Review Article

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Progress in erectile dysfunction therapy through drug delivery system

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ABSTRACT

A man's aptitude to acquire and continue an erection is frequently equated with masculinity and virility and can greatly influence men's confidence. The sexual healthiness is a significant determinant of the worth of life. Erectile dysfunction (ED) as the inability to have or sustain a penile erection long enough to have momentous sexual intercourse with a partner. As per the literature, it is revealed that the millions of men populations are suffering from ED and there is an extreme need to overcome the ED. The various natural traditional herbs, synthetic pioneered chemical entities/potentials are preferred to treat ED. The present review discusses ED therapy including drug selection, application site, and choice of formulation. Moreover, this review updates the various pharmaceutical formulation such as liposomes, ethosomes, transfersomes, nanoemulsion, self-nano-emulsifying drug delivery system, solid dispersion, penetrosomes, solid lipid nanoparticles, and nanostructured lipid carriers development in ED therapy through the oral route, topical and nasal route, etc., which are helpful for researchers to develop new nanocarriers based formulations.

Keywords: Erectile dysfunction, formulation development, nasal route, oral formulation, transdermal route

INTRODUCTION

The millions of men's population affected not only by erectile dysfunction (ED) but also premature ejaculation (PE).[1,2] ED is an inability to maintain/initiate an adequate erection throughout satisfying sexual intercourse.[2-6] The sufficient erected penis has been a representation of a man's virility and sexual ability. Although it is not a lethal situation, the attention surrounding ED and its remedies have been invariable throughout the ages.[7] ED is a general disorder that increases with age and majorly observed in men aged 50 and older than.[8] A literature survey evinced that 75% of people aged over 70 years are the sufferer of ED in the United States,[9] while one more study claimed that the 40% man population over 60 years of age are probable to have ED.[10] In addition to this, 30 millions of the men population has been added to the ED each year, of which, only 2 lakhs men pursue treatment from a physician. Moreover, a large number of the population remains unrecognized as people do not discuss the sexual dysfunction issue with their doctors.[11] Furthermore, it is a depending on majorly observed more common chronic disordered such as cardiovascular, neurological, and diabetes in older age men's.[12] It may be the partial reason for prevalence in older males. In addition, it is more common in the obese age group and more specifically in the existence of hypertension, diabetes, dyslipidemia, etc.[13,14] Hence, the prevalence and incidence of ED problems are highly correlated with the known risk factors, aging factors, and comorbidities. Moreover, lifestyle-based individual factors such as obesity, tobacco chewing, and frequency of exercise have all been associated with ED.[15] Nowadays, predominantly ED is a rising issue in under 40 age men's.[16] A literature survey resolved that near about 20–25% of cases of ED observed in the same age group.[17] ED influences unsatisfactory sexual life and severely impaired the quality of life of men and their sex partners also.[18,19] Moreover, it is a major route cause of depression, anxiety etc.[20]

Hence, there is a huge demand from the suffered population to investigators for the treatment of ED. The

currently engaged treatment showed a positive effect on sexual life. Consequently, this engaged treatment showed satisfaction in male and their sex partners.[21] The ED and PE may be caused due to the low levels of testosterone hormone. However, replacement therapy can potentially overcome the limits. However, this is not helpful in the case of ED and normal levels of hormones. For the treatment of such cases, the selective serotonin reuptake inhibitors have been majorly utilized.[1,22] Nowadays, phosphodiesterase 5 inhibitors (PDE5-Is) are mainly used as first-line therapy for ED treatment.[10] The medicaments belong to PDE5-Is show a 70% positive effect on the ED patients.[10,21] As per the data, the therapy failure rate is between 11 and 44% and it may depend on the population used for the study.[23] In addition, the PDE5-Is have to be taken among 30 min and 2 h sooner than sexual intercourse, leading to a be deficient in of spontaneity.[24] Besides, it divulged that there is an increase in the number of severe adverse effects such as back pain, facial flushing, and headache.[10,25] Furthermore, the use of such PDE5-Is inhibitors showed the contraindication with nitrates in the patients. Furthermore, the PDE5-Is showed potential interaction with alcohol and foods.[3,10] Based on such limiting steps, the faithfulness PDE5-Is in ED treatment has been decreasing potentially. Moreover, because of a lack of efficacy, cost, loss of spontaneity during sexual intercourse, adverse effects, and around 50% of patients discontinue the ED treatment in the past 1–2 years.[26,27]

An alternative to first-line ED treatment local treatments such as vacuum erection devices, intracavernosal injection, intraurethral alprostadil selected as a second-line treatment with a combination of first-line therapies.[10,28] However, such types of alternatives are having a list of adverse events such as hematoma and petechiae pain with suppositories and injections (in the use of vacuum devices).[3,10] Nowadays, there are huge demands to meet a strong need for ED therapies to local effective therapy. Thus, there is a remarkable need for simple, easy to admit, well-tolerated, low risk of adverse effect, fast-acting, and spontaneity enhancement treatment to treat ED.

