tract. This became a motivation to Yuan et al., who tend incorporate PG in NLCs using oleic acid as liquid lipid while stearic acid and monostearin as solid lipid. Melt-emulsification technique was used to develop PG loaded NLC, advantageously due to the non-residue of organic solvent, no dispersions with high lipid concentration and no initial burst release. It was observed that the release of drug was increase with an increase of drug loading. Thus, NLC with 11.57% loaded drug had the highest rate of release. With an increase in charged amounts of drug, the drug distribution at NLC surface might increase. An addition of polyethylene glycol (PEG) shielded the NLCs by forming a hydrophilic layer. Hydrophilic PEG solubilized the surface with water fastening the release and achieve a higher over-all drug release [46].

Elmowafy et al. also developed progesterone loaded NLC using fatty alcohol. Rationale behind the development of NLC was controlled drug release, easiness of manufacture, stability and lipid biocompatibility. Since NLC consists of liquid lipid and solid lipid causing an imperfection. This in turn will created pockets to entrap the drug and prevent in leakage during storage. Ten different developed NLC had surface charge ranging in between -22.1±1.47 to -28.1±3.4 mV, in which the concentration of fatty alcohols (cetostearyl alcohol and cetyl alcohol) was varied. Such a range is essentially required to promote their stability through electrostatic repulsion and hence would prevent agglomeration. The entrapment efficiency (EE) was between 93.7±2.7 and 97.2±1.5%. Such satisfying results was due to considerable solubility of PG in sesame oil, which reduced the crystallinity of drug and aided in high PG entrapment. However, the effect of fatty alcohol on EE was negligible. The in-vitro release study was performed using dialysis bag method. Two different kinds of NLC (NLC1 and NLC2) were taken, placed in dialysis bag and then subjected for in-vitro release analysis by initially keeping in simulating gastric media and then to pH simulating the intestinal environment. Following the burst release, both the NLC showed protecting ability in gastric fluid required for oral delivery. A controlled release pattern was observed in the intestinal pH. At initial stage, stearic acid remained un-ionized retaining its hydrophobicity, while at second stage (higher pH), ionization increased causing a release of PG. The release of PG was also fatty alcohol type and concentration dependent. Cetyl alcohol revealed a lowest degree of drug retardation while cetostearyl alcohol had highest degree of retardation, which is due to longer aliphatic chain that restricted its wetting showing an improved hydrophobicity. Shorter chain of aliphatic groups is more hydrophilic that failed to capture the PG. The controlled release pattern of fatty alcohols is due to participating stabilized structures of lipidic particles. The ex-vivo permeation study through gut confirmed penetration of NLC (67.3±8.4% @ 8 hours) through the gut wall as compared to PG suspension (34.8±6.2% @ 8 hours). This is due to nanometric size of lipidic system that enhanced its uptake. Overall, cetyl alcohol showed better results in terms of release, uptake, stability and efficient duodenal permeation. Thus, NLCs are promising tool for the oral delivery of PG [47].

Delivery of drug through the oral route is highly preferred due to non-invasiveness, stability and high patient demand. The major hiccup of hydrophobic agents are low bioavailability and faster clearance. Self-nanoemulsifying drug delivery systems (SNEDDS) are lipid-based preparation that have drawn considerable attention and eventually commercial success in the oral delivery of hydrophobic drugs [48]. Semisolid SNEDDS are found to be more advantageous in contrast to the liquid ones. Owing to higher viscosity, they could afford higher stability that could protect the poorly soluble drugs from precipitation [49]. The log value of progesterone is 3.87 which are generally present in 2 polymeric forms: one is alpha and other is beta. This drug extensively undergoes hepatic first pass metabolism. This is the reason that despite being a wonderful candidate for gynaecological ailments, it failed to achieve a wide therapeutic window. Thus, Hassan and team, worked on development of semisolid SNEDDS incorporating PG. The team especially focussed on in vitro pancreatin digestion assay under both fed and fasted state. The PG loaded SNEDDS (PG-SNEDDS) were characterized by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) while their physical state was assessed using Powder X-ray diffraction (PXRD). It was reported that more than 80–90% of PG remained in the solubilized state ever after 4h of digestion which is due to the semisolid SNEDDS. SNEDDS elevated the equilibrium solubility of PG at different media even in very low concentration (1% m/V). It was also observed that PG remained in the solubilized form in lipids without getting crystallized. Thus, PEG-30-di-(polyhydroxystearate) (Cithrol DPHS) containing SNEDDS are essential for developing bio robust therapeutic systems [50].

