IJBPAS, May, 2023, 12(5): 2228-2239

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION, OPTIMIZATION AND EVALUATION OF ORAL DISSOLVING FILMS OF TADALAFIL SOLID DISPERSION

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Received 10th June 2022; Revised 15th July 2022; Accepted 26th Sept. 2022; Available online 1st May 2023

https://doi.org/10.31032/IJBPAS/2023/12.5.7141

ABSTRACT

The objective of the present study was to develop solid dispersion of Tadalafil with HPMC E3 and formulate an oral dissolving film for the treatment of hypertension and erectile dysfunction with enhanced disintegration, morphological properties, and optimal mechanical strength. Hydroxy propyl methyl cellulose E50 was used as a hydrophilic film-forming polymer and propylene glycol as a plasticizer. The solvent casting technique was used for preparing the films. Parameters such as In- vitro disintegrating time, tensile strength, content uniformity, folding strength, swelling index, and in vitro drug release were evaluated. 3^2 factorial designs were used to optimize the amount of polymer and plasticizer. In vitro dissolution studies showed that 99% of Tadalafil was released within 10 minutes with a mean disintegration time of 20 seconds in the F9 formulation. Polynomial regression analyses were done to study the effect of plasticizer and polymer on disintegrating time, folding strength, and in vitro drug release. FTIR spectroscopy was used to determine drug-excipient interactions. SEM study showed a smooth surface of the optimized formulation.

Keywords: Tadalafil, solid dispersion, hypertension, oral dissolving films, solvent casting technique

INTRODUCTION:

Drug absorption and therapeutic efficacy are influenced by solubility, which is an important physicochemical factor. Poor water solubility can hinder formulation development. The main reason for the poor bioavailability of the drug is its low solubility in aqueous media **[1]**. Today, a large number of hydrophilic enhancers are being studied that have shown significant results in improving solubility. One of the most promising and effective techniques for improving solubility is solid dispersion formulation **[2]**.

Among the different routes of administration, the oral route is preferred. Almost 90% of drugs are taken orally for the treatment of various disorders and diseases, as it is considered the safest, most convenient, and economical method of dosing and is more compliant with the patients **[3, 4]**. The drug is dissolved or swallowed, then enters the systemic circulation to produce the desired effect **[5, 6]**. Tadalafil is a selective phosphodiesterase-5 inhibitor used in the treatment of erectile dysfunction (ED), pulmonary arterial hypertension (PAH), and benign prostatic hyperplasia. Tadalafil works to treat erectile dysfunction by increasing sexual stimulation-dependent smooth muscle relaxation in the penis, allowing the corpus cavernosum to fill with blood to produce an erection. The relaxation of smooth muscle in the pulmonary vasculature helps induce vasodilatation in the PAH, which lowers the blood pressure in the pulmonary artery. Tadalafil has a t max of 0.5 to 6 hours with a median of 2 hours in healthy adults. The mean half-life of tadalafil is 15-17.5 hours in healthy adults **[7-9]**. The main objective of the study was to improve the solubility of tadalafil using a hydrophilic carrier by solid dispersion and to prepare a rapidly dissolving oral film.

PREPARATION OF SOLID DISPERSIONS:

Materials:

Tadalafil, HPMC E 3, HPMC E50, Propylene glycol, Citric Acid, and Aspartame were procured from yarrow chemicals.

Solvent evaporation method:

Solid dispersion of tadalafil was prepared by a solvent evaporation method using HPMC E 3 in different ratios (1:1, 1:2, 1:3, and 1:4 of drug: polymer) Table 1. A small amount of ethanol was used to dissolve the required amount of tadalafil and HPMC E 3 by continuous stirring with a magnetic stirrer at room temperature. The solvent was completely removed under reduced pressure by a rotary evaporator maintained at 40 °C. The dispersed solids formed were then dried in an oven at 40 °C for 24 h. All the

dispersed solids obtained were scraped, pulverized in a mortar, and sieved through a 60 mesh sieve. All solid dispersions were then stored in amber glass vials and kept in a desiccator until further use **[10]**.

