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Research Article
Development and Characterization of Spray-dried Amorphous Solid Dispersion of Sildenafil: *In vivo* Evaluation

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Abstract

Background and Objective: Erectile Dysfunction (ED) is a non-satisfactory age-related sexual condition caused due to physiological and psychological illness. Phosphodiesterase-5 inhibitor (PDE5I) sildenafil used for the treatment of ED, has and poor aqueous solubility and low bioavailability. Therefore, the objective of this study was to develop spray-dried amorphous solid dispersion of sildenafil using novel drug carriers; Glycyrrhizin and soluplus. **Materials and Methods:** Spray-drying technology was employed for the preparation of Spray Dried Amorphous Solid Dispersion (SDASD) of sildenafil by varying drug-polymer ratios. Prepared solid dispersions were characterized for yield, drug entrapment, particle size, Polydispersity Index (PDI) and zeta potential. Drug-polymer interaction was studied by Fourier-Transform Infrared Spectroscopy (FTIR), X-ray Powder Diffraction (XRD) and scanning electron microscope (SEM) examination alongside of drug release studies were done followed by *in vivo* evaluation of the optimized formulation in the male rats. **Results:** The optimized formulation SN2 showed a 90.3% yield, 40.90% drug entrapped, whereas particle size was found to be 0.710 µm with 0.239 PDI and -33.7 mV zeta-potential. The cumulative drug released percentage (%) for SN2 was found to be 75.34 % in comparison with 32.93% for pure drug sildenafil. Optimized SN2 showed acceptable yield, stable dispersion system with 2.28 folds enhanced drug release. Furthermore, SN2 *in vivo* assessment of sexual behavior activity in male rats suggests enhanced sexual interest, libido, and erection in comparison to pure drug sildenafil and control group. **Conclusion:** The developed novel SDASD of Sildenafil showed increased aqueous solubility, drug release and improved therapeutic effectiveness supported by the enhanced sexual behavior of male rats as per the *in vivo* evaluation.

Key words: Erectile dysfunction, sildenafil, glycyrrhizin, soluplus, spray drying, *in vivo, sexual behavior*

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Erectile Dysfunction (ED) is a non-satisfactory sexual condition caused by consistent or recurrent inability to attain and maintain a full erection adequate for sexual intimacy. It's the most common disturbing ailment in men that vanish the sexual boisterous from life[1]. The knowledge and understanding of causes and origins of ED are complex, interlinked with multidimensional disorders such as hormonal, vascular, the status of psychological well-being[2]. It's important to note that ED is not only an early warning of vascular impairment such as atherosclerosis but also considered as a harbinger of upcoming unscrupulous cardiovascular events[3]. Besides this, the drugs used in the treatment of the aforementioned disorders and conditions also contribute to ED in older men. Sexual dysfunction is an age-related condition that persists due to androgen deficiency and decreased in the testosterone levels. The medicines such as beta-blockers, hydrochlorothiazide, and drugs used in the treatment of depression have the side-effects that cause ED[4]. Survey and case studies around the globe indicate younger men with habitual cigarette smoking are most likely to be impotent. Concomitant to smoking, excessive use of alcohol and consumption of illicit drugs leads to ED[5]. Epidemiology of Erectile dysfunction (ED) suggests, globally 5% of 38 years old age men and 15% of the geriatric population suffered from ED conditions[6]. Rosen *et al.*[7] multi-center study conducted in eight countries with twenty-seven thousand participants showed occurrence of ED was 8% in 20-29 years and 11% among 30-39 years, age group. Another study has identified a higher prevalence of ED in almost 70% of 70 years old men. There are multifarious approaches to treat ED, historians have documented that since the late 1800s, physicians understood testosterone as a masculinity enhancer and consider this male sex hormone as anabolic steroids to maintain the youthful physique despite aging[8]. The first-ever treatments of ED were discussed in the Yellow Emperor's classic of internal medicines, this traditional medicine was a mixture of 22 ingredients[9]. Thereafter, Egyptian Papyrus Ebers document surfaced that describes a mixture of crocodile heart submerged in the wood oil, a topical application of it considered for treatment of impotence. Apart from this holistic approaches, 30 min walk with moderate exercise in a day will decline the risk of ED by 41% [10,11]. Eating natural foods with reduced consumption of cholesterol, triglycerides and less sedentary lifestyle will boost health and psychological state[12]. It was also observed that the man with a 42 inch waist is 50% prone to ED compared to one with a 32 inch waist[13]. However, improved sexual behavior was observed in couples whose male partner is taking phosphodiesterase-5 inhibitor (PDE5I) in comparison to the couple receiving placebo as per the results of randomized clinical trials[14]. ED can be reversible by the use of PDE 5 inhibitors, that act by inhibiting the phosphodiesterase type 5 enzyme responsible to degrade cGMP[15,16]. Increased level of intracellular cGMP leads to Nitric Oxide (NO) enabled the relaxation of vascular smooth muscles[17]. Sildenafil compound was discovered for the treatment of hypertension and ischemia, but during the clinical trials, researchers observed that this drug was more effective at inducing the erection, so in 1998 sildenafil was the first regulatory approved sex pill for ED discomfort[18]. Later on, in 2003 tadalafil and vardenafil drugs from PDE5I were discovered for the treatment of ED. As per the data, as many as thirty million men suffered from ED in the United States alone[19]. Yet only 4.2 million men seek medical attention from which 3.8 million received sildenafil drug, fewer than 2.2 million continued sildenafil sex-pill[20]. This lack of medication adherence could be due to reduced pharmacologic efficacy, adverse drug reactions, or side effects followed by psychological and partner issues[21]. Besides, up to 20-40% of men may fail to elicit therapeutic effects with PDE5I[22]. It is therefore essential to improve sexual dysfunction therapy with regards to drug efficacy and drug delivery efficiency. Among the four approved phosphodiesterase-5 (PDE5) inhibitors, all are classified in BCS class II and reported to be insoluble in water[23]. Sildenafil and Tadalafil are the clinically significant abundantly used drugs for erectile dysfunction. A Natural super drug carrier glycyrrhizin - triterpenoid saponin glycoside reportedly increase the solubility of BCS – class II drugs[24]. Novel drug carriers, drug delivery systems fabricated as supramolecular complex exhibit enhanced solubility, dissolution rate, and therapeutics efficacy. Glycyrrhizin (GZN) testified to be one of that drug carrier. GZN is amphoteric that has hydrophilic-glucuronic acid and hydrophobic-glycyrrhizic acid fragments. Due to this property GZN is widely used in the solubility enhancement process, reduce the toxicity, bitterness, enhance the dissolution rate, and bioavailability of drugs. Another novel carrier with solubilization property is Soluplus (SLP), it's a grafted copolymer possessing polyethylene glycol (PEG) 6000 backbone with single or double vinyl acetate side chain copolymerized by vinyl caprolactam. SLP reported to increase the solubility due to amphiphilic property by inducing micelles in the water, therefore used to enhance the solubility, dissolution rate and bioavailability of the poorly water soluble drugs[25]. There are numerous technologies used to increase the solubility of