Apart from oral delivery, scientists had also focussed upon other routes of delivery as well. PG possess overwhelming features including release of mature oocytes, embryo implantation as well as development and maintenance of pregnancy. PG is also responsible for mediating sexual signals in brain and milk secretion in mammary gland. Thus, PG could be an excellent candidate in overcoming fertility issues as well as in hormone replacement therapy. PG delivery through vaginal route could thus be preferred to avoid the extensive hepatic metabolism. Several dosage forms are available for vagina-based delivery including vaginal

capsules, tablets, semisolid preparations such as ointment, emulsions, creams and others like pessaries. Among these, pessaries are highly advantageous due to oval shape which will help in administration while having uniform dose and low leakage of drug. To add extra-ordinary benefits, delivery of novel compounds in form of pessaries could be highly efficient as they are mucoadhesive which will in turn intensify the drug residence time in the vagina. On this note, Correia et al., developed PG-NLC loaded pessaries for prolonged release. The ultrasonic technique was used to prepare the NLC first. PG was initially added to the liquid and solid lipids followed by heating at temperature above the melting point of the solid lipid. Simultaneously, at the temperature, the aqueous phase comprising of waer and emulsifier was heated, added to the lipidic solution and homogenized for 5 minutes using Ultra-Turrax® T25. The developed emulsion was then subjected to ultrasound energy utilising sonicator for 15 minutes. It was observed that 10% of NLC s had a size of more than 90% of NLC had size less than or equal to 21.82 ± 0.00 nm, 50% had size less than or equal to 74.60 ± 0.00 nm while more than 90% had size of 315.60 ± 0.01 nm, respectively. The %EE of PG in the developed nanosystem was 96.42 ± 0.00%, indicating the feasibility of lipid-based nanosystem in the incorporation of drug. The biocompatibility assay was performed for PG-NLC and placebo NLC (PCB-NLC) by seeding the human immortalized keratinocytes (HaCaT) cells in 96 well plate for a duration of 24 hours. Herein, Triton-X was used as positive control. The cytotoxic effects of both preparations were evaluated after exposing them for 24 hours based on resazurin (REZ) reduction, neutral red (NR) uptake and sulforhodamine B binding. It was observed that nor PCB-NLC neither PG-NLC showed significant NR uptake. In fact, the uptake declined significantly in a concentration dependent manner. The REZ reduction assay is also similar to NR uptake assay. After exposure to PG-NLC, a reduction of REZ was observed showing 81.5%, 68.9%, 63.7% and 59.5%, 63.7%, 68.9% and 81.5% after exposure to 100, 75, 50 and 25 µg/mL, respectively. Additionally, no significant binding was illustrated by SRB binding assay for concentrations equal to and more than 25 µg/mL. A highly confident data was observed by the three mentioned cytotoxic assay indicating the biocompatibility of the developed systems. The in-vitro release study showed a sustained release behaviour (Figure 1). The author also mentioned the importance of ex vivo and in vivo studies to confirm the efficiency before entering the market [51].