Preparation of buccal films:

Films were prepared by solvent casting technique. The required amount of polymer was accurately weighed and left to soak in water for 1 h until a homogeneous viscous solution was formed. Other ingredients, propylene glycol, aspartame, and citric acid were added to the polymer solution and the mixture was sonicated to remove trapped air. The solid drug dispersion was dissolved in the polymer mixture and the solution was mixed using a vortex mixer. The solution was left aside until a clear solution was obtained. The solution was then molded into a film on a Petri dish and left to dry for 24 h in a hot-air oven at 45 ºC. The optimization was performed through a 3^2 factorial design **(Table 1)**. The compositions of the different oral soluble films were given in **Table 2**.

Statistical Design:

3^2 full factorial design was used to optimize the polymer and plasticizer ratios. In this design, each factor was evaluated at 3 levels, and empirical tests were performed in 9 possible combinations. The amount of HPMC E50 polymer (X1) and the amount of propylene glycol plasticizer (X2) were selected as independent variables and each factor was studied at -1, 0, and 1. Disintegration time and percentage of drug release were chosen as dependent variables. **Table 1** gives the respective levels of independent variables used and the full layout of the factorial plan of the variables.

Table 1: Experimental Design of polymer HPMC E50 (X1) and plasticizer propylene glycol (X2)

Factor	Level used		
Independent Variables	Low (-1)	Medium (0)	High (+1)
X2 = Concentration of polymer HPMC E50	50mg	100 mg	150 mg
X2 = Concentration of plasticizer Propylene Glycol	0.5 ml	1 ml	1.5ml

Table 2: Formulation development of oral dissolving films of Tadalafil

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tadalafil :HPMC E 3 SD (1:4)	100	100	100	100	100	100	100	100	100
HPMC E50	50	50	50	100	100	100	150	150	150
Propylene glycol	0.5	1	1.5	0.5	1	1.5	0.5	1	1.5
Citric Acid	20	20	20	20	20	20	20	20	20
Aspartame	15	15	15	15	15	15	15	15	15
Water	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml

EVALUATION OF SOLID DISPERSIONS [11-14]:

Practical Yield Percentage:

The Practical Yield Percentage was calculated to know the efficiency of the solid dispersion manufacturing process and help you choose the proper manufacturing process. Solid dispersions of tadalafil containing HPMC E3 were collected and weighed to determine actual yields.

Drug content:

A solid dispersion containing an equal amount of 10 mg tadalafil was accurately weighed and dissolved in 10 ml phosphate buffer 6.8. Then 2.5 mL aliquot was removed and diluted to 25 mL using phosphate buffer. Samples were filtered through Whatman filter paper, diluted, and analyzed spectrophotometrically at 285 nm UV. The drug content was calculated from a calibration curve prepared in the concentration range of 2-10 µg / ml.

Solubility study:

Excess tadalafil and solid dispersion were placed in a 25 mL Erlenmeyer flask containing 6.8 phosphate buffer, marked separately, and the sample was rotated in a shaking incubator at 25 ° C for 24 hours and filtered using Whatman filter paper. The filtrate was appropriately diluted with phosphate buffer 6.8 and spectrophotometrically analyzed at 285 nm using a UV / VIS spectrophotometer for detection of tadalafil.

Evaluation test:

Morphological properties of the manufactured film, homogeneity, color, transparency, surface, and other properties were visually tested. All formulations were wrapped in butter paper, then in aluminum foil, and stored at room temperature (25 ° C) at a relative humidity of 65 ± 5% Rh.

Thickness Assessment:

Film thickness was measured using a calibrated digital caliper. Thickness was assessed in 5 different locations.

Weight variation:

This test was performed by cutting 2 x 2 cm film from cast film at three different locations. The weight of each film was measured individually using an electronic balance. Three measurements were averaged for weight variability studies.

Folding Endurance:

The folding endurance of a film was measured manually by firmly holding and folding the film repeatedly through the middle. The number of folds in the same place, required to produce a crack in the film was noted as the value of folding endurance.

pH assessment:

Surface pH is determined using a pH meter. The film were allowed to swell by keeping it in contact with 1 ml of distilled water at room temperature. The pH was recorded by placing an electrode in contact with the surface of the film, letting it equilibrate for 1 min, and then pH was recorded.

Tensile Strength:

The tensile strength of the film was evaluated using the TAXT Plus Texture Analyzer (Structural Technologies, Scarsdale, NY) and the TA-96B Small Tensile Clamp for each process. The 2 × 2 cm films without air bubbles or physical defects were held vertically in the pulley on the texture analyzer. The test was carried out at an initial distance of 6mm from the handle to both sides at a cutting head speed of 2mm/s until the film broke.