Drug Selection and Formulation Development

In the recent era, a major key area for researchers in formulation development of ED is immediate delivery of active compounds (example: Vasoactive) to the corpus cavernosum and consequently accomplish and sustains the penile erection for a long time and less systemic contact. Concerning this, nitric oxide provides a key role in the development of an erection. Thus, based on nitric oxide donors, ED treatment is the most effective approach. At the conclusion, it is the urge to select the most appropriate active candidate and most important to develop its topical formulation to the penile application. The appropriate ratio of skin penetration and drug potency may be utilized to choose the drug candidates. In that, the various parameters should affect the outcomes of the formulation. It includes drug potency, skin penetration, and local adverse effects.[10]

An Assortment of Application Site for Formulation in ED

To overcome, the limitation of engaging therapy investigators focused on the various types of techniques to treat the ED. The surface layer of the glans penis based on a thin squamous mucosal epithelium which is more similar to the inner lips. These days the topical application to the glans penis as well as the penile shaft, intra-urethral drug administration has been believed as a non-invasive therapy for ED management.[29] The dorsal nerve branches of the penis extend ventrolateral through the glans of the penis, such that it is filled with nerve endings supporting its function as a sensory structure.[10,30] The nitric oxide is synthesized by neuronal nitric oxide synthase and endothelial nitric oxide synthase within the corpora cavernosa. Therefore, the topical application of a semisolid dosage form onto the glans part of the penis should lead to immediate signaling and consequently release of nitric oxide into the corpus cavernosum. It is a potentially challenging step for nitric oxide donor formulation to deliver an exogenous nitric oxide into the corpus cavernosum within this period frame. However, it is an advantageous step for penile erectile function.[10]

Factors Affecting the Choice of Drug Formulation in ED

To overcome, the problem associated with drug formulation used in ED treatment there is a need to understand the basics behind the formulation development rationale in ED. The drug journey from the glans of the penis surface to the body of the glans penis follows the diffusional process, explained by Fick's law of diffusion. The rate of drug diffusion is depending on the independent formulation variables. The first factor includes a formulation thermodynamic activity of active in the residual, non-volatile phase after application. The second factor includes the presence of a partition coefficient enhancer to enhance the drug solubility in the penile part of the skin. The third factor covers the presence of a diffusion coefficient enhancer to enhance the drug diffusivity in the skin of the penis.[10] For effective treatment, the spontaneity and speed of action are vital considerations in ED therapies. However, permeation enhancers more particularly diffusion coefficient enhancers[31] necessitate a noteworthy time frame to begin their result within the diffusional barrier.[10] The thermodynamic activity of the drug in solution-based formulation shows the rapid loss of the volatile solvent and finally forms the thin film layer on the penis skin and results in saturation or supersaturation of drug solution. Consequently, this transdermal drug delivery will lead to the enhanced activity of the active ingredient to the targeted site.

Treatment Strategy and Novel Perspective in ED

ED treatment strategies include especially pharmacological and non-pharmacological process. The non-pharmacological treatment includes lifestyle changes, counseling from the practitioner, and medication changes.[32]

Herbs used in the treatment of ED

In the modern era of medication of ED, the oral formulation of famous sildenafil (viagra) is most effective, but in some men's population, it is not suitable. Moreover, sildenafil works <70% of men's population along with various crises and certain severe side effects. Yet, the availability of sildenafil formulation

(Viagra) has brought millions of population to ED treatment. The use of testosterone can reduce the chances of ED in some men population with low levels of natural testosterone hormones, but it is often an unproductive effect and may cause liver problems. Yohimbine, papaverine hydrochloride, phentolamine, and alprostadil are clinically used to widen blood vessels. Hence, this modern era of medication for ED treatment is having huge drawbacks and very expensive for the rural population of the country.[33] As per the traditional medical knowledge, there are numerous medicinal plants [Table 1] that have been relied on for utilization in the ED treatment.[11] Moreover, the ethnobotanical indigenous knowledge source was not documented and scientifically authenticated for the efficacy as well as the safety of drugs and its future drug discovery and development. In the past few decades, the researcher focused on the development of herbal drug delivery for its safety and efficacy in ED therapy.[33]

PHARMACEUTICAL DOSAGE FORM DEVELOPMENTS FOR ED TREATMENT

From its inception, the pharmaceutical dosage form widely accepted to overcome health-related problems. Beginning last decades, advance in the drug delivery system is majorly focused on overcoming the issue of ED. The various alternative routes were preferred for ED treatment such as oral, nasal, and topical route and the formulation includes topical cream, gel, tablet, and spray.

