Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Development and Characterization of Sildenafil Citrate Oral Thin Films

Divya J. Yadagiri, Mounika Kuchukuntla, Mounika Konatham, Mounika T. Gorle, Vasudha Bakshi, Rajendra K. Jadi*

School of Pharmacy, Anurag University (Formerly Anurag Group of Institutions), Venkatapur, Medchal, Hyderabad – 500 088, Telangana State, India

ARTICLE INFO

Article history:

Received: 21 August, 2020

Revised: 18 February, 2021

Accepted: 25 February, 2021

Published: 30 March, 2021

Keywords:

Dyspepsia, Folding endurance, Oral thin films, Sildenafil citrate, Solvent casting, Tensile strength.

DOI:

10.25004/IJPSDR.2021.130205

ABSTRACT

The current work aimed to develop sildenafil citrate (SC) oral thin films. SC oral thin films (OTF) were prepared by solvent casting method. The ingredients include hydroxypropyl methylcellulose (HPMC), E4 (as film former), glycerol (as lubricating agent), polyethylene glycol 600 (as plasticizer), rose oil (as flavoring agent), and de-ionized water (as solvent). The SC-OTFs were successfully prepared by the solvent casting method. The drug excipient compatibility studies showed the absence of drug excipient interactions in fourier transform infrared spectroscopy (FTIR) spectra. All the prepared formulations (F1 to F6) were evaluated for several physicochemical parameters like morphology (i.e., size, shape, color), thickness, uniformity (i.e., content and weight), surface pH measurement, *in vitro* disintegration time, *in vivo* studies (i.e., taste), tensile strength, folding endurance and *in vitro* drug release and all were found within pharmacopoeial limits. *In vitro,* drug release studies (F1 to F6) in simulated salivary fluid (6.8 pH phosphate buffer) showed that 98 ± 1.26% drug was released from F4 in 60 sec. The OTF is a promising formulation for SC that results in high solubility, rapid onset of action, and enhanced systemic bioavailability (BA).

Introduction

To discover or develop a new chemical entity or a molecule or a drug is a time being and expensive also. Hence the industries, particularly in the pharmaceutical field, are just beginning innovative concepts for existing drugs.[1] One of the advanced drug delivery systems is oral thin films. As per the United States of Pharmacopeia (USP), "Films" or "Oral films" are defined as single or multi-layer thin sheets with or without drug substance to be placed in the oral cavity.[2-4] The fast disintegrating tablet, which is devoid of friability and choking risk, is more acceptable to pediatric, bedridden, and geriatric patients.[5-7] The oral films are generally prepared by 'solvent casting or 'extrusion,' which is intended for fast disintegration and may allow more rapid mucosal absorption of the loaded drugs.[8-10]

A comprehensive spread review of the literature was initially performed to collect up to date and allowed for new oral film technology supplementary progress. Marketed oral films were analyzed to develop experimental knowledge and suitable quality and process parameters.[11] The mainstream of the fast disintegrating oral films was designated by oro-dispersible films (ODFs) based on hydrophilic polymers. The characteristics of ODF's are usually associated with undesirable texture, lower stability, and appearance, especially when exposed to ordinary environmental conditions.[12-13]

Oral films are complex polymeric matrices, usually in a postal stamp shape, which may be used efficiently as a drug release platform. Oral films are relatively recent dosage forms, especially in the pharmaceutical market, in which the first prescription product was introduced in 2010.[14-15] The recent inclusion of this dosage form in the

***Corresponding Author:** Rajendra Kumar Jadi

Address: Department of Pharmaceutics, School of Pharmacy, Anurag University, Venkatapur, Medchal, Hyderabad – 500 088, Telangana State, India.

Email ✉**:** rajendrapharmacy@cvsr.ac.in

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

European Pharmacopeia (EP) accelerated research in the field during the last years.[16] OTF's are relatively new, thin polymeric films formulated to disintegrate or dissolve almost instantaneously when placed on the tongue without water.[17] A drug in an OTF is absorbed through the oral mucosa and enters the systemic circulation without undergoing the first-pass metabolism. This formulation is administered easily and provides fast pharmacological action, improving patient compliance and convenience.[18]

Sildenafil citrate (SC), a biopharmaceutical classification system (BCS) class I drug which is bitter and thus taste masking is a critical factor for patient acceptance.[19] SC is one of the most successful agents for the treatment of erectile dysfunction. SC has been successfully proved effective in curing erectile dysfunction. Patients may take from 0.5 to 4 h. before starting sexual activity.[20-25] It is in existing tablet form (i.e., Viagra) in the market. Still, it has some significant problems such as extensive first-pass metabolism, dyspepsia, and burning sensation in the gastrointestinal tract (GIT).

