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ORIGINAL ARTICLE

Formulation and Evaluation of Oral Thin Films of Tadalafil

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ABSTRACT
The current study aimed to optimise the nanosuspension of tadalafil and stabilise it in an oral thin film formulation. Nanosuspension laden oral thin films(OTFs) were created using a solvent casting process to address the problem of nanosuspension stability and low bioavailability of tadalafil. Preparing oral thin films is straightforward, and the process is easily scalable. The thickness, percent of moisture absorption and loss, surface pH, weight fluctuation, folding endurance, drug content, disintegration time, in vitro drug release, and stability of nanosuspension-loaded OTFs were measured. After studying their stability for three months, the resulting OTFs exhibited that the particle size-range was preserved. All tadalafil oral thin films had a markedly improved dissolving rate compared to the commercially available oral formulation. To sum up, oral thin films may be able to stabilise nano-suspension and enhance medication release.
Keywords: *Oral thin film, tadalafil, solvent casting method, nanosuspension, stabilization.*

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INTRODUCTION

Due to great patient's compliance & adaptability in formulation, oral medication delivery is the most appropriate, cost-effective, and common route for drug delivery. Many of the medicines have low water solubility and high oral bioavailability [1-2]. Despite the possibility of increased aqueous solubility and dissolution rate, the nanosuspension presents a stability problem [3-4]. The oral thin film (OTF) is the innovative formulation [3, 5]. OTFs are about the postal-stamp in morphology. Oral thin films are stable against changes in pH and GI enzymes because they quickly dissolve in oral cavity [3-6]. Oral thin films may help stabilise the nanosuspension by allowing for more controlled medication delivery. Nanoparticles are less likely to clump together in the film because of its high viscosity, and the film's stability is improved by drying [7]. Without altering the drug's molecular structure, such a changed formulation is crucial for producing rapid start of action in critical situations [7-8]. BCS class II phosphodiesterase drug tadalafil [9, 10]. It has a great log-P value, useful in developing nanosuspensions, and a poor aqueous solubility [9, 10]. Present work was to create tadalafil oral thin films that were filled with a stable nanosuspension.

MATERIALS AND METHODS

MATERIALS

Cipla Pvt. Ltd. Goa generously provided tadalafil; poloxamer 188 [Pluronic F68], and HPMC K4M [Hydroxypropyl Methylcellulose K4M] was purchased from Loba Chemie Pvt Ltd. All additional compounds employed possess great quality.

METHODS

Preparation and optimization of tadalafil nanosuspension

The nanoprecipitation method was used to create tadalafil-loaded nanosuspensions. Sonication was used to dissolve precisely measured amounts of tadalafil and HPMC K4M in methanol (co-solvent). A syringe

[26 G] was used to gradually inject the organic phase of the medication into the distilled water containing poloxamer 188 with a speed of 0.5 ml per min. After an hour of mechanical stirring at set rates, we sonicated the mixture for 15 minutes. Zeta potential, particle size distribution, and drug entrapment efficiency were all taken into account during development of the ideal tadalafil nanosuspension.

Experimental Design

To verify the effect of formulation parameters on dependent variables of tadalafil nanosuspension loaded oral thin films, preliminary selection experiments were conducted (OTFs). The two most crucial formulation factors were determined to be HPMC K4M concentration and glycerin concentration. A 3^2 factorial design with three levels (-1, 0, and +1) was utilised to estimate and optimise the selected formulation parameters via the design of experiment. No changes were made to the batch size or medicine concentration.

Preparation of films

Solvent casting was used to create OTFs of tadalafil [11-13]. The optimised nanosuspension (equal to 100 mg of tadalafil) was mixed with HPMC K4M and glycerol using a magnetic stirrer for 40 minutes. The doctor used his blade to cast the resulting slurry onto the glass plate. They were dried in a hot air oven for 2.5 hours at 40°C, and then the films were cut away with a sharp blade. We used aluminium foil and cut it to size to store the films. The same method and ingredients were used to create oral thin films (TOTF) with pure tadalafil powder.

Optimization of formulations

Nanosuspensions of tadalafil were optimised by adjusting their particle-size, particle distribution index, zeta potential & entrapment efficiency. Nanoparticle Analyzer SZ-100 equipped with a Zetasizer measured particle size and zeta potential (Horiba Scientific, Japan).