In-vitro disintegration time:

The in-vitro disintegration time of the film was determined using a Petri dish containing 25 ml of pH 6.8 phosphate buffer at 37.0 ± 0, 5 °C. The time at which the film begins to disintegrate is recorded.

Percent moisture loss:

The film was cut into 2 × 2 cm and accurately weighed and stored in a desiccator containing molten anhydrous calcium chloride. After 72 h, the membranes were removed and reweighed. The decrease in the weight of the film causes the loss of moisture. The moisture loss percentage was calculated using the following formula:

Moisture loss % = (Initial mass - final mass) / (Initial mass) × 100.

Moisture absorption:

The films were placed for one day in a desiccator containing a saturated solution of calcium chloride solution (75% relative humidity) at ambient temperature. An increase in the weight of the film was observed due to moisture absorption. The % moisture gain of the film is calculated by the following formula:

$$\%\ \textbf{moisture absorption} = \frac{\textbf{final weight} - \textbf{initial weight}}{\textbf{initial weight}} \times 100$$

Swelling index:

The films were placed on the plate containing 2% jelly. The increased mass of the films was recorded until the mass remained constant.

Drug content:

The drug content of all formulations was determined by UV spectrophotometry. For this 2x 2 cm film was cut out and dissolved in 100 ml of pH 6.8 phosphate buffer. The solution was filtered and the absorbance was recorded at 285 nm. The drug concentration was calculated from the drug standard curve.

***In-vitro* Drug Release Study:**

The *in-vitro* dissolution test was carried out in a USP I basket dissolution apparatus. The

films of appropriate size (2 × 2 cm2) were cut and placed in the basket. The dissolution medium consisted of 900 ml freshly prepared phosphate buffer pH 6.8, maintained at 37 ± 0.5 ºC, and stirred at 100 rpm. 5 ml of samples were withdrawn at predetermined time intervals and replaced with fresh buffer. The samples were subjected to UV analysis at 285 nm (λ max).

Surface Morphology Study:

The surface morphological properties of prepared films were investigated using a scanning electron microscope (Hitachi S-3000). The samples were mounted on an aluminum stub by coating with a thin layer of gold at approximately 20 nm in a vacuum. The scanning electron microscope was operated on an accelerated voltage and microphotographs were taken at appropriate magnifications.

Drug-Excipient Interaction Studies using FTIR Spectral Analysis*:*

The FTIR spectra of pure drug, physical mixture, and formulation were recorded using an FTIR spectrophotometer (Agilent Cary 630) over a range of 4000-500 cm-1.

RESULTS AND DISCUSSION:

Solubility of pure drug and solid dispersion of drug with different ratios of HPMC E 3 was done and the highest solubility was found in ratio 1:4. Percentage yield and drug content were high in 1:4 ratio **(Table 3)**.

Morphological properties of ODF:

Films were stored at room temperature (25 °C) with a relative humidity of about 65 ± 5% Rh are transparent and have a smooth surface texture.

Thickness Assessment:

It is essential to check the uniformity of the film thickness as this is directly related to the accuracy of the dose distribution in the film. The thickness of the film gradually increased with increasing amounts of polymer and was found in the range of 0.09 ± 0.02 to 0.31 ± 0.07 mm **(Table 4)**.

Weight Variation:

All batches were of uniform weight and there were no significant differences in the weights of the individual formulations from the mean. The weight change was found to range from 18 ± 0.04 to 29 ± 0.12 mg for the prepared films **(Table 4)**.

Folding Strength:

The folding strength of different ODFs ranges from 156 to 361 as shown in **(Table 4)**. The folding strength of the film increased with increasing concentrations of HPMC and propylene glycol. This could be due to the higher polymer elasticity at higher HPMC levels in the film, and as the plasticizer concentration increased, the film flexibility

also increased which increase folding strength.

In-vitro disintegration time studies of films:

The disintegration times in all formulations ranged from 15 ± 1.0 to 30 ± 4.0 s. It was observed that as the polymer concentration increased, the thickness of the film increased, and thus the time for the film to disintegrate increased. The rapid disintegration of ODFs due to the increase in the plasticizer concentration which is due to the rapid water absorption of the hydrophilic plasticizer, followed by the immediate swelling and breaking of the H-bonds **(Table 4)**.