Extensive research work pays attention to flash release dosage forms, and films are widely acceptable in patients, too, because of the quick onset of action and user-friendliness. The present work emphasizes potential benefits, design, and development of robust, stable, innovative orally fast disintegrating thin films.

Materials and Methods

MATERIALS

Sildenafil citrate was received as a gift sample from Shilpa Health care, Hyderabad, Telangana, India), hydroxypropyl methylcellulose (HPMC) E4 was received from DOW chemical company, USA. Polyethylene glycol (PEG) 600 and glycerine were procured from Finar Chemicals Ltd, Ahmedabad, India. Sucralose was purchased from JK sucralose Inc., India. Rose oil and other excipients were either pharmaceutical or analytical grade.

METHODS

Drug Excipient Compatibility Study

Fourier transforms infrared spectroscopy (FTIR) studies were carried out to find the interaction between the pure drug (SC) and other excipients such as polymer and plasticizer. An FTIR (Bruker) was used for the analysis in the frequency range between 4000–400 cm^{-1} and with 4 cm^{-1} resolution.[26]

Construction of Sildenafil Citrate Calibration Curve

Accurately weighed, 100 mg of SC was transferred to a 100 mL volumetric flask and dissolved in de-ionized water. The medium was adjusted up to the mark (i.e., 100 mL) with de-ionized water to get 1000 µg/mL (i.e., stock solution) of the drug. The 1000 µg/mL was further diluted to get the SC concentrations in the range of 5 to 25 µg/mL in the buffer. These solutions scanned for the maximum absorbance using a UV-visible spectrophotometer (Shimadzu, Kyoto, Japan). The absorbance of all drug solutions estimated at a maximum wavelength (λ_{max}) 226 nm.[27]

Preparation of Sildenafil Citrate Oral Thin Films

In the formulation study, particular preference was given to selecting a suitable plasticizer and disintegration time to prepare the blank film, which could disintegrate fast and had a suitable elasticity and flexibility. The formulation with HPMC E4 was developed using 5, 10, 15, 20, 25, and 30% polymer in formulations. The drug and polymer mixed uniformly formulated as a film. Different concentrations of HPMC E4 were transferred into a 50 mL beaker and dissolved in de-ionized water and other excipients according to quantities (i.e., F1 to F6) shown in Table 1. By using a magnetic stirrer, mixed the formulations until they cloudy appearance. Keep the solution on an ice bath until the clear solution is received, then add SC to the above solution under continuous stirring. Initially, the cloudy nature is obtained and continues the mixing until getting a transparent and thick viscous solution. Add glycerine (1 mL), rose oil (1 mL), sucralose (2 mL) to the resultant mixture, and continue stirring until you get a clear solution. After that, the solution was placed on the ultrasonicator for 30 minutes to remove the air bubble from the formulation, then poured into molds with equal distribution, then dried by using a hot air oven at 40 ^{0}C for about 24 h. and cut to pieces of 2×2 cm (i.e., 4 cm^2).[28-29]

Characterization of Prepared Sildenafil Oral Films

The disintegration and mechanical properties of films are the essential qualities attributed to evaluating the OTF. Thickness was measured by micrometer at various random

Table 1: Formulation of SC-OTF

Formulation code	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
Drug	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
HPMC E4	5%	10%	15%	20%	25%	30%
PEG 600	5%	5%	5%	5%	5%	5%
Glycerine	2%	2%	2%	2%	2%	2%
Sucralose	2%	2%	2%	2%	2%	2%
Rose oil	1%	1%	1%	1%	1%	1%
De-ionized water	10	10	10	10	10	10

locations. Drug content was measured for uniformity using the developed calibration curve. The drug content was determined by UV visible spectrophotometric method. For this, 4 cm^2 strips from each batch were cut and dissolved in 50 mL of 6.8 pH phosphate buffer; then, the solution was filtered through What-man filter paper and dilute if necessary. The resulting solution was to measure spectrophotometrically at 226 nm.[30]

As the thickness of the film is directly related to the tensile strength, it is necessary to ascertain uniformity in the film's width. It can be measured by micrometer or screw gauge at different strategic locations.