Drug Delivery through Skin

Abundant literature appealed that the transdermal patches are an excellent alternative to oral drug delivery. The transdermal patches provide several benefits over conventional method, namely, it is a safe, painless method, easy to use and bypasses the liver which overcomes the problem of the first-pass metabolism of drugs. In addition to that, some potent drugs show an acceptable therapeutic level through adequate skin penetration only.[48] However, a list of active pharmaceutical ingredients showed poor aqueous solubility and it affects bioavailability. Thus, there is a huge demand to form the market which will conquer such limitations. In the past few decades, the researchers focused on self-nano-emulsion drug delivery systems to enhance the solubility of the active. The diabetes male patient case, a major task is oxidative damage and it is a very common health problem in ED patients. Herein, Fahmy *et al.* have developed the alpha-lipoic acid (ALA)-based tadalafil transdermal patch using a self-emulsion drug delivery system (SEDDS). In brief, the ALA can guard the endothelial cell against oxidative damage in a diabetic patient. This patch enhances the skin permeability of tadalafil and reduces/protect the epithelial cells lined penile vessels from oxidative stress in hyperglycemic condition. The formulation was developed by different ratio of the oil phase (anise oil), surfactant (tween 80), and cosurfactant (PEG 200) using the ternary phase diagram. The anise oil and tween 80 demonstrated the highest solubility of actives. The developed formulation is of anise oil, tween 80 and PEG 200 (1:4:5) show 134 nm globule size. After 10 h, the release of the drug of the optimized batch was enhanced by 2.83 fold as compared with raw tadalafil. Moreover, the penetration efficacy of the formulation was confirmed using fluorescence microscopic images. The cell viability study of endothelial cells (EA hy 926) reported that the ALA improves the cell survival rate of about 1.3 fold. Hence, it concludes that ALA with tadalafil loaded SEDDS is a new strategy for the treatment of ED in diabetic male patients.[49] Unfortunately, the stratum corneum is a skin barrier that diminishes the advantages of transdermal drug delivery. Hence, the limited permeability of the stratum corneum toward drugs represents the main problem encounter the transdermal drug delivery. Mehanna *et al.* reported that the penetration enhancer-containing tadalafil loaded nanoliposomes (penetrosomes) were formulated by the hydration-sonication method. The prepared drug-loaded penetrosomes were spherical, unilamellar-closed structure, and nanometric narrow size range.[50]

Sildenafil is a novel drug used for ED treatment. The literature claimed that the use of sildenafil reported side effects such as cardiovascular deaths in a patient. In a few cases, termination of treatment is a must, but in tablet case after administration of dosage from its too difficult to terminate the action of sildenafil. Hence, to overcome these limitations, Elnaggar *et al.* selected the transdermal route for the delivery of sildenafil. Moreover, the iontophoresis

Table 1: Medicinal plants used in erectile dysfunction treatment

plant name	Biological source	Family	Part used	Dose (mg/kg)
Ginkgo[34,35]	*Ginkgo biloba*	Ginkgoaceae	Seeds, Leaves	240
Asparagus[36]	*Asparagus racemosus* Wild.	Liliaceae	Root	200
Ginseng[37]	*Panax ginseng*	Araliaceae	Root	250
Catuaba[38]	*Erythroxylum catuaba*	Erythroxylaceae	Bark	50
Garlic[39,40]	*Allium sativum* L.	Liliaceae	Bulb	200
Safed musli[41]	*Chlorophytum tuberosum* Baker.	Liliaceae	All part of a plant	500
Punarnava[42]	*Boerhavia diffusa* L.	Nyctaginaceae	Root	400
Yohimbine[43]	*Pausinystalia yohimbe*	Rubiaceae	Bark	5.4
Nutmeg[44]	*Myristica fragrans* Houtt	Myristicaceae	Seed	500
Ashwagandha[45]	*Withania somnifera* Linn.	Solanaceae	Leaf, Root	500
Chinese chive[46]	*Allium tuberosum*	Zingiberaceae	Seed	500
Damiana[47]	*Turnera aphrodisiaca*	Turneraceae	Areal part	100

was used for the delivery of sufficient sildenafil (positive charge molecules) across the skin in a controlled manner. The sildenafil penetration through rabbit skin showed similar to human skin (log kp = −2995 [human], log kp = −2982 [rabbit]). The sildenafil penetration has increased using the iontophoresis technique and penetration enhancer in all formulations. Sildenafil based gel formulation was used for testing by iontophoresis (0.5 mA/cm^2). With a comparison of oral formulation and passive delivery, the gel formulation with iontophoresis shows the higher blood concentration. Moreover, the rabbit skin irritation test of gel confirmed the absence of irritation.[51] Sildenafil citrate delivery in the form of transdermal application is challenged due to low oil and water solubility, amphoteric nature, poor membrane permeability, and pH-dependent characteristic, etc. The various lipidic nanocarriers could successfully circumvent the drug delivery obstacle.[52]