drugs; crystal engineering, use of surfactants, micronization, complexation, solid dispersions and so forth. Recently, spray-dried amorphous solid dispersions (SDASD) are applied for many poorly soluble drugs to increase the aqueous solubility in order to achieve improved bioavailability and biological activity[26]. Spray drying is an industry-accepted technique in the pharmaceutical field to prepare solid dispersion, in controlled temperature environment to dry the particles The spray-dried amorphous solid dispersion (SDASD) improves the solubility by controlling the particle size and effective surface area, besides amorphous solids (AS) has relatively more solubility in comparison to the crystalline[27]. Increased effective surface area due to decrease particle size of amorphous solids leads to improved aqueous solubility, enhanced dissolution rate and absorption as proposed by Nernst Brunner equation.

The current investigation aimed to increase the drug release and efficacy of sildenafil using GZN and SLP. The amorphous solid dispersion of sildenafil prepared by spray drying technique was evaluated for physicochemical characterizations and *in vivo* sexual behavior analysis in male rats. The optimized SDASD of sildenafil could be an acceptable alternative for the treatment of men with erectile dysfunction.

MATERIALS AND METHODS

Study area: The formulation development and characterization were carried out in industrial lab, whereas the sexual behavior study was conducted in pharmaceutical preparation lab of pharmaceutics department, Prince Sattam bin Abdulaziz University, AlKharj, Saudi Arabia. This research project was conducted from November 2019-June 2020.

Chemical collection: Sildenafil (SL) and Glycyrrhizin, (GZN) was obtained as gift samples from Jazeera Pharmaceuticals (JPI), Riyadh. Soluplus® (SLP) was obtained from BASF (Ludwigshafen, Germany) with no commercial value. Acetone (ACN) and Acetic Acid (AA) were purchased from Sigma Aldrich, Germany. All the other chemicals used were of analytical grades. Freshly prepared ultra-purified water was used throughout the work.

Development of Spray-dried amorphous solid dispersion of sildenafil: Spray drying technique was used to prepare Spray-dried amorphous solid dispersion; common solvents of different polarity were used to make the dispersion of drug and polymers combination. Model drug sildenafil and soluplus were dissolved in acetone and whereas glycyrrhizin was solubilized in acetic acid (1%). The concentration of drug carrier was fixed with 1:1 for GZN and SLP. The sildenafil (SL) to drug carriers (GZN and SLP ratios were 1:0.5, 1:1 and 1:1.5 (w/w). Solute to solvent ratio was selected as 1.5, 2 and 2.5% w/v for batches SN1, SN2 and SN3, respectively (Table 1). The drug-carriers solution was ultra-sonicated for about 2 hrs. Once solids get saturated with the solvents, the solution was placed on the magnetic stirrer (100 rpm). The solution was then allowed to pass through the pump into the spray drier through the nozzle feed rate of 30% and aspirator rate of 100%. The inlet temperature was set in such a way that; the outlet temperature should be equivalent to boiling point of the solvent(s) used. For the present study inlet temperature adjusted to get the outlet temperature of 60°C.

Droplet within a millisecond converted to solid. Nitrogen gas will be used along with the temperature to evaporate the solvents. The dry solid will be collected by cyclone mechanism in the collector and preserved in a desiccator for the characterization[28].