For determining the consistency of drug content in the film, ten films were taken and assayed; the same procedure was repeated for the batches as above.

Three films were randomly selected and weighed individually, and then the mean weight and standard deviation of films were calculated for uniformity of weight. It is a desire that films should have nearly constant weight. It is helpful to ensure that a film contains the proper amount of excipients and drugs.

The surface pH was determined by a digital pH meter to investigate the possibility of any side effects *in vivo* and keep the surface pH as close to neutral as possible. As an acidic, an alkaline pH may irritate the oral mucosa. The film is slightly wet with the help of water. The procedures repeat in triplicate and calculate the average with standard deviation.

The percent moisture loss study was carried out to check the physical stability and integrity of the films. Place the known weight and pre-determined size of the film in desiccators containing anhydrous calcium chloride ($CaCl_2$) for three days. The films were removed and reweight, and the percent moisture loss of the films was measured using the following formula.

$$\text{Percent moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. The film should be free of physical imperfections was placed between two clamps. The applied load calculates it at rupture divided by the cross-sectional area of the strip as given in the equation below:

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness X Strip width}}$$

The folding endurance was repeatedly determined by wrapping a small strip of the film simultaneously until the number of times the film could be folded at the same place without cracking until it broke or folded up to 300 times was considered satisfactory to reveal excellent film properties.

In vitro disintegration time is the time when the film starts to break and is determined visually in a Petri dish containing 20 mL of 6.8 pH phosphate buffer with swirling every 10 seconds. All the results were shown in Table 2.

These studies were performed on all the film formulations (F1 to F6). Using an apparatus called Franz diffusion cell apparatus maintained a volume capacity of 15 mL used for the study. The film equivalent to 50 mg of SC placed in between the two compartments of an apparatus, and pipette 15 mL of 6.8 pH buffer (i.e., pH of saliva) added to the receptor compartment. The cell kept on a magnetic stirrer, and bead in the cell maintained at a specified speed RPM (i.e., revolution per minute), and medium maintained at a temperature of nearly 37°C ± 0.5°C. It withdrew 1 mL of sample each time at specified time intervals. Dilute with 6.8 pH phosphate buffer and measure the absorbance at 226 nm against the same medium.

Results and Discussion

Fourier Transformed Infrared Spectroscopy (FTIR)

FTIR spectra of pure SC shows significant peaks at 3327.94 cm^{-1} (N-H stretch-secondary amine), a peak at 1718.79 cm^{-1} (C=O stretch of amide), a peak at 1437.72 cm^{-1} (CH_3 group terminal), a peak at 1248.31 cm^{-1} (SO_2 stretching) and some of the minor peaks also observed. FTIR spectra of F4 formulation shows significant peaks at 3282.47 cm^{-1} (N-H stretch-secondary amine), a peak at 1678.96 cm^{-1} (C=O stretch of amide), a peak at 1441.83 cm^{-1} (CH_3 group terminal), a peak at 1343.46 cm^{-1} (SO_2 stretching), some of the additional minor peaks also observed. It was confirmed with the literature studies as well (ref) and shown in Fig. 1 and 2.

Construction of Sildenafil Citrate Calibration Curve

A standard concentration of SC prepared in 6.8pH phosphate buffer, and the absorbance's measured at 226 nm. Sildenafil was showed excellent linearity between 5 to 25 µg/ml with a correlation coefficient (R^2) = 0.998 and shown in Fig. 3

Three film strips of 4 cm^2 were cut from each film, estimated for uniformity of drug content using a UV visible

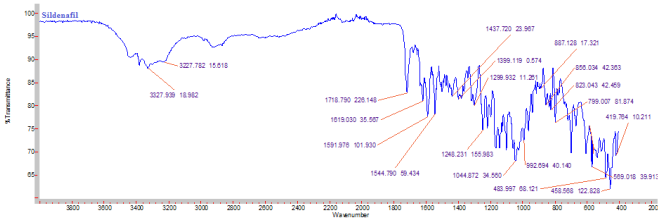

Fig. 1: FTIR spectra of a pure drug (i.e., Sildenafil)