Over the past few decades, there have been extensive works on nano-droplet emulsifying systems. Due to their nanosize and high stability (kinetic/thermodynamic), the application of such systems is broad in the pharmaceutical area and directed toward the solubility and bioavailability enhancement of the drugs. In that, the micro-emulsions are thermodynamically stable, whereas the nanoemulsions are unstable in the form.[53] In fact, nanoemulsion that has the particle size larger than 100 nm, it might be non-transparent. It should be quite translucent. It provides ultra-low interfacial tension and large oil/water interfacial areas. Moreover, nanoemulsion has a high solubilization ability than the simple micellar solution.[54,55] Self-nano-emulsifying drug delivery system (SNEDDS) or nanoemulsion pre-concentrate consists of isotropic mixtures of surfactant, cosurfactant, and oils. Such systems spontaneously emulsify into oil-in-water nanoemulsions with nano-metric droplet size (<200 nm) when exposed to gastrointestinal fluids. SNEDDS are well recognized to enhance the oral bioavailability of active pharmaceutical ingredients vulnerable to pre-systemic clearance and first-pass effect. Elnaggar *et al*. developed two liquid-lipid based nanocarriers, which includes drug-loaded nanoemulsion and SNEDDS using Cremophor RH40® as a surfactant. Besides this, nanocarriers include an oil blend of Maisine 35-1 and Caproyl 90 and cosurfactant (propylene glycol). The nanoemulsion showed the spherical shaped globules and 70 nm in size. All dispersions showed a higher point enough than 37°C. Moreover, the *in vitro* release from both drug-loaded nanocarriers was significantly higher than the sildenafil citrate suspension. Furthermore, these nanocarriers enhanced the permeation rate and prolonged drug release. Paradoxically, drug-loaded SNEDDS exhibited scanty transdermal permeation, which attributed to the low water content of stratum corneum.[52] Avanafil is an approved phosphodiesterase-5 enzyme inhibitor and used as a second-generation medication for ED. It is more selective for the PDE5 isoenzyme and cellular targets than the tadalafil and sildenafil. However, avanafil is practically insoluble in water, which affects the bioavailability. Hence, there is a need to overcome the problem of solubility and bioavailability. Hosny and Aldawsari prepared the liposomes multilamellar liposomal vesicles [MLVs] and unilamellar vesicles (ULVs) of avanafil using thin-film hydration technique and reverse-phase evaporation technique, respectively. The liposomal lipid composition, including di-palmitoyl-L-α-phosphatidylcholine: Lecithin:cholesterol (CH) (3:1:3) showed the 95.61–60.01% entrapment efficiency for MLVs and ULVs, respectively. It showed that the increase in C-H content up to a certain limit increased the percent entrapment efficiency. The mean particle diameter of the MLVs showed the larger as compared to the ULVs. The permeation study demonstrated that the cumulative amount of avanafil permeated from liposomal dispersion after 12 h was 52.30%, and the avanafil suspension was only 12.36%. Hence, *ex vivo* permeation studies showed that the liposomal drug suspensions showed a 4-fold higher permeation than aqueous drug suspension. Optimized liposomal transdermal formulation showed the value for C_{max} (8.42 ng/mL), T_{max} (3.5 h), and AUC0-t (108 ng.h/mL) while the suspension showed C_{max} (3.64 ng/mL), T_{max} (1.5 h), and AUC0-t (13.10 ng.h/mL) which clearly showed a 7.3 fold ($P < 0.05$) increase in the avanafil liposomal formulation bioavailability as compared to a topical drug suspension.[56] Thus, the study revealed that introducing the liposomal formulation in normal drug suspension would be more clinically efficient.