Thickness

A digital-micrometer was used to determine the film's thickness. Ten distinct film's average thicknesses were measured.

The % moisture absorption & loss test

A % moisture absorption test was used to evaluate the film's physical stability in humid conditions. The pre-weighed films were then subjected to 79.5% RH [saturated AlCl3 solution] in a desiccator for 72 hours at room temperature [13-15]. By following equation the moisture absorption capacity was calculated [14-17]:

$$\text{Percentage moisture absorption} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

The film's durability was evaluated after being stored in anhydrous CaCl2 in desiccators for 72 hours. By following equation the percentage moisture loss was calculated:

$$\text{Percentage moisture loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight.}} \times 100$$

Percentage drug content

Six films were chosen at random from each batch, then weighed separately and sonicated in 10ml of methanol for two hours. The resulting solution was filtered, diluted with the appropriate amount of methanol, and then measured using a Shimadzu UV-Spectrophotometer at 284nm in comparison to a blank of methanol. The mean amount of drugs was determined.

Surface pH

Researchers evaluated the surface pH of oral thin films [15-19] due to concerns that either an alkaline or acidic pH could irritate the mouth mucosa. Aim for utter objectivity. A combination pH electrode was kept at film moistened layer to measure its pH.

Folding Endurance

The longevity of folding was tested on a sample of strips chosen at random. Folding endurance refers to the count of a strip may be bent at same spot before snapping in half [14-18].

Weight Variation

A test for weight fluctuation was conducted by weighing each of 10 randomly chosen films and averaging the results.

In-vitro disintegration time

A Petri dish containing 10 ml of water was used, and the film was placed in its exact center. The amount of time needed for the film to disintegrate into its component parts was estimated.

In-vitro drug release studies

100 cc of phosphate buffer [pH 6.8] was used as the dissolving medium in the USP Type II equipment for the drug release tests, which were conducted at 37 ± 0.5°C. There were also modifications made to the experiment's other variables, such as the stirring speed [100rpm], the aliquot size [2 ml], and the sampling interval [2, 4, 6, 8, 10 min]. A Shimadzu UV Spectrophotometer 1800 set at 284nm was used to measure the amount of ultraviolet light emitted by the materials under test.

Comparative physico mechanical characterization of Tadalafil OTF and Nanosuspension loaded OTF1

The formulations TOTF and optimised OTF1 were compared for their physicochemical properties.

Stability Studies

The optimised formulation [OTF1] was tested in accordance with ICH requirements for 3 months at [40°C ± 2°C] and [75% ± 5%] RH [19]. The films were tested at regular intervals to determine their physical quality, disintegration rate, drug content, and in vitro drug release.

Statistical Analysis

The statistical readings recorded as mean and standard deviation using Microsoft Excel [2010] programme. Using Design Expert software, one-way ANOVA was used to examine the data.

RESULTS AND DISCUSSION

Experimental Design

Regression analysis was performed on the experimental data, and the following statistically significant [$p<0.05$] equations with Adj-R2 values in the range of 0.95-0.97 were generated [Table 1]. Model equations provided the best fit to the data, and the lack of fit values was statistically insignificant [$p> 0.05$]. The positive sign in the equations indicates synergism, while the negative sign indicates antagonism [20–22].

Drug content = $91.79 - 1.11 \times X_1 + 0.74 \times X_2 + 1.42\, X_1X_2$ (Surface 2FI model) ..... (1)

Drug release = $92.55 - 2.35 \times X1 - 0.62 \times X2 - 0.09\, X_1X_2 - 0.66\, X_1^2 + 2.49\, X_2^2$ (Quadratic Model) ..... (2)

Disintegration time = $33.97 + 6.22 \times X1 + 0.61 \times X2 + 1.48 \times X_1X_2$ (Surface 2FI model) ..... (3)