Characterization

Yield, particle size, polydispersity and zeta-potential: The product after spray drying was weighed and correlated with the weight of the precursors. The percentage yield was calculated using equation-1

$$\text{Yield (\%)} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100 \quad (1)$$

Prepared SDASD of SL was characterized for particle size, polydispersity index and zeta-potential by Dynamic Light Scattering (DLS) theory using a Malvern particle size analyzer at 25°C. All the samples were measured in triplicate with 20 cycles in each measurement. The sample under investigation

Table 1: Yield, particle size, polydispersity and zeta-potential of SDASD

Batch code	SL: Carriers Ratio (w/w)	Yield (%)	DEE (%)	Size (μm)	PDI	ζ potential (mV)
SN1	1:0.5	85.6	41.62	0.88	0.275	-27
SN2	1:1	90.3	40.9	0.71	0.239	-33.7
SN3	1:1.5	98.8	53.89	1.45	0.301	-32

SN1, 2 and 3: Formulation code given by the author, SL: Carrier Ratio : Drug-carrier ratio, PDI: Polydispersity index, DEE : Drug entrapment efficiency

diluted with (1:200) milli-Q water (Milli-Q® Direct 8 water purification system) followed by ultrasonication for 3 min. The suspended particles in the solvent will collide with each other and solvent molecules, considered being in Brownian motion. Following equation involved in the Quasi-Elastic Light Scattering technique using Non-Invasive Back Scatter technology in which the sample under investigation exposed with a laser beam in multidirectional to measure particle size[29]. Autocorrelation function[30] was carried out by:

$$g \overset{(2)}{\Leftarrow} (\tau) = \frac{I(t).\, I(t+\tau)}{[i(t)]^2} \quad (2)$$

Where:

g = Autocorrelation function, I is the intensity of laser beam

τ = Delay time and t is a normalization factor

Particle size measurement in movement calculated by Stokes-Einstein equation[31].

$$d = \frac{k_B T}{3\pi D\eta_0} \quad (3)$$

Where:

d = Hydrodynamic particle diameter

D = Diffusion coefficient

K_B = Boltzmann's constant

η = Absolute temperature and η is the viscosity

The instrument also gives the polydispersity index reading in the same run.

Zeta potential over a particle of (diameter >25 μm), measured by Phase Analysis Light Scattering in the same instrument (Malvern Instruments Ltd, made in the USA) using Helmholtz and Smoluchowski equation that correlates streaming potential and current passed.

For planar solids zeta potential investigations, surface charges calculated by the equation.

$$\zeta = \frac{dl_{str}}{d\Delta p} \text{ X } \frac{\eta}{\varepsilon X \varepsilon_0} \text{ X } \frac{L}{A} \quad (4)$$

Where:

dl/dp = Slope of streaming current vs. differential pressure

η = Electrolyte viscosity

ε = Dielectric coefficient of electrolyte

ε_0 = Permittivity

L = Length of the streaming channel

A = Cross-section of the streaming channel

For irregularly shaped samples solids zeta potential calculated by the equation[32].

$$\zeta = \frac{dU_{str}}{d\Delta p} \text{ X } \frac{\eta}{\varepsilon X \varepsilon_0} \text{ X } K_B \quad (5)$$

Where:

dU/dp = Slope of streaming potential vs. differential pressure

K_B = Electrolyte conductivity

Quantification of the sildenafil calibration plot: Quantification of the sildenafil was done by the UV-spectroscopy technique (Jasco V-630 Made in Japan), maximum absorption was observed and reported at λ-max 294 nm. A stock solution was prepared by dissolving 10 mg SL drug in 5 mL Dimethyl sulfoxide (DMSO) followed by dilution with methanol to give the concentration of 1000 μg mL^{-1}. Different aliquots were prepared from 0-200 μg mL^{-1}, absorbance was noted against the blank (methanol). The calibration graph was plotted by concentration *vs* absorbance.

Drug encapsulation efficiency: Encapsulation efficiency (EE) was determined by measuring the amount of drug in the filtrate after the encapsulation process using a UV-spectrophotometer at λ-max 294 nm (Jasco V-630 Made in Japan). Following equation is used in the calculation of encapsulation efficiency.

$$\text{Encapsulation efficiency} = \frac{\text{actual drug content}}{\text{theoretical drug content}} \text{ X } 100 \quad (6)$$

X-ray diffraction: XRD diffractograms of pure drug SL, GZN, SLP and optimized SDASD of SN2 batch were obtained using the X-ray diffractometer of Cu target/filter monochromator (Ultima IV Multipurpose X-ray Diffraction System, Rigaku, Tokyo, Japan). The diffractometer was run at voltage/current of 40 kV/40 mA with continuous scan mode and a scan speed of 0.500 deg./min at scan-axis; 2 theta/theta.

Scanning electron microscopy (SEM): The selected SDASD SN2 was subjected to the SEM after suspending the sample in water, vortexed suspension then smeared on the glass slide followed by drying. The dried sample was mounted on carbon tape, and sputter- adhered on SEM stubs using gold sputter under reduced pressure evaporator (Zeiss EVO LS10; Cambridge, UK). The sample in the micro stage was then observed and spotted with the magnification to analyze and study the microstructure of the prepared SDASD of sildenafil[33].

***In vitro* Drug Release study:** All three batches SN1, SN2, SN3 along with pure drug SL and marketed formulation were subjected to the *in vitro* drug release study using the USP-Paddle–II method (Erweka DT 600, Heusenstamm, Germany). The sample under investigation was submerged in a 900 mL 0.1 N HCl dissolution medium. The paddle was rotated at 50 rpm, dissolution medium was maintained at 37±0.5°C, and at a predetermined time interval 5 mL samples were withdrawn and replaced with 5 mL fresh dissolution media. The aliquots were passed through 0.4 µm syringe filters and suitably diluted. The drug concentration was measured by a UV- spectrophotometer at λ-max 294 nm (Jasco V-630 Made in Japan). The mean of at least three determinations was considered to calculate the drug release. The drug released was cumulated and presented against the respective time interval[34].