Tensile Strength:

It was observed that as the polymer concentration increased, so did the tensile strength increased. F9 shows the maximum tensile strength and F1 is the smallest **(Table 4)**. This may be due to the presence of plasticizers that give flexibility to the polymer due to the formation of strong hydrogen bonds between the polymer and the plasticizer.

Evaluation of pH:

The surface pH of the ODF was determined to investigate the possible adverse effects caused by pH changes in living organisms, as acidic or alkaline pH can irritate the oral mucosa. The surface pH of the prepared ODFs ranged from 6.2 ± 0.10 to 6.9 ± 0.32. **Table 5** indicates that the prepared ODFs are in the neutral pH range and will not cause irritation after being placed in the oral cavity.

Percent Moisture Loss:

Percent moisture loss was calculated to verify the integrity of the membrane in the dry state. The percentage of moisture loss is inversely proportional to the HPMC concentration in the membrane. In addition, as the polymer and plasticizer concentrations decrease, the moisture loss rate increases. It is important to note that these hydrophilic excipients tend to retain moisture and their reduced levels in the film may lead to higher moisture loss **(Table 5)**.

Percent Moisture Absorbed:

The percent moisture absorbed test is performed to verify the physical stability or integrity of the film in wet conditions. The hygroscopicity of the film was determined by exposing the membrane to an environment with 75% relative humidity (saturated calcium chloride solution) at room temperature for 1 day. Among all formulations, the formulation containing higher concentrations of HPMC and propylene glycol showed higher hygroscopicity than the formulation containing lower concentrations of HPMC **(Table 5)**. Since propylene glycol and

HPMC are both hydrophilic, they tend to have increased hygroscopicity.

Swelling Index:

The purpose of the swelling index measurement is to determine the ability of the hydrophilic polymers used in the formulation to absorb water during hydration. The rate and extent of hydration and membrane swelling also affect drug release from the membrane. A pre-weighed film is placed on a 2% agar plate. The increased mass of the membrane was recorded until the mass remained constant. This study showed that the degree of swelling was proportional to the concentration of the hydrophilic polymer and the hydrophilic plasticizer **(Table 5)**.

Uniformity of drug content:

Drug content testing is performed uniformly to ensure that the drug is distributed evenly. Consistency in content was achieved for all formulations. The results indicated that in all formulations there was good homogeneity in drug content, ranging between 97 and 99% **(Table 5)**.

In vitro dissolution study:

Data show that the percentage of drug release at the end of 5 minutes ranges from 98-85% for formulations F1-F9. All formulations have the same basic form of release, i.e. rapid release within the first few minutes, followed by a relatively slow release and finally reaching a steady state within about 10 minutes at F1 to F3. and 15 minutes at F4 to F9 except at F7. The release rate during the initial rapid release phase was slightly different in different formulations due to different polymer and plasticizer concentrations in each formulation. Formula F9 shows a maximum percentage of drug release of 99%. This may be due to the higher rate and degree of swelling of the larger ratio of hydrophilic polymers and plasticizers. Formula F9 shows maximum drug release along with other properties such as tensile strength and folding strength **(Figure 1)**.

Statistical Analysis:

The relationship between the independent variables and the response variables was estimated by including the results in the statistical evaluation. MS Excel 2007 software was used to perform linear regressions to identify control factors that significantly influenced the responses. Polynomial equations can be used to conclude after considering the magnitude of the coefficient and the mathematical sign it bears (ie positive or negative). From the results, it was observed that as the polymer concentration increased, % drug release decreased, disintegration time and folding

endurance increased. As the plasticizer concentration increased, the disintegration time decreased and the % drug release, and folding endurance increased **(Table 6)**.

Drug - Excipient Interaction Studies: FTIR studies were used to study interaction if any between the drug & excipients. The physical mixture of drug and excipients exhibited peaks similar indicating that there was no interaction between the drug and the selected excipients **(Figures 2 and 3)**.

Surface Morphology Study by SEM: SEM studies were performed to assess the surface morphology of the prepared films. ODFs showed a smooth surface without any scratches and transverse striations indicating that the drug is uniformly distributed and no crystals of the drug were observed in the prepared films **(Figure 4)**.