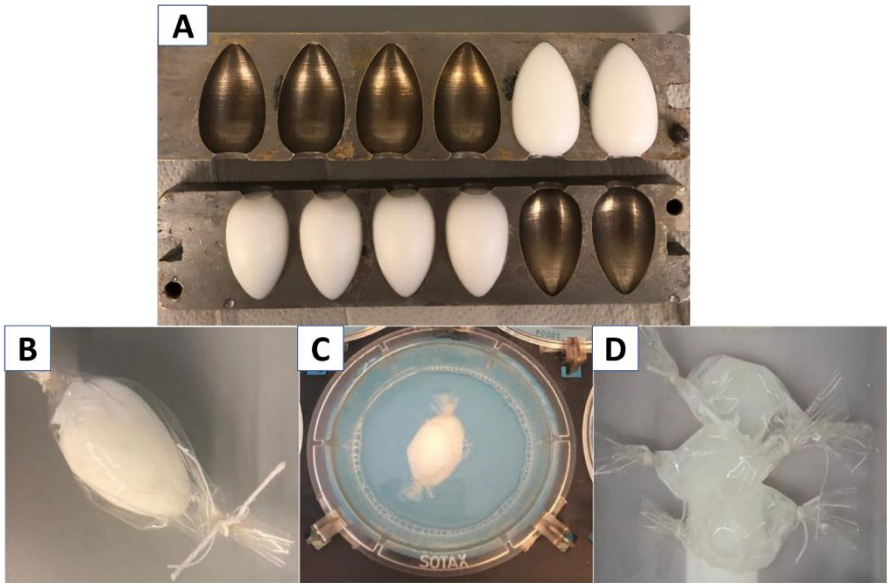

Figure 1: Representation of PG-NLC loaded pessaries (A); illustration of in vitro release study of PG-NLC loaded pessaries before (B), at 1h (C) and 24h (D). Adapted from Ref. [51].

The drug development system has encountered numerous technologies endorsing several benefits one over other. To mark the strong scientific interest, polymeric nanoparticles have been endorsed for targeted drug delivery and modifiable drug release properties [52,53]. Wide polymeric chemistry variety and structural enhancement as well as modifications has enabled resilient interaction within the physiological system, nanometric size could enhance passive uptake and enormous surface area enable faster diffusion [54]. Taking such advantages, such polymeric nanosystems could infilterate deep into the tissues. Polycaprolactone (PCL) is an aliphatic polyester available in semi-crystalline form, that has shown promising results in the field of biomedicine [55]. Depending on the molecular weight, PCL shows plastic behaviour owing to the low glass transition temperature ranging between -10°C and -60°C. The emulsification of amalgamated polymers could be great strategy to develop nanoparticles, however, at the time of drying, their size and related properties alter. scCO2 antisolvent expansion technology (SAS) could be a better approach while dealing with the nanopreparations. Thus, Guilherme and team fabricated PG loaded PCL nanoparticles SAS technology. It was observed that in comparison to the conventional drying technique, nanoparticles dried using SAS technique were small having a size of 82nm. Image obtained from atomic force microscopy confirmed that nanoparticles after drying from SAS technique had uniform distribution of size and regular shape (Figure 2). Thus, it is important to understand the effect of drying mechanism for drying of nanoparticles [56].

Infertility is the major issue encountered in 15% of couples in the reproductive age group. Thanks to the in vitro fertilization (IVF) technique that aided in overcoming infertility. Nearly one million of couples takes the advantages of IVF worldwide. PG is highly administered in IVF cycles for luteal phase support (LPS). Women undergoing IVF are prescribed luteal supplements through three different routes; vaginal, oral and intramuscular (IM). Oral route shows least efficiency after PG administration while interference in coitus is reported after administration through vaginal route. IM route in comparison to vaginal delivery is considered better however, moderate pain, erythema and inflammatory reactions are common side effects.

Poly (lactic-co-glycolic acid) (PLGA) is a biocompatible polymer approved by European Medicine Agency (EMA) and United States Food and Drug Administration (US FDA) due to its toxicological safety, biodegradability and biocompatibility. PLGA nanoparticles are efficient for loading hydrophobic drugs, improving their pharmacokinetics and pharmacodynamic profile and low side effects following IM administration [57–59].