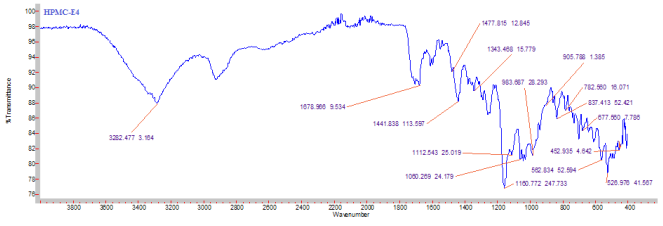

Fig. 2: FTIR spectra of optimized formulation (F4)

Table 2: Evaluation of Prepared SC-OTF

Formulation	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
Uniformity of weight (mg)	49.09 ± 0.05	48.06 ± 0.09	47.68 ± 0.01	49.82 ± 0.03	48.15 ± 0.92	46.98 ± 0.15
Film thickness (mm)	0.45 ± 0.002	0.51 ± 0.009	0.48 ± 0.006	0.46 ± 0.001	0.47 ± 0.004	0.52 ± 0.003
Drug content (%)	95.68 ± 0.09	101.02 ± 1.4	100.09 ± 0.9	98.64 ± 1.3	99.12 ± 0.5	96.83 ± 1.6
Surface pH measurement	6.69 ± 0.004	6.65 ± 0.071	6.67 ± 0.046	6.72 ± 0.063	6.65 ± 0.005	6.78 ± 0.049
Moisture loss (%)	1.9 ± 0.062	2.1 ± 0.046	2.0 ± 0.005	1.7 ± 1.002	1.8 ± 0.008	1.6 ± 0.001
Tensile strength (N/cm^2)	8.06 ± 0.12	5.37 ± 0.24	13.06 ± 0.90	9.10 ± 1.82	7.38 ± 1.64	11.03 ± 0.89
Folding endurance	98 ± 3.5	98 ± 2.1	100 ± 3.6	102 ± 1.5	99 ± 1.0	101 ± 2.4
Disintegration time (sec.)	32 ± 1.6	30 ± 0.4	31 ± 0.5	25 ± 1.3	28 ± 1.9	32 ± 1.7

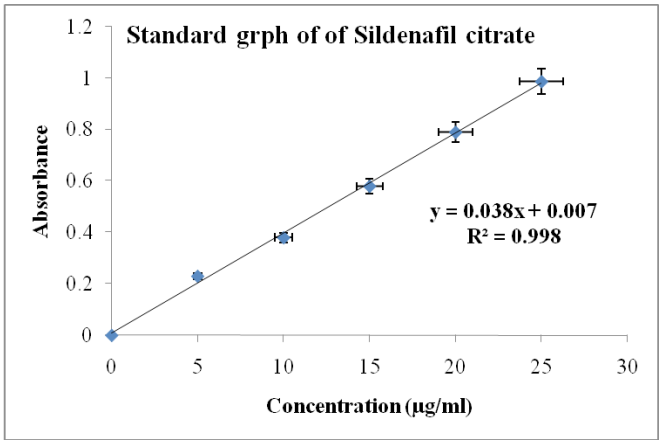

Fig. 3: Calibration curve of sildenafil citrate

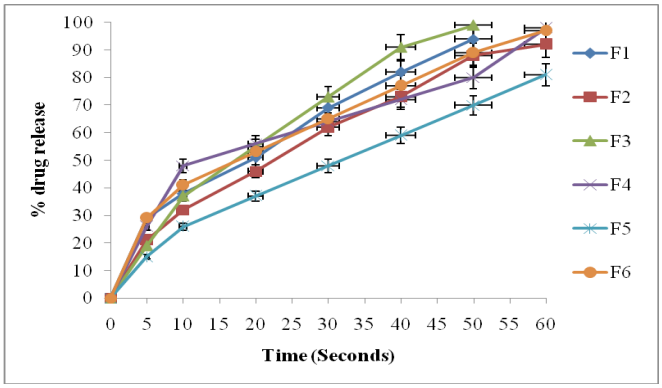

Fig. 4: *In vitro* drug release studies of sildenafil citrate oral thin films (SC-OTF)

spectrophotometric method. They observed that all the formulations were found within limits (46.98 ± 0.15 (F6) to 49.82 ± 0.03 (F4).

A screw gauge measured each sample's thickness at five locations, and the mean widths were calculated. As the formulations contain different polymers concentrations, the films' thickness was found in the range of 0.45 ± 0.002 mm (F1) to 0.52 ± 0.003 mm (F6).