Table 3: Preparation of different ratios of solid dispersions of Tadalafil + HPMC E3

Sl. No	Solid dispersion mixture	Ratio	Solubility in Phosphate buffer pH 6.8 µg/ml	%Yield	Drug content
1	Pure drug Tadalafil		0.22		
2	Tadalafil + HPMC E3	1:1	1.177	86	50.6
3		1:2	1.588	96	79.4
4		1:3	1.61	101	80.5
5		1:4	4.03	102	100

Table 4: Evaluation of Physical Parameters of ODFs of Tadalafil solid dispersion

Formulation codes	Physical Parameters				
	Weight variation	Folding endurance	Thickness	Disintegration Time (secs)	Tensile strength
F1	18±0.04	156	0.09±0.02	12±2.0	0.321±0.04
F2	18.5±0.06	204	0.12±0.06	13±1.0	0.344±0.02
F3	19±0.02	248	0.15±0.09	11±2.0	0.382±0.01
F4	23±0.04	264	0.15±0.03	20±1.0	0.419±0.05
F5	23.5±0.02	291	0.18±0.04	17±3.0	0.454±0.06
F6	24±0.08	302	0.20±0.08	15±3.0	0.482±0.02
F7	28±0.06	315	0.24±0.03	30±3.0	0.504±0.03
F8	28.5±0.09	324	0.27±0.05	25±3.0	0.543±0.04
F9	29±0.12	361	0.31±0.07	20±4.0	0.564±0.02

Table 5: Evaluation of Chemical Parameters of ODFs of Tadalafil solid dispersion

Formulation codes	Chemical Parameters				
	Drug content	pH	Swelling index	%Moisture loss	% Moisture absorption
F1	98	6.2±0.10	42%±1.08	8.22±0.43	5.51±0.15
F2	97	6.3±0.20	44%±2.16	7.76±0.22	5.71±0.34
F3	99	6.1±0.14	45%±1.15	8.22±0.43	5.83±0.55
F4	97	6.3±0.25	64%±2.13	5.97±0.31	7.60±0.26
F5	99	6.5±0.17	68%±1.15	5.65±0.38	7.68±0.47
F6	98	6.4±0.28	70%±3.12	4.97±0.57	7.85±0.50
F7	98	6.6±0.16	89%±1.26	2.85±0.17	10.13±0.46
F8	99	6.8±0.11	92%±3.23	2.62±0.36	10.39±0.73
F9	97	6.9±0.32	93%±1.28	1.59±0.23	10.60±0.65

Table 6: Statistical Analysis of dependent and independent parameters

Statistical Analysis		Disintegration Time	Folding endurance	Drug Release
Regression Statistics	Multiple R	0.972028	0.979572	0.984191
	R Square	0.944838	0.959562	0.968632
ANOVA	F	42.82096	59.32317	77.19848
	Significance F	0.000715	0.000329	0.000174
Polynomial equations		y = -0.333x2 - 2.666x + 18.33	y = 1.333x2 + 29.33x + 273	y = 0.333x2 + 3.333x + 89