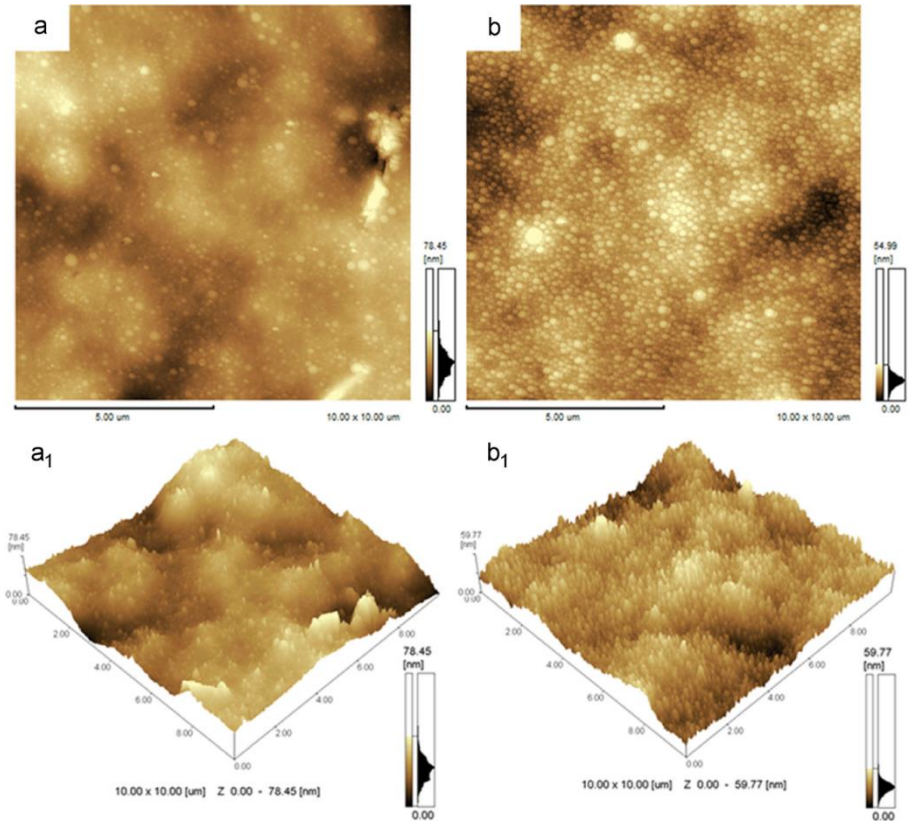

Figure 2: Representation of AFM images of PCL nanoparticles after drying via conventional technique (a and a1) and cCO2 antisolvent expansion process (b and b1). Adapted from Ref. [56].

The major hurdles cannot be neglected while dealing with the nanoparticles. Following IM administration, chronic inflammation is reported due to enriched neovascularization and infiltration of macrophages. Neovessels may enhance the lymphatic or systemic absorptive pathway while infiltrating macrophages could elevate surface dissolution. Moreover, rapid burst release is always encountered due to deposition of drug on surface and an uneven drug distribution. The nanoparticles are majorly up taken by mononuclear phagocyte system (MPS) rendering a minute quantity to reach the plasma. A combined particle-hydrogel could ameliorate such drawback. Hydrogel could obstruct premature release and penetration of active compounds. However, sufficient drug loading is inconvenient for a hydrogel-based depot to attain the therapeutic level.

Concerning such points, Cao et al., developed sucrose acetate isobutyrate (SAIB)-PLGA based depot for the sustained delivery of progesterone. SAIB, a highly viscous liquid or semi-solid at room temperature, is basically a derivative of sucrose. The advantages of SAIB over other polymeric hydrogen in situ system are robust structure and morphology, no acidic metabolites and elevated hydrophobicity. Thus, IVF using PG loaded SAIB-PLGA nanoparticles could be advantageous. The obtained formulation obstructed the burst release as SAIB acted as a physical barrier. The cumulative release of PG from in situ nano-depot system after 1 day was only 19.63% as compared with that of plain PG NPs (52.16%). The in vivo results declared that the PG and SAIB based composite depot system had a long-term release with a potency to reduce dose, which is essential for assisted reproduction treatment for several months. As compared to the plain PG oil, the nano-in-situ depot system using PLGA and SAIB demonstrated higher concentration in blood and adequate AUC. Thus, such a depot system is ideal for sustained release of progesterone [60].

4. CONCLUSION

In the current article, we have highlighted the major problems associated with the oral delivery of progesterone. Despite being an important candidate for major hormone related deficiencies and hormone replacement therapy, the clinical market of oral PG is highly limited. The reason is poor aqueous solubility and low bioavailability. To improve the pharmacokinetic and pharmacodynamic profile, researchers are focussing of nanomaterials to improve the delivery of PG. NLCs, PLGA nanoparticle, PCL nanoparticles along with micro-sized particles have been developed that protected its rapid release. Such system protected PG from acidic environment and maintained its release at the intestinal pH. Still, extensive in vivo and ex vivo are required before reaching the clinical market. Noteworthily, delivery of progesterone using nanoparticles is highly appreciated.

5. REFERENCES

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