***In vivo* studies in male rats: Sexual behavior analysis:** The experiment was conducted in a calm laboratory under faint red light in transparent cages. Male albino rats (300-350 g weight aged around 5-6 months and female albino rats of weighing 150-180 g, aged 3-4 months were procured from the animal house of the Pharmacology Department, Prince Sattam Bin Abdulaziz University-Alkharj, Saudi Arabia. Three groups of sexually experienced male rats that were showing reactive sexual activity (n = 5) were selected for the experiment and kept singly in separate cages. Group I served as normal control and was given the vehicle; 1% sodium carboxymethylcellulose. Group II (Reference): received sildenafil at a dose of 5 mg kg^{-1}. The SN2 test Group-III was also administered with 5 mg kg^{-1} of the optimized formulation SN2. The vehicle and other drugs were administered orally as single doses through an orogastric tube. SDASD batches of SN2 were considered as test (GROUP III) whereas, 1% sodium carboxymethylcellulose and sildenafil at a dose of 5 mg kg^{-1} served as control (GROUP I) and reference (GROUP II), respectively.

Sexual behavior analysis: After 30 min, female rats were introduced into the male cages with one female to one male ratio and the sexual behavior of the male animals was immediately begin and continued for the end of the first mating series. The following parameters were measured as mentioned by Fouche *et al.* [35].

- Mount latency (ML): The time from the introduction of a female rat into the cage of the male until the first mount.
- Intromission latency (IL): The time from the introducing of a female rat into the cage until the first intromission by the male.
- Mount frequency (MF): The number of mounts before ejaculation.
- Intromission frequency (IF): The number of intromissions before ejaculation.
- Ejaculation latency (EL): The time from the first intromission of a series until the ejaculation.

Depending on the previously mentioned parameters, the followings can be computed:

$$\text{Copulatory efficiency (CE)} = \frac{IF}{MF} \times 100 \quad (7)$$

$$\text{Intercopulatory efficiency (ICE)} = \frac{IF}{MF + IF} \times 100 \quad (8)$$

Statistical Analysis: The significance of the results values was determined by one-way analysis of variance (ANOVA) with post –hoc t-test, p-value<0.05 was considered as significant.

RESULTS AND DISCUSSION

Spray dried amorphous solid dispersions were prepared using different drug to drug carriers ratio as shown in Table 1. Drug: carriers ratio was varied in all three batches whereas the drug amount was kept constant. The proportion of solvents and process parameters were kept constant in all the batches. The results of change in the drug-carrier ratio on yield, drug entrapment efficiency, average particle size, polydispersity index and zeta potential are shown in Table 1. SDASDS were formed by rapid evaporation of solvent by spray drying technique. According to Table 1 and based on the equation-1, SN1, SN2 and SN3 showed 85.6, 90.3 and 98.8% of product yield, increase in the drug-carrier ratio increases the production yield [36]. The variation in the yield and loss of the product may be related to the adherence or deposit of powder to the cyclone walls and piping of the spray chamber and the outlet filter of the receiver chamber. To avoid oxidation of the product during the drying process inert gas such as nitrogen and carbon dioxide alone or in combination could be used[37]. These gases could alter the yield (%) and solid-state behavior of the product, for instance, carbon dioxide may act as a plasticizer. SN2 and SN3 batches could be considered as successful with optimized parameters and cost-effective processes[38], as the yield from these batches was