Badr-Eldin and Ahmed developed the sildenafil citrate loaded transfersomal transdermal patch using a modified lipid hydration technique and compared with sildenafil citrate film without transferosomes. Formulation optimization was carried out using central composite design. The optimized batch of transfersomes was showed unilamellar, spherical, about 130 nm vesicular sizes, and 94.74% entrapment efficiency. This optimized batch incorporated into hydroxypropyl methylcellulose and used as a transdermal film. Furthermore, the transfersomal films demonstrated a controlled, gradual release, and the maximum amount of drug permeated 1.54 folds as compared with the control transdermal films. Moreover, the diffusion coefficients and computed permeability for the optimized films were 1.57 and 1.25 folds more. The transfersomes have the potential to penetrate the stratum corneum barrier and achieve dermal tissue penetration and finally reach into systemic circulation due to their flexibility and deformability. In addition, the small nano vesicle sizes could potentially contribute to the permeation through the membrane and bioavailability enhancement. Thus, the optimized drug-loaded transfersomal films showed significantly higher C_{max} (114.83 ng/mL), T_{max} (15 h), and AUC ($AUC_{0–36,}$ and $AUC_{0–\infty:}$ 2,103.77 and 2,326.65 ng h/mL, respectively) as compared to control films without transferosomes. Since sildenafil citrate oral administration facing the problem of poor bioavailability and short duration of action that requires frequent administration. As this study, evidenced nano-transfersomal films enhance the transdermal permeation and the bioavailability of the drug with the possible consequence of reducing the dose and administration frequency; makes the system more efficient clinically.[57] The sildenafil citrate loaded nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) were prepared for permeation enhancement using a modified high-shear homogenization method. The vesicle size of NLCs and SLNs was found between 180 and 100 nm, respectively. The higher percentage of Span 85 resulted in a significant decrease in particle size. Furthermore, the percent entrapment of sildenafil was found at about 96.7% and 97.5%, respectively. The increasing drug resulted in an increase in the entrapped

weight in both SLNs and NLC. Moreover, the engineered nanoparticles have significantly enhanced *in vitro* drug release and transdermal permeation as compared with drug suspensions.[58]

The vardenafil is a more selective five phosphodiesterase inhibitors than the tadalafil, sildenafil, etc., and it has 15% oral bioavailability but 10 times more potent than the sildenafil and tadalafil. Along with that, it gives several advantages as compared to the sildenafil and tadalafil. Nowadays, the vascular carrier-based drug delivery gained huge attention due to its dose accuracy and permeation rate. Fahmy developed vardenafil nano-ethosomes using thin-layer evaporation techniques. The batch optimization was carried out using Box–Behnken design. The optimized batch showed an average size of 128 nm and a percent entrapment efficiency of about 76.23%. The permeation data revealed that the significant improvement in permeation with an enhancement ratio of 3.05-fold as compared to powder. The vardenafil transdermal film showed significantly ($P < 0.05$) higher AUC (271.67 ng/mL·h), $t_{1/2}$ (14.40 h), T_{max} (2 h), and C_{max} (25.76 ng/mL) as compared to oral suspension (AUC: 128.30 ng/mL·h, $t_{1/2}$:3.89h, T_{max}:4, C_{max}:14.54). A significant ($P < 0.05$) augmentation of C_{max} was observed with transdermal film as compared with the aqueous suspension. Thus, it could be a potential alternative that improves patient tolerability and compliance for the ED treatment.[59] The second line therapy includes injections (intracavernosal) that provide immediate action, but the pain at the site, prolonged erection time, and priapism; hence, there is a need to overcome such a problem. Ali *et al.* prepared the topical nanocarrier gel (nano-transfersome) to enhance the penetration of papaverine hydrochloride (vasodilator). The optimized batch showed 72% entrapment efficiency, about 220 nm average particle sizes, along with this −33.4 mV zeta potential. The percent drug release was shown by nano-transfersomes gel about 73% in 2 h. The clinical data divulged that the increase in diameter of the cavernous artery from 0.53 mm to 0.78 mm also an increase in peak systolic flow velocity from 5.95 to 12.2 cm/s. It is evident from the performed study of transfersomes that can be used as a carrier of papaverine hydrochloride for treatment of the ED and it becomes more clinically efficient than papaverine hydrochloride without nano-transferosomes.[60]