$X1$ = Conc. of HPMC K4M & $X2$ =Conc. of Glycerin

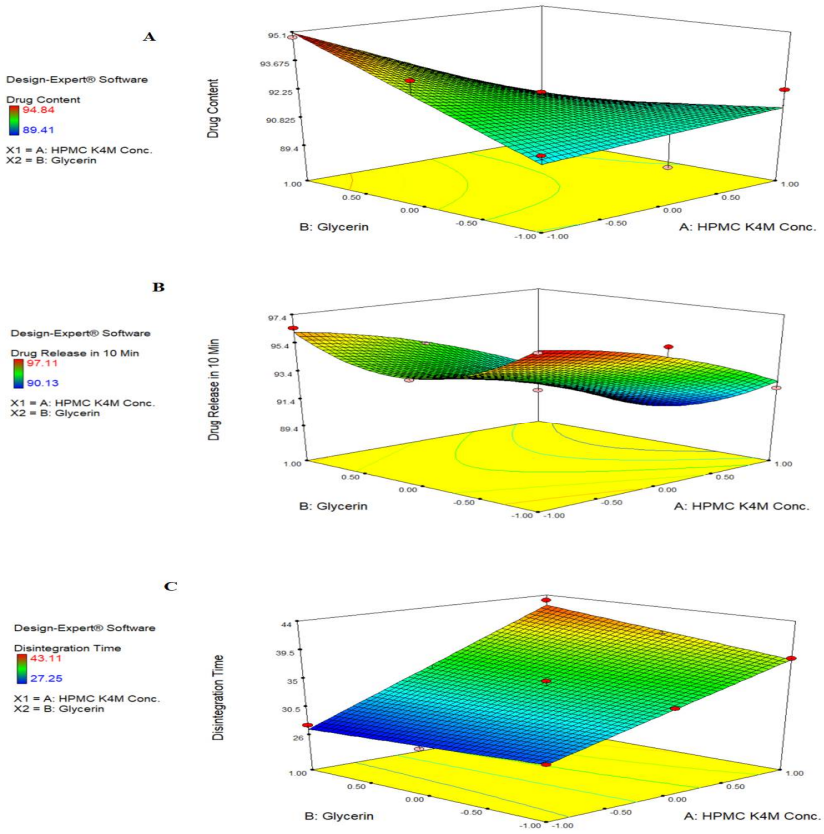

Fig. 1: Response surface plots showing the effect of concentration of HPMC K4M & concentration of glycerin on (A) drug content, (B) drug release & (C) disintegration time

Table 1: Statistical analysis

Responses	Sources		
	Model *p* value	Adj-R^2	Lack of fit test *p* value
Drug content	0.0319	0.9632	8.69
Drug release	0.029	0.9532	14.38
Disintegration time	0.0219	0.9736	10.76

Table 2: Comparative analysis

Factors		Predicted value			Observed value*		
Concentration of HPMC K4M (%)	Concentration of Glycerin (%)	Drug Content (%)	% Drug Release After 10 min	Disintegration Time (sec)	Drug Content (%)	% Drug Release After 10 min	Disintegration Time (sec)
1	1.5	92.36	98.12	26.13	91.14 ± 0.85	97.11 ± 0.63	28.65 ± 1.58

*All values are mean ± standard deviation (n=3).

Model-Verification

Optimized batches of oral thin films loaded with nanosuspension were evaluated for their desirability using the Design-Expert software. With the dependent variable model equations presented in Table 2, we were able to verify the model by comparing observed and predicted values.

Table 3: Evaluation of OTFs

Formulation Code	Transparency	Surface Texture	Thickness	Surface pH	Folding Endurance	Moisture Absorption (%)	Moisture Loss (%)
OTF1	Transparent	Smooth	0.185±0.060	6.69±0.02	75±1.43	5.5±0.3	6.3±0.1
OTF2	Transparent	Smooth	0.233±0.033	6.71±0.02	81±2.38	5.6±0.2	6.0±0.4
OTF3	Transparent	Smooth	0.291±0.018	6.72±0.03	94±1.41	5.4±0.4	5.9±0.2
OTF4	Transparent	Smooth	0.188±0.071	6.81±0.03	80±3.50	5.6±0.4	5.7±0.4
OTF5	Transparent	Smooth	0.250±0.092	6.82±0.03	85±3.42	6.1±0.3	5.5±0.3
OTF6	Transparent	Smooth	0.308±0.091	6.78±0.03	104±2.58	6.3±0.1	5.3±0.5
OTF7	Transparent	Smooth	0.211±0.087	6.75±0.03	93±4.11	7.4±0.2	4.8±0.3
OTF8	Transparent	Smooth	0.283±0.012	6.84±0.02	91±3.13	8.0±0.4	4.4±0.4
OTF9	Transparent	Smooth	0.305±0.019	6.75±0.03	106±3.14	9.1±0.3	4.2±0.1