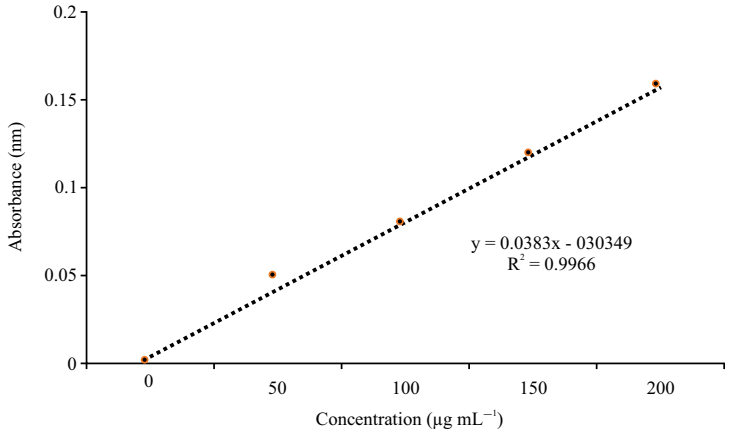

Fig. 1: Calibration plot of Sildenafil citrate

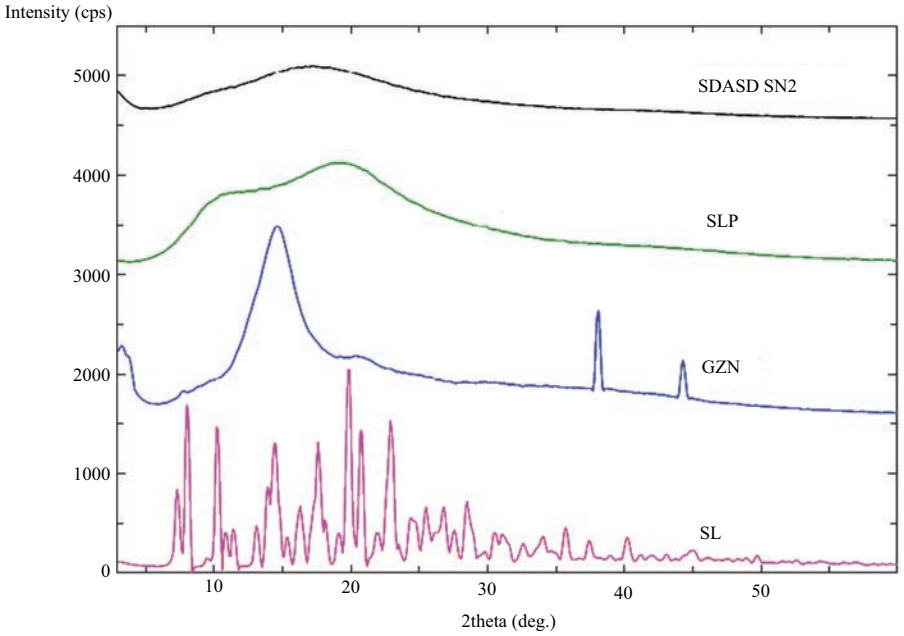

Fig. 2: XRD spectrums of SL, GZN, SLP and optimized SDASD SN2

found to be ≥90 %. The particle size of prepared solid dispersion was found to be ranged between; 0.710-1.45 µm. All prepared SDASD were more or less monodispersed based on the PDI value which was ≤0.3[39]. The results of particle size, PDI, and zeta potential are shown in (Table 1). The difference in the particle sizes could be due to variation in the viscosity of the spray solution and solid loading, moreover atomizer size and conditions applied also plays a crucial role in end product solid sizes. The SN2 formulation showed particle size 0.710 µm and PDI of 0.239, considered as optimized. Small collapsed hollow spheres with reduced particle size, increased surface area could improve the dissolution rate and bioavailability[40]. Zeta potential indicates charges over the particles; all batches showed a negative charge. SN2 batch showed -33.7 mV zeta potential, any dispersion with an electrokinetic intensity of ≥30mV considered as stabilized formulation[41]. The calibration graph was plotted (Fig. 1) good correlation coefficient (R^2) 0.9966 was obtained that obeyed the Beer-Lambert's law. The results of the calibration curve were sensitive, accurate, precise, and reproducible. The results of SN1, SN2 and SN3 showed 41.62, 40.90 and 53.89% drug encapsulation respectively, from these results it could be revealed that an increase in the drug: polymer ratio enhances the drug encapsulation[42]. The x-ray diffraction spectrum of SL, GZN, SLP and optimized SN2 SDASD peaks at 2θ showed in Fig. 2. Intense peaks of SL revealed the crystallinity nature of the drug that affects the solubility and bioavailability[43]. Besides, GZN and SLP showed broad peaks. However, XRD spectra of

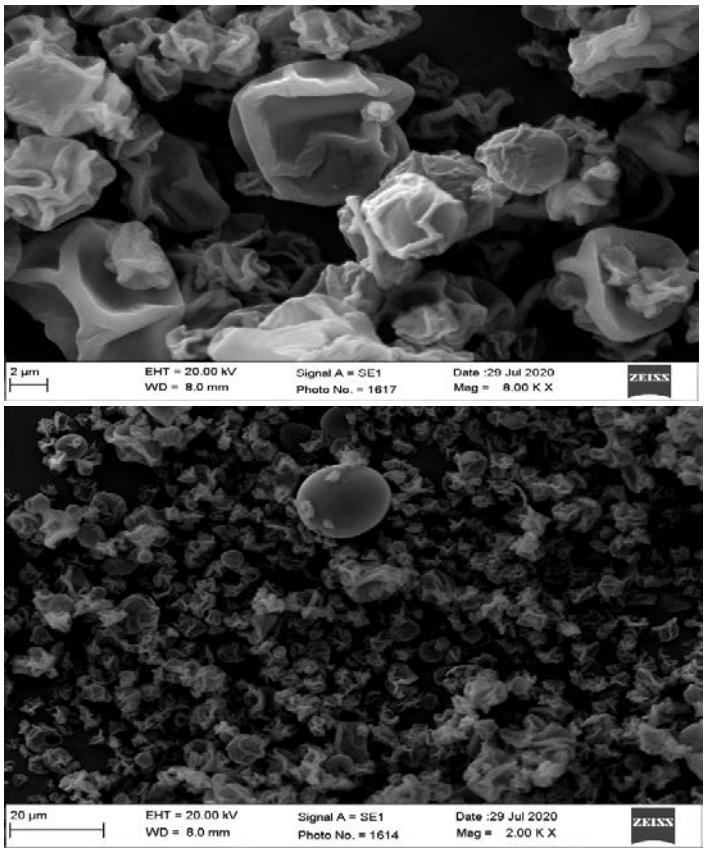

Fig. 3: SEM microphotographs of SN2 solid dispersion obtained using a spray drying technique