Oral Route Formulation

In pharmaceutical applications, the oral route is more preferred; which provides several benefits over the other therapies and treatments. The oral dosage form includes orodispersible tablets, films, conventional tablets, and capsules. Due to some drawbacks of conventional methods, the researcher focuses on new alternatives. As per the literature, the tadalafil starting dose for men populations is 10 mg once a day, required before sexual contact. Moreover, the tadalafil dose may be increased to 20 mg and decreased to 5 mg, as per its efficacy and the man's tolerance of the tadalafil. There is a need to avoid the inconvenience of the patient. Hence, Prabhu developed the tadalafil loaded immediate-release oral jelly for the treatment of ED. The jelly formulation was prepared using carbopol 940 as a gelling agent. The percent drug content, drug release of optimized batch showed about 98.00% and 98.80%, respectively. It concludes that, when increasing the concentration of polymer, the alteration between the polymer and drug will be increased. Thus, it increases the concentration of drug in a dosage form. The similarity factor (f_2) values of optimized formulation were found about 93.58 as compared with clinically availed products. The release kinetics showed the first-order release; hence, the tadalafil release rate depends on its concentration present in jelly. Furthermore, it showed the release component (n) < 0.5, which concludes that the drug transport mechanism of tadalafil oral gelly followed the Fickian (diffusion) drug transport mechanism. It showed admirable stability, better result, hence it could be more beneficial to improve drug bioavailability.[61] From the last decades, the advancement if drug delivery has been taking place such as films, gels, and chewing gum it improves patient compliance, convenience, and acceptability. The orally dispersible films are much convenient than conventional ones. It can bypass the swallowing problem, daily fluid intake issues in the patient. Moncada and Cuzin demonstrated the clinical safety and efficacy data for Vitaros©/Virirec©. Vitaros©/Virirec© is a new topical, non-invasive treatment for ED that offers the combination of an active drug (alprostadil, and a synthetic PGE1) with a skin enhancer that improves its local absorption directly at the site of action. Clinical data were performed by stratifying patients with different levels of disease severity and comorbidities. Patients were divided into five categories according to medical history: Cardiac, diabetes, prostatectomy, sildenafil failure, and hypertension. In addition, each category could be divided into subcategories: Mild, moderate, and severe according to baseline ED severity; changes in the International Index of Erectile Function (IIEF)-EF, sexual encounter profile, the patient self-assessment of erection, and global assessment questionnaire scores were analyzed. Its clinical efficacy has been demonstrated in both Phases II and III trials, showing a global efficacy up to 83% with the 300 μg dose in patients with severe ED significantly better than placebo. Its fast onset of action together with its favorable toxicity profile and lack of interactions with other drugs makes Vitaros©/Virirec© a first-line therapeutic option for patients with ED.[62]

Cocci *et al.* demonstrated the first clinical trial to assess the efficacy of a new formulation of sildenafil in patients with ED. In which 139 patients administered sildenafil (100 mg) film-coated tablet (FCT) for 4 weeks, followed by a 2-week washout period and then took sildenafil (75 mg) oral dispersible film (ODF) for 4 weeks. The evaluation for this clinical trial involved parameters such as The IIEF, hospital anxiety and depression scale (HADS), patient global impressions of improvement (PGI-I), and Clinician Global Impressions of Improvement (CGI-I). This clinical trial divulged that differences in mean IIEF scores for erectile function, orgasmic function, sexual desire, and intercourse satisfaction were significantly in favor of sildenafil 100-mg FCT, whereas the mean score for overall satisfaction was in favor of sildenafil 75-mg ODF. A significant difference in changes in the HADS score was found from washout to final follow-up (mean difference ¼ 0.19; $P < 0.01$). For the ODF formulation, the median CGI-I score was 3.5 (interquartile range [IQR] ¼ 2.5e4.5) and the median PGI-I score was 3.0 (IQR ¼ 2.0e4.0). The median action time was 20.0 min (IQR ¼ 15.0e30.0) and the median mouth time was 60.0 s (IQR ¼ 30.0e120.0). The median action time of sildenafil film