The drug content was found to be low for F2 formulation and more for F4 formulation and found to be in the range of 98 ± 2.1 % to 102 ± 1.5 %, respectively.

The surface pH of all the selected formulations ranged from 6.65 ± 0.005 (F5) to 6.78 ± 0.049 (F6); since the film's surface pH around neutral pH, there will not be any irritation to the oral mucosal cavity.

The moisture loss of all the formulations was measured, ranging from 1.6 ± 0.001 (F6) to 2.1 ± 0.046 (F2), and the F6 formulation showed the lowest moisture loss than other formulations; hence, it is more stable.

The results revealed that all the films showed moderate to high tensile strength values ranged from 5.37 ± 0.24 (F2) to 13.06 ± 0.90 (F3). The results were given in Table 2.

The film was folded at the same place around 180° angles, till it broke and found between 98 ± 3.5 (F2) to 102 ± 1.5 (F4). The values indicate that the films have excellent flexibility. The formulation with a high concentration of polymers has a low amount of folding endurance because it offers a specific increase in the concentration of polymers decreases in folding endurance due to film thickness. More thickness lower will be folding endurance. The studies performed in a trice and calculated the average mean.

In-vitro disintegration time was found between 25 ± 1.3 sec. (F4) to 32 ± 1.7 sec. (F6) seconds. The formulation F4 had shown fast disintegration as compared to other formulations.

In vitro drug release studies were carried out using 6.8 pH phosphate buffer. The cumulative drug release of all the formulations (F1-F6) showed rapid solubility and quick release. The study was carried out for 60 seconds. And release rates of all prepared formulations were compared. The release profiles of all formulations were shown in Fig. 4.

The maximum release rate was observed in F4 formulation, with 98.68 ± 1.6% within the specified time. The formulation (F5) exhibited a slow drug release rate with 81 ± 0.3%, and the F3 formulation released 99.4 ± 0.8%. Based on various factors that play a vital role in regulating the release rates, including particle size, shape, drug wettability, and the particle's nature, i.e., amorphous or crystalline, a ratio of drug and polymer and solubilization of drug and polymer formulation F4 was optimized.

Conclusion

All the formulations show excellent physicochemical properties. It was observed that the polymer concentration

has a more significant impact on the property and release rate. The physicochemical properties of all the formulations were established to be within the prescribed official limits. This drug delivery platform is being under surveillance from both start-up and established pharmaceutical companies. The companies strive to design a wide range of thin films for oral, buccal, sublingual, ocular, and transdermal routes. Therefore, as an alternative to conventional dosage forms, polymeric thin films are expected to stand out as a dosage form to overcome the limitations of existing dosage forms. The film dosage form encounters several challenges during the phases of formulation development and manufacture. Such issues should be addressed to optimize the overall formulation even after transferring to large-scale manufacturing.

Acknowledgment

All authors have contributed equally.