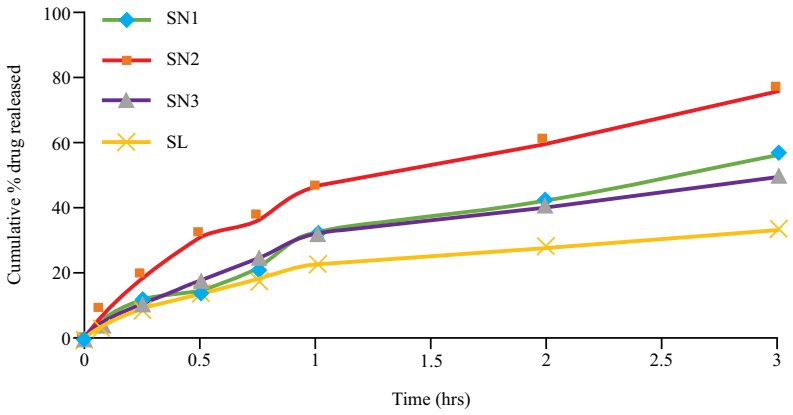

Fig. 4: Cumulative (%) drug release of SDASD and sildenafil (SL)

Sildenafil in SN2 SDASD powder showed the absence of characteristic intense peaks of SL, which mean the transformation of SL from crystalline to an amorphous state (Fig. 2). The amorphous form of drug entity regarded as higher solubilized form with improved bioavailability[44]. The SEM photomicrographs of optimized SN2 SDASD obtained by exposure of sample under study with the electron beam followed by higher magnifications. The image revealed spray-dried sildenafil product was roughly spherical with a shrivelled surface, small dents on the outer surface could be due to rapid solvent evaporation under reduced pressure of the spray drying process[45]. Irregular surfaced particles have an increased effective surface area, that could increase the solubility, dissolution, and bioavailability of model drug used (Fig. 3).

The drug release from the prepared SDASD of sildenafil was studied for 3 h; the results were plotted in (Fig. 4). Drug

Table 2: Effect of sildenafil SDASD on male rats

Groups	ML (sec)	MF	IL (sec)	IF	EL (sec)
Control	96.4±4.37	5.2±0.22	294.5±8.47	2.6±0.11	265.6±9.17
SL	63.5±3.14	8.8±0.30	95.3±4.33	5.6± 0.21	377.4±13.40
SN2	57.8±3.62	8.3±0.31	90.6±5.18	5.8±0.17	382.7±15.65

ML : Mount latency, MF : Mount frequency, IL: Intromission latency and IF : Intromission frequency, EL : Ejaculation latency and SL: Sildenafil

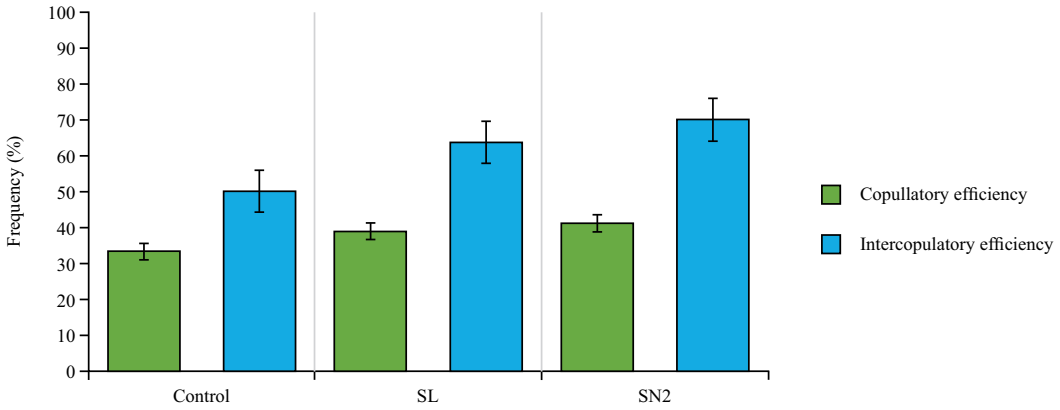

Fig. 5: Effect of SL and SN2 complex on the copulatory efficiency and intercopulatory efficiency of male rats

release was found to be 55.88, 75.34 and 49.21% for SN1, SN2 and SN3 solid dispersions respectively, whereas for the pure drug SL it was only 32.93%, this indicate increased in drug release with the carrier combination and at the same time further increase in drug carrier ratio reduces the drug release[34]. As per the Fig. 4, it was evident that there is a rapid and continuous drug release from the SDASDs compared to pure drug. Optimized SN2 showed the highest drug release amongst all prepared formulation and in comparison to pure drug. The drug release was ordered as SN2>SN1>SN3>SL.

The MF and the ML reflect sexual interest or libido, whereas the IF and IL are useful indices of the sexual excitement and the efficiency of erection. Therefore, the reduced duration of ML and IL as well as the increased values of MF and IF recorded in SN2-treated rats suggests enhanced sexual interest, libido, and erection in comparison with both C and D. Besides, SN2 prolonged ejaculation latency of male animals as compared to rats of C and D groups (Table 2). The significant increase in the duration of ejaculation latency confirms that SN2 has the potential to improve the copulatory performance of male rats.

The percentages of copulatory and the intercopulatory efficiencies were the highest in the male rats Group III administered with SN2 compared to control and the reference groups (Fig. 5). The present results revealed that the highest aphrodisiac activity in male rats was exhibited by SN2.

Spray-dried amorphous soiled dispersions (SDASD) is a novel approach and are applied for many poorly soluble drugs to increase the solubility in order to achieve improved bioavailability and biological activity.

CONCLUSION

The aforementioned results revealed that Spray-dried amorphous solid dispersion developed by using Glycyrrhizin and soluplus has an optimum yield, particle size, and drug entrapment. Drug release results showed relatively higher release compared with pure drug. Enhanced drug release data was supported by the better sexual behavior of optimized formulation compared to pure drug. Therefore, SDASD of sildenafil could be a potential remedial complex for the treatment of erectile dysfunction.