was found for about 20 min. Furthermore, it showed a greater rapidity of absorption, which can be credited to its pre-gastric absorption. Hence, this prepared film of sildenafil with the same effectiveness and safety of film-coated conventional tablets showed better appreciation by the patient in overall fulfillment.[63] Poor solubility is a major barrier of bioavailability, it means improvement of bioavailability based on its aqueous solubility. Out of various approaches of solubility enhancement, Fahmy *et al.* selected the self-emulsifying approach to enhance the solubility of avanafil. The objective of work was to improve solubility and ultimately bioavailability of avanafil using oils, surfactant, and cosurfactant. The ternary phase diagram was used for the formulation of stable nanoemulsion of avanafil. The optimized formulation showed a droplet size range from 65 to 190 nm. The self-emulsifying system including dill oil (25%), tween 80 (80%), and propylene glycol (20%) provides improved solubilization of anti viral assay over 80% within 30 min as compared to powder (35% within 30 min). It showed that the significant increase in C_{max} 40.36 ng/ml compared with 25.37 ng/ml for SNEDDS and control groups, respectively. Moreover, the T_{max} decreased significantly from 70 to 32.5 min for control and SNEDDS groups, respectively. Hence, the bioavailability of drug-loaded self-emulsifying formulation was increased by 1.4 fold as compared to the pure drug.[48] Sheu *et al.* developed rapid-onset sildenafil sublingual drug delivery systems. Briefly, the sildenafil loaded sublingual microemulsion spray and sublingual tablet were developed and subjected for evaluation. It evinced that sublingual absorption of sildenafil spray prepared with propylene glycol was fairly rapid. At a 0.5-mg dose, the mean onset of action was 1.3 ± 0.6 min and lasted for about 1.5 h according to the pharmacokinetic studies. Besides this, the propylene glycol-based sublingual tablet prepared using Cyclocel® as the binder and Ac-Di-Sol® as a disintegrant. It showed the onset of action for about 1.9 min and lasted about 1 h. Hence, it suggests that the sublingual delivery of sildenafil provides tremendous potential over conventional oral administration.[64] The literature revealed that the sildenafil exhibited poor aqueous solubility, delays onset of action, extensive first-pass metabolism, gastric burning, dyspepsia, and low bioavailability (40%).[65,66] Hosny *et al.* have developed the orodissolved film to overcome the above-mentioned problem using sildenafil citrate by solid dispersion method. The Box–Behnken design was used for the optimization of the formulation. The hydroxyl-butyl-β-cyclodextrin showed eight-fold enhancement in solubility of sildenafil citrate. The prepared film showed 89 s of disintegrating time and drug release by about 86%. The bioavailability was increased by 2.25 fold as compared to a market tablet.[66] The effervescence phenomenon is gaining more attention for a researcher in the pharmaceutical field. In generaly, dissolution or dispersion of dosage form before the administration can achieve by effervescent tablets. Furthermore, it improves the gentle action of patient, taste, etc. Patel and Patel developed the effervescent tablet of sildenafil citrate to achieve a rapid onset of action on the body. The use of aspirin in combination with sildenafil citrate tablets reduces the major side effects of sildenafil. The formulation was optimized using 3^2 factorial design. It showed that the effervescent agent and binder concentration effect on the hardness and effervescent time. The high concentration of bicarbonate source gives less effervescent time and a high concentration of binder increase the hardness of the tablet. The optimum composition of citric acid, tartaric acid, sodium bicarbonate, potassium bio carbonate, and polyvinylpyrrolidine K_{30} (PVP K30, binder) was found to be 23.65%, 6.30%, 37.85%, 12.61%, and 2%, respectively. The optimized batch showed 3 kg/cm^2 hardness value. Moreover, it showed 99.39 % and 99.48% cumulative drug release of sildenafil citrate and aspirin, respectively, up to 10 min.[67] Recently, foam drying technology is widely used to overcome the poor dissolution problem of active pharmaceutical ingredients. Sawatdee *et al.* prepared the sildenafil foam dried tablet using sodium dodecyl sulfate, mannitol, and maltodextrin. The foam of formulation was obtained by passing to the nozzle spray bottle. It showed that the high concentration of excipient gives an enhanced dissolution rate. The optimized tablet formulation showed about 5 kg hardness, <5 min disintegration time, and <1% friability test limit. The dissolution in 0.1 N HCl showed a high dissolution rate as compared to the wet granulation method and direct compression.[68] From its inception, the oral drug delivery of poorly soluble drugs is more problematic. These poorly soluble drugs contain low bioavailability and dose proportionality issues. Meda *et al.* developed oral nanosuspension of tadalafil by nanoprecipitation method using different excipients such as sodium lauryl sulfate, Pluronic F127, TWEEN 80, and TWEEN 20. The TWEEN 20 (0.3 %w/v), acetone (5 mL) and water (4 mL) gives 95.46 and 97.77% drug content and entrapment, respectively. The particle size of nanosuspension was found at about 126 nm. The optimized formulation showed first-order release kinetic (R^2:0.972) and 99.74% tadalafil release within 30 min.[69] Nanoformulation gives numerous benefits over conventional drug delivery, but there is a major issue of stability. Ubgade *et al.* prepared tadalafil nanosuspension by a high shear homogenization technique which contains hydroxypropyl methylcellulose E 15, sodium dodecyl sulfate as a suspension stabilizer. The stability of prepared nanosuspension was increased by converting into the solid pellets formulation using κ-carrageenan (pelletizing agent). The optimized formation drug:polymer:surfactant (1:1:2) showed about 247.3 nm particle size, -11.9 mV zeta potential, 98.2% drug content and 0.75 polydispersity index. The pellet showed more than 85% drug release (45 min) in contrast to a pure drug (about 70%), and marketed tablets (about 66%). Hence, it concludes that the solubility enhancement of tadalafil can be possible by high shear homogenization. Moreover, the dissolution rate of IR pellets can be improved by κ-carrageenan. The solidification of prepared nanosuspension in the form of pellets can be used for increasing solubility of the drug and stabilization of nanosuspension.[70] Jani and Patel designed sildenafil citrate fast dissolving film for the treatment of ED. The hydroxypropyl methylcellulose E15:polypropylene glycol:glycerin (28.69%:19.13%:6.38%) demonstrated the more than 90% drug dissolution within 10 min. Moreover, the use of the drug:kryon T-134 (1:0.75) ratio mask the bitter taste of the drug. The plasticizer concentration has no major effect on the disintegration time of the film. Moreover, the concentration of polymer showed a positive effect (directly proportional) on tensile strength and disintegration time. The increase in polymer and plasticizer concentration increases the tensile strength. Furthermore, the polymer high concentration retards the disintegration and consequently prolonged the