The % moisture absorption & loss test

The concentration of polymer was observed to enhance the rate of moisture absorption from 5.4±0.4% to 9.1±0.3%. Opposite to it, as the polymer conc. raised from 6.3 to 4.2 percent, moisture loss decreased. Additionally, the formulation's ability to absorb moisture is aided by the polymer's hydrophilic character and enhanced viscosity.

Table 4: Experimental design

Formulation Code	Independent parameters				Dependent parameters		
	Formulation parameters				Y_1	Y_2	Y_3
	X_1	Concentration of HPMC K4M (%)	X_2	Concentration of Glycerin (%)	Drug Content (%)	% Drug ReleaseAfter 10 min	Disintegration Time (sec)
OTF1	-1	1	-1	1.5	91.14 ± 0.85	97.11 ± 0.63	28.65 ± 1.58
OTF2	0	2	-1	1.5	89.41 ± 1.09	96.32 ± 1.44	33.45 ± 2.11
OTF3	+1	3	-1	1.5	92.26 ± 1.12	92.25 ± 1.25	38.27 ± 1.86
OTF4	-1	1	0	3	93.59 ± 0.88	94.12 ± 1.21	27.25 ± 2.14
OTF5	0	2	0	3	92.15 ± 1.74	92.09 ± 1.96	34.71 ± 1.54
OTF6	+1	3	0	3	90.35 ± 0.85	90.13 ± 1.21	39.41 ± 2.25
OTF7	-1	1	+1	4.5	94.84 ± 0.96	96.47 ± 0.58	27.56 ± 1.85
OTF8	0	2	+1	4.5	92.13 ± 1.21	94.23 ± 1.36	33.36 ± 0.98
OTF9	+1	3	+1	4.5	90.27 ± 0.94	91.25 ± 1.36	43.11 ± 1.13

Evaluation of OTFs of tadalafil

Thickness

Films with flat surfaces and no discernible fractures were created using HPMC K4M and glycerin, and their thickness was then measured. The thickness ranged from 0.185 mm to 0.308 mm indicating relationship between thickness and the film-forming agent's concentration is one of direct proportionality. It has been demonstrated that glycerol increases the mechanical strength of films. Each film displayed excellent thickness uniformity.

Percent Drug Content

All movies had drug content between 89.41±1.09 and 94.84±0.96, as required.

Surface pH

For the film to dissolve in the oral cavity without irritating, its surface pH should match that of saliva. Each sample's pH, which ranged from 6.69 to 6.84, showed that the formulation would be suitable for use in the oral cavity.

Folding Endurance

At the folding endurance point, the film produced the distinct clear strain marks. Formulations showed measurements between 75.14 and 106.3, which represents effective mechanical strength. The film's ability to fold longer is improved as viscosity and polymer concentration rise [22-23].

Weight Variation

All of the films were displayed with less than 5% weight variance to ensure uniformity.

In vitro disintegration time

Disintegration times were reduced and other negative effects were eliminated across the board for all film formulations. The readings found between 27.25±2.14 and 43.11±1.13 seconds. According to the data [24], the disintegration time tends to increase with increasing polymer concentration.

In vitro drug release studies

According to experiments, cumulative drug release ranged from 90.13±1.21% to 97.11±0.63% in under 10 minutes [Table 4]. Because of the polymer's low viscosity, an initial fast release was seen [25]. Films that disintegrated more quickly had a shorter disintegration period. This might be because HPMC K4M, which works with glycerol to solubilize drugs, is present. OTF1 demonstrated superior drug release in comparison to TOTF and pure tadalafil, as shown in Fig. 2. Based on regression coefficient values (R2 = 0.996), To best fit OTF1, zero-order kinetics was used.