SIGNIFICANCE STATEMENT

This study discovers the increased solubility and enhanced sexual activity of prepared sildenafil SDASD that can be beneficial for the treatment of erectile dysfunction and may restore perished sexual behavior and increases relationship bonding.

This study will help the researcher to uncover the critical areas of spray-dried amorphous solid dispersions by the use of hydrophilic polymers to increase the solubility of BCS – class II drugs that many researchers were not able to explore. Thus a new theory on this glycyrrhizin and PDE-5 inhibitor and possibly other combinations of polymers may be arrived at.

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REFERENCES

1. Rastrelli, G. and M. Maggi, 2017. Erectile dysfunction in fit and healthy young men: psychological or pathological? Transl. Androl. Urol., 6: 79-90.
2. Hamed, S.A., B.P. Hermann, E.M.M. Moussa, A.H. Youssef, T.A. Rageh, Y.E. Elserogy and E. NasrEldin, 2015. Evaluation of penile vascular status in men with epilepsy with erectile dysfunction. Seizure, 25: 40-48.
3. Javaroni, V. and M.F. Neves, 2012. Erectile dysfunction and hypertension: Impact on cardiovascular risk and treatment. Int. J. Hypertens., Vol. 2012 10.1155/2012/627278
4. Conaglen, H.M. and J.V. Conaglen, 2013. Drug-induced sexual dysfunction in men and women. Australian Prescriber, 36: 42-45.
5. Gareri, P., A. Castagna, D. Francomano, G. Cerminara and P. De Fazio, 2014. Erectile dysfunction in the elderly: An old widespread issue with novel treatment perspectives. Int. J. Endocrinol. 10.1155/2014/878670
6. Kubin, M., G. Wagner and A.R. Fugl-Meyer, 2003. Epidemiology of erectile dysfunction. Int. J. Impot. Res., 15: 63-71.
7. Rosen, R.C., W.A. Fisher, I. Eardley, C. Niederberger, A. Nadel and M. Sand, 2004. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence oSf erectile dysfunction and related health concerns in the general population. Curr. Med. Res. Opin., 20: 607-617.
8. Tatem, A.J., J. Beilan, J.R. Kovac and L.I. Lipshultz, 2020. Management of anabolic steroid-induced infertility: novel strategies for fertility maintenance and recovery. World J. Mens Health, Vol. 38. 10.5534/wjmh.190002
9. Shah, J., 2002. Erectile dysfunction through the ages. BJU Int., 90: 433-441.
10. Lee, J.K.C., R.B.W. Tan and E. Chung, 2017. Erectile dysfunction treatment and traditional medicine-can East and West medicine coexist? Transl. Androl. Urol., 6: 91-100.
11. Esposito, K., M. Maiorino and G. Bellastella, 2015. Lifestyle modifications and erectile dysfunction: what can be expected? Asian J. Androl., 17: 5-10.
12. Gerbild, H., C.M. Larsen, C. Graugaard and K.A. Josefsson, 2018. Physical activity to improve erectile function: a systematic review of intervention studies. Sexual Med., 6: 75-89.
13. Hallanzy, J., M. Kron, V.E. Goethe, F.M. Köhn and M. Schmautz *et al*., 2019. Erectile dysfunction in 45-year-old heterosexual German men and associated lifestyle risk factors and comorbidities: results from the German male sex study. Sexual Med., 7: 26-34.
14. Carson, C.C. and T.F. Lue, 2005. Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU Int., 96: 257-280.
15. Kniotek, M. and A. Boguska, 2017. Sildenafil can affect innate and adaptive immune system in both experimental animals and patients. J. Immunol. Res., 10.1155/2017/4541958
16. Puzzo, D., 2008. Role of phosphodiesterase 5 in synaptic plasticity and memory. Neuropsychiatr. Dis. Treat., 4: 371-387.
17. Friedman, J.M. and A.J. Friedman, 2015. Development and therapeutic applications of nitric oxide-releasing materials. Future Sci. OA, Vol. 1. 10.4155/fso.15.50
18. Srinath, N. and S.V. Kotwal, 1999. Sildenafil-oral medication for erectile dysfunction-a review. Med. J. Armed Forces India, 55: 233-236.
19. Ferguson, J.E. and C.C. Carson, 2013. Phosphodiesterase type 5 inhibitors as a treatment for erectile dysfunction: Current information and new horizons. Arab J. Urol., 11: 222-229.
20. Levine, S.B., 2004. Pharmacologic treatment of erectile dysfunction. BMJ., 329: E310-E311.
21. Kim, S.C., Y.S. Lee, K.K. Seo, G.W. Jung and T.H. Kim, 2014. Reasons and predictive factors for discontinuation of PDE-5 inhibitors despite successful intercourse in erectile dysfunction patients. Int. J. Impot. Res., 26: 87-93.
22. Lowe, G. and R. Bahnson, 2009. Non-invasive management of primary phosphodiesterase type 5 inhibitor failure in patients with erectile dysfunction. Ther. Adv. Urol., 1: 235-242.
23. Gupta, M., A. Kovar and B. Meibohm, 2005. The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. J. Clin. Pharmacol., 45: 987-1003.
24. Kang, M.J., J.Y. Cho, B.H. Shim, D.K. Kim and J. Lee, 2009. Bioavailability enhancing activities of natural compounds from medicinal plants. J. Med. Plants Res., 3: 1204-1211.
25. Alopaeus, J.F., E. Hagesæther and I. Tho, 2019. Micellisation mechanism and behaviour of soluplus®–furosemide micelles: preformulation studies of an oral nanocarrier-based system. Pharmaceuticals, Vol. 12. 10.3390/ph12010015
26. Kwon, J., B.R. Giri, E.S. Song, J. Bae, J. Lee, and D.W. Kim, 2019. Spray-dried amorphous solid dispersions of atorvastatin calcium for improved supersaturation and oral bioavailability. Pharmaceutics, 10.3390/pharmaceutics11090461
27. Tambosi, G., P.F. Coelho, S. Luciano, I.C.S. Lenschow, M. Zétola, H.K. Stulzer and B.R. Pezzini, 2018. Challenges to improve the biopharmaceutical properties of poorly water-soluble drugs and the application of the solid dispersion technology. Matéria (Rio J.), Vol. 23. 10.1590/s1517-707620180004.0558