References

1. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R and D costs. *J Health Economics,* 2016; 47:20-33.
2. Borges AF, Silva C, Coelho JF, Simões S. Oral films: current status and future perspectives: I-galenical development and quality attributes. J Control Release, 2015; 206:1-9.
3. Bhattarai M, Gupta AK. Fast dissolving oral films: a novel trend to oral drug delivery system. Sunsari Technical College J, 2015; 2:58-68.
4. Barnhart SD, Full AP, Moritz CM, inventors; Adhesives Research Inc, assignee. Rapidly disintegrating films for delivery of pharmaceutical or cosmetic agents. United States patent US 9,937,123. 2018.
5. Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: A new approach to oral drug delivery system.Int. J Pharm Invest, 2013; 3:67.
6. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: an innovative drug delivery system and dosage form. Int J ChemTech Res, 2010; 2:576-583.
7. Ghosh T, Ghosh A, Prasad D. A review on new generation orodispersible tablets and its future prospective. Int J Pharm Pharm Sci, 2011; 3:1-7.
8. Sharma D. Fast Disintegrating Tablets: A review on an emerging trend in novel oral drug delivery technology and new market opportunities. J Drug Delivery Ther, 2012; 2:74-86.
9. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bio-adhesive drug delivery—a promising option for orally less efficient drugs. J Control Release, 2006; 114:15-40.
10. Madhav NS, Shakya AK, Shakya P, Singh K. Oro-transmucosal drug delivery systems: a review. J Control Release, 2009; 140:2-11.
11. Batchelor HK, Fotaki N, Klein S. Paediatric oral bio-pharmaceutics: key considerations and current challenges. Adv Drug Delivery Rev, 2014; 73:102-126.
12. Kathpalia H, Gupte A. An introduction to fast dissolving oral thin film drug delivery systems: a review. Curr Drug Deliv, 2013; 10:667-684.
13. Geetha A, Rajendra Kumar J, Pavani U, Kalyani CH, Design and *in vivo* characterization of amlodipine besylate orodispersible tablets. J Global Trends Pharm Sci, 2017; 8:4325- 4336.
14. Karki S, Kim H, Na SJ, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. Asian J Pharm Sci, 2016; 11:559-574.
15. Trofimiuk M, Wasilewska K, Winnicka K. How to modify drug release in paediatric dosage forms? Novel technologies and modern approaches with regard to children's population. Int J Mol Sci, 2019; 20:3200.
16. Hoffmann EM, Breitenbach A, Breitkreutz J. Advances in orodispersible films for drug delivery. Expert Opin Drug Deliv, 2011; 8:299-316.
17. Nagaraju T, Gowthami R, Rajashekar M, Sandeep S, Mallesham M, Sathish D, Shravan Kumar Y. Comprehensive review on oral disintegrating films. Curr Drug Deliv, 2013; 10:96-108.
18. Dixit RP, Puthli SP. Oral strip technology: overview and future potential. J Control Release, 2009; 139:94-107.
19. Han X, Zhang S, Chai Z, Dong Y, He W, Yin L, Yang L, Qin C. *In vitro* and *in vivo* evaluation of the taste-masking efficiency of Amberlite IRP88 as drug carries in chewable tablets. J Drug Deliv Sci Technol, 2019; 49:547-555.
20. Carson CC. Sildenafil: a 4-year update in the treatment of 20 million erectile dysfunction patients. Curr Urol Reports, 2003; 4:488-496.
21. Lue TF. Erectile dysfunction. New England journal of medicine. 2000; 342:1802-1813.
22. Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction. Drugs, 2005; 65:1621-1650.
23. Porst H, Burnett A, Brock G, Ghanem H, Giuliano F, Glina S, Hellstrom W, Martin-Morales A, Salonia A, Sharlip I. SOP conservative (medical and mechanical) treatment of erectile dysfunction. The J Sex Med, 2013; 10:130-171.
24. Hatzimouratidis K, Hatzichristou DG. Looking to the future for erectile dysfunction therapies. Drugs, 2008; 68:231-250.
25. Aversa A, Bruzziches R, Pili M, Spera G. Phosphodiesterase 5 inhibitors in the treatment of erectile dysfunction. Curr Pharm Des, 2006; 12:3467-3484.
26. Kamenov ZA. Comparison of the first intake of vardenafil and tadalafil in patients with diabetic neuropathy and diabetic erectile dysfunction. The J Sex Med, 2011; 8:851-864.
27. Ghasemian E, Vatanara A, Najafabadi AR, Rouini MR, Gilani K, Darabi M. Preparation, characterization and optimization of sildenafil citrate loaded PLGA nanoparticles by statistical factorial design. DARU J Pharm Sci, 2013; 21:1-10.
28. Hosny KM, El-Say KM, Ahmed OA. Optimized sildenafil citrate fast orodissolvable film: a promising formula for overcoming the barriers hindering erectile dysfunction treatment. Drug delivery, 2016; 23:355-361.
29. Patel H, Panchal M, Shah S, Vadalia KR. Formulation and evaluation of transdermal gel of sildenafil citrate. Int J Pharm Res Allied Sci, 2012; 1:103-118.
30. Elshafeey AH, Bendas ER, Mohamed OH. Intranasal microemulsion of sildenafil citrate: *in vitro* evaluation and *in vivo* pharmacokinetic study in rabbits. AAPS Pharm Sci Tech, 2009; 10:361-367.

HOW TO CITE THIS ARTICLE: Yadagiri DJ, Kuchkuntla M, Konatham M, Gorle MT, Bakshi V, Jadi RK. Development and Characterization of Sildenafil Citrate Oral Thin Films. Int. J. Pharm. Sci. Drug Res. 2021;13(2):147-151. **DOI:** 10.25004/IJPSDR.2021.130205