release from the film. Hence, the development of sildenafil loaded fast dissolving film opens new alternative routes to existing formulation to provide the rapid onset of action.[71] Sildenafil is majorly used active in the treatment of ED, but orally administered dose showed low bioavailability (41%). The fast-dissolving dosage form can improve bioavailability, decrease the dosing frequency, and due to this the increase the therapeutic effect of sildenafil. Adena *et al* reported the fast dissolving tablet of sildenafil citrate by a wet granulation method using crospovidone, croscarmellose sodium (25:25 mg) as super disintegrant. The optimized batch showed promising disintegration time (34.11 s) and dissolution (about 100.6% within 45 min) which is more than market formulation viagra (98.02%). The drug release from the tablet followed the zero-order release kinetics (R^2:0.99), hence the drug release rate is independent of its concentration present in the tablet.[72] Due to the numerous advantages of a fast-dissolving tablet, Zafar *et al.* prepared the fast-dissolving tablet of sildenafil citrate using fenugreek seed mucilage (4.5 mg) as a superdisintegrant and compared with sodium starch glycolate, microcrystalline cellulose (MCC 101,102). The optimized tablet showed 15 s disintegration times and 90% *in vitro* drug release within 20 min. The disintegration time, wetting time, and water absorption of the tablet showed a significant difference ($P < 0.5$, one-way ANOVA). Hence, it concludes that the use of naturally obtain super disintegrant can be an excellent alternative to fast dissolving tablet dosage form as compared to sodium starch glycolate and MCC.[73]

Miscellaneous

The above-mentioned routes are most preferably engaged to treat ED. Out of this, the scientific fraternity is searching for the new alternative to overcome the obstacle of existing ones by selecting different routes and formulation, etc., lately, the systemic delivery through, the intranasal route has received great attention due to its numerous privileges by its exceptional anatomical features. It includes a large surface area of the respiratory region, porous nasal endothelium allows for a rapid onset of action, high blood flow, and bioavailability. It showed high patient compliance due to low administered dose and low systemic adverse effects. Besides this, the intranasal route is bypassed first-pass metabolism, non-invasive, improves protein bioavailability. Nanoemulsion is an optically isotropic dispersion composed of water, oil, and a surfactant. The droplet size of nanoemulsion is about 20–200 nm. It provides a high surface area and other physical properties. Hence, nanoemulsion can be used as an alternative formulation to overcome the crisis of physiological and anatomical barriers. Due to the numerous benefits of the intranasal route and nanoemulsion, Elbardisy *et al.* developed the tadalafil intranasal nanoemulsions using phase diagram construction. The o/w and w/o nanoemulsion were prepared using different ratios of labrasol:transcutol-HP (1:1), Capmul-MCM-EP, and water. The final optimized batch showed the 4000-fold increase in tadalafil solubility as compared to its aqueous solubility. Nasal toxicity of nanoemulsion study revealed that there was no significant difference in values of caspase-3 and tumor necrosis factor-α between the nanoemulsion treated and the control groups. Moreover, the drug-loaded emulsion demonstrated the significant enhancement in cGMP levels. Hence, it suggested that the intranasal administration of the developed nano-emulsion could provide a safe and effective alternative.[74] Hence, it concludes that pharmaceutical formulation had overcome the several obstacles of the conventional method of ED treatment. Till to date, there is a huge scope for researchers to develop the specific site targeted novel formulation to conquer the crisis of ED. Future perception, the researchers and pharmaceutical sectors should develop the advanced drug delivery system, which can resolve the man's population from ED. Consequently, it will improve the quality of life of the activity partners.

CONCLUSION

Sexual ability is an important factor in the quality of life and more essential for personal well-being in humans. ED is a widely spread sexual problem and adversely affects well-being, mood, interpersonal relations, and consequently the quality of life. This review has dealt with various pharmaceutical approaches such as nanocarriers, solid dispersion, and transfersomes to obtain and maintain the erection. This is very important because of the issues and side effects of conventional drug delivery systems, now the world is fast turning into the novel drug delivery system for managing ED. At the conclusion, a novel drug delivery system can be a new alternative to the ED conventional dosage form.

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