28. Rahman, M., S. Ahmad, J. Tarabokija, N. Parker and E. Bilgili, 2020. Spray-dried amorphous solid dispersions of griseofulvin in HPC/Soluplus/SDS: elucidating the multifaceted impact of SDS as a minor component. Pharmaceutics, 10.3390/pharmaceutics12030197
29. Patel, B.B., J.K. Patel, S. Chakraborty and D. Shukla, 2013. Revealing facts behind spray dried solid dispersion technology used for solubility enhancement. Saudi Pharmaceut. J., (In Press). 10.1016/j.jsps.2013.12.013
30. Stetefeld, J., S.A. McKenna and T.R. Patel, 2016. Dynamic light scattering: a practical guide and applications in biomedical sciences. Biophys. Rev., 8: 409-427.
31. Costigliola, L., D.M. Heyes, T.B. Schrøder and J.C. Dyre, 2019. Revisiting the Stokes-Einstein relation without a hydrodynamic diameter. J. Chem. Phys., 10.1063/1.5080662
32. Polaczyk, A.L., J.E. Amburgey, A. Alansari, J.C. Poler, M. Propato and V.R. Hill, 2020. Calculation and uncertainty of zeta potentials of microorganisms in a 1:1 electrolyte with a conductivity similar to surface water. Colloids Surf., A, 10.1016/j.colsurfa.2019.124097
33. Bashardoust, N., J.J.L. Jenita and P. Zakeri–Milani, 2013. Physicochemical characterization and dissolution study of ibuprofen compression-coated tablets using locust bean gum. Dissolution Technol., 20: 38-43.
34. Vyas, V., P. Sancheti, P. Karekar, M. Shah and Y. Pore, 2009. Physicochemical characterization of solid dispersion systems of tadalafil with poloxamer 407. Acta Pharm., 59: 453-461.
35. Fouche, G., A.J. Afolayan, O.A. Wintola, T.E. Khorombi and J. Senabe, 2015. Effect of the aqueous extract of the aerial parts of Monsonia angustifolia E. Mey. Ex A. Rich., on the sexual behaviour of male Wistar rats. BMC Complementary Altern. Med., 15: 1-10.
36. Moin, A., T.K. Deb, R.A.M. Osmani, R.R. Bhosale and U. Hani, 2016. Fabrication, characterization, and evaluation of microsponge delivery system for facilitated fungal therapy. J. Basic Clin. Pharma, 7: 39-48.
37. Singh, A. and G. Van Den Mooter, 2016. Spray drying formulation of amorphous solid dispersions. Adv. Drug Delivery Rev., 100: 27-50.
38. Gu, B., B. Linehan and Y.C. Tseng, 2015. Optimization of the Büchi B-90 spray drying process using central composite design for preparation of solid dispersions. Int. J. Pharm., 491: 208-217.
39. Wang, C., B. Cui, L. Guo, A. Wang and X. Zhao *et al*., 2019. Fabrication and evaluation of lambda-cyhalothrin nanosuspension by one-step melt emulsification technique. Nanomaterials, 10.3390/nano9020145
40. Ekdahl, A., D. Mudie, D. Malewski, G. Amidon and A. Goodwin, 2019. Effect of spray-dried particle morphology on mechanical and flow properties of felodipine in PVP VA amorphous solid dispersions. J. Pharm. Sci., 108: 3657-3666.
41. Cui, B., C. Wang, X. Zhao, J. Yao and Z. Zeng *et al*., 2018. Characterization and evaluation of avermectin solid nanodispersion prepared by microprecipitation and lyophilisation techniques. PLoS ONE, Vol. 13. 10.1371/journal.pone.0191742
42. Dey, S., S. Pramanik and A. Malgope, 2011. Formulation and optimization of sustained release stavudine microspheres using response surface methodology. ISRN Pharm., 2011: 1-7.
43. Rodde, M.S., G.T. Divase, T.B. Devkar and A.R. Tekade, 2014. Solubility and bioavailability enhancement of poorly aqueous soluble atorvastatin: *in vitro*, *ex vivo* and *in vivo* studies. BioMed. Res. Int., Vol. 2014. 10.1155/2014/463895
44. Khadka, P., J. Ro, H. Kim, I. Kim and J.T. Kim *et al.,* 2014. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian J. Pharm. Sci., 9: 304-316.
45. Teixeira, M.I., L.R. Andrade, M. Farina and M.H.M. Rocha-Leão, 2004. Characterization of short chain fatty acid microcapsules produced by spray drying. Mater. Sci. Eng.: C, 24: 653-658.