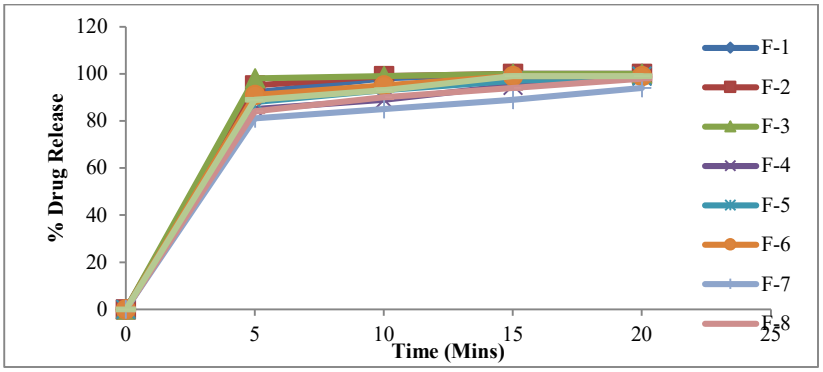

Figure 1: Dissolution profile of tadalafil oral dissolving films

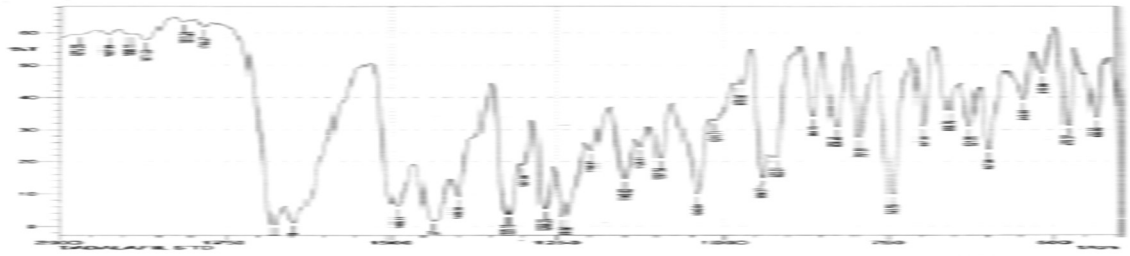

Figure 2: FTIR Spectra of pure Tadalafil

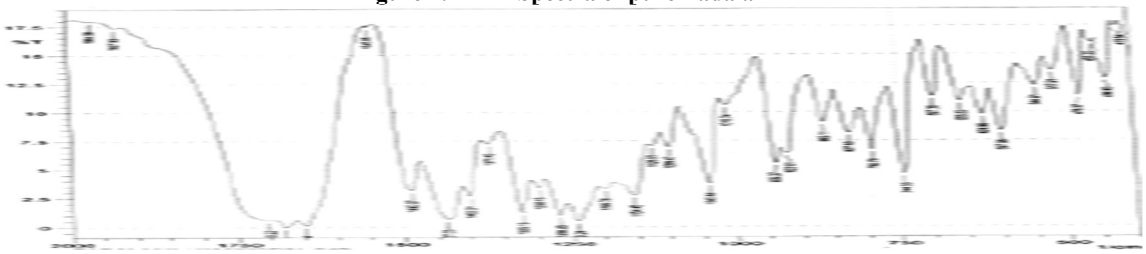

Figure 3: FTIR Spectra of Tadalafil optimized formulation

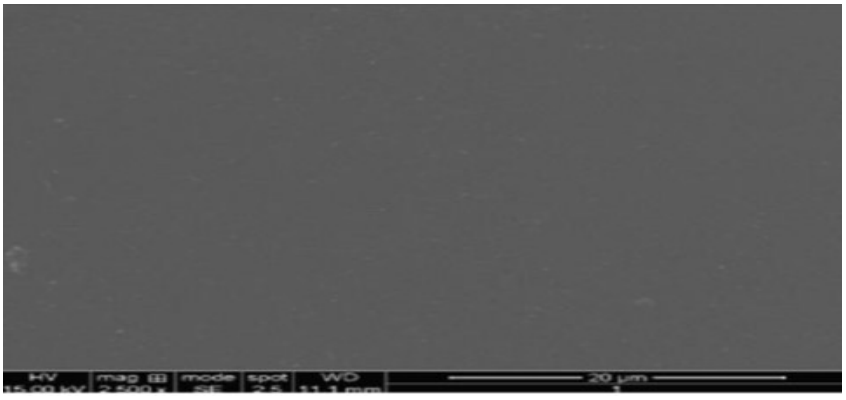

Figure 4: SEM study of optimized formulation

CONCLUSION

The present study revealed that the ODFs of tadalafil could be successfully prepared by solvent casting technique to obtain better therapeutic efficiency with increased bioavailability and improve patient compliance. From among the different concentrations of polymer HPMC E 50 (1.5 ratios), F9 showed minimum *in-vitro* disintegration time and maximum tensile strength, and faster drug release when compared to other concentrations of polymers and plasticizers. Further, it was concluded that amongst all the formulations F9 formulation was found to be having satisfactory physicochemical and mechanical properties. Hence, the present study confirms the enormous potential of ODFs for improving patient convenience and compliance, by hastening the onset of action and circumventing hepatic first-pass metabolism, especially in geriatric patients.

ACKNOWLEDGEMENT: We thank M. Chinna Eswaraiah, principal of Anurag Pharmacy College, and the department of pharmaceutical sciences for their support and facility to carry out the research.

CONFLICT OF INTEREST: Authors of this publication declare no conflict of interest.

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