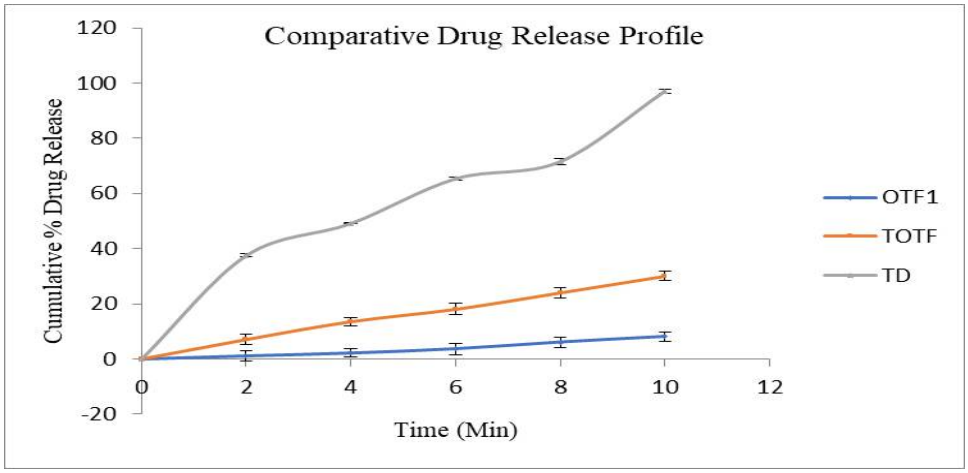

Fig. 2: Comparative dissolution profile of pure tadalafil (TD), TOTF and OTF1

Table 5: Kinetics of OTF1

Formulation	Zero Order	First Order	Higuchi Model	Hixon-Crowell	Korsmeyer – Peppas	
	R^2				R^2	Release Exponent (n)
OTF4	0.997	0.856	0.932	0.934	0.986	0.813

Comparative Physico-Chemical characterization of TOTF and Optimized OTF1

Table 6 contains the findings of the comparison between TOTF and improved OTF1. Both films were discovered to be translucent and to have a smooth surface. Both films displayed similar mechanical characteristics with minimal variance. It can be because of little variations in how they approach formulation. OTF1 disintegrated more quickly than TOTF, which may be related to the suspended nanoparticles' improved ability to mix.

Table 6: Comparative analysis

Sr. No.	Parameter	TOTF	OTF1 (Initial and after stability study)	
			Initial	After 3 months
1.	Appearance	Translucent with smooth surface	Translucent with smooth surface	Translucent with smooth surface
2.	Thickness (mm)	0.214±0.063	0.185±0.060	0.190±0.014
3.	Folding endurance	93±2.28	75±1.43	89±3.68
4.	Moisture absorption (%)	6.5±0.1	5.5±0.3	7.8±0.3
5.	Moisture loss (%)	5.0±0.2	6.3±0.1	5.4±0.2
6.	Surface pH	6.61±0.02	6.69±0.02	6.63±0.01
7.	Disintegration time (sec)	28.04 ± 1.04	28.65 ± 1.58	28.08 ± 1.18
8.	Drug content (%)	95.96 ± 0.78	97.11 ± 0.63	94.98 ± 0.74

Stability Studies

Developed OTF1 were found in predetermined ranges, according to stability studies (Table 6). Films appeared visually transparent and had a smooth surface. They found that while moisture loss (%) dropped marginally from 6.3 to 5.4 percent, moisture absorption (%) rose from 5.5 to 7.8 percent. Thickness, surface pH, and folding durability just slightly varied and stayed within acceptable ranges. After three months, the drug concentration dropped from 97.11±0.63% to 94.98±0.74%, and the film disintegrated at 28.08 1.18 sec.

CONCLUSION

Tadalafil oral thin films with nanosuspension loading were successfully created by solvent casting with HPMC K4M. To increase the film's flexibility and minimise its fragility, glycerin was added as a plasticizer. There is evidence that glycerin increases polymer strength. In terms of thickness and other parameters the prepared films were determined to be superior. OTF1 was optimised as the best of the best batch with good outcomes based on the results. These formulations offer a potential oral drug delivery strategy for improving tadalafil's rate of dissolution and patient compliance.

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