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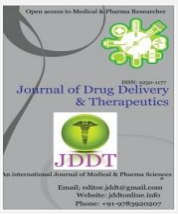

Open Access Research Article

FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF TADALAFIL

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ABSTRACT

This research work was aimed to enhance the oral bioavailability and provide faster onset of action of Tadalafil (used for the treatment of the erectile dysfunction (ED) and pulmonary arterial hypertension) by formulating its mouth dissolving film (MDF). Tadalafil belongs to BCS class II and the oral bioavailability of it's about 28%. The MDF of Tadalafil was prepared by solvent casting method using HPMC-E5 (film forming agent), Methyl cellulose (thickening agent), Propylene glycol (plasticizer), Tween-80 (solubilizing agent), Microcrystalline cellulose (disintegrating agent), Citric acid (saliva stimulating agent), Sucrose (sweetening agent), Vanillin (flavoring agent), EDTA disodium (preservative). The formulation was optimized by two factors, three level (2^3) full factorial design using concentration of Plasticizer (X1) and concentration of film forming agent (X2) as independent variables and formulation was evaluated for uniformity of mass, thickness, folding endurance, drug content uniformity, in-vitro disintegration, in-vitro drug dissolution study and stability study. Based on results it was concluded that MDF (F5) showed enhanced bioavailability and faster onset of action as compared to available tablet dosage form.

Keywords: Tadalafil, Mouth dissolving film (MDF), Bioavailability.

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INTRODUCTION

Currently, 90% of the new chemical entities (NCEs) filling belongs to the poorly soluble BCS Class II and IV compounds. Poor aqueous solubility and/or permeability of drug candidates often leads to poor absorption and bioavailability from the gastrointestinal (GI) tract, which presents the formulation scientists with considerable challenges when trying to deliver these drug molecules via oral route. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms. However, the function and concept of all these dosage forms are similar. There is no need for the administration of water if a solid dosage form that dissolves or disintegrates rapidly in the mouth and such form is known as mouth dissolving dosage form[1].

Mouth dissolving film (MDF) is new drug delivery system for the oral delivery of the drugs. MDFs are the most advanced forms of oral solid dosage forms due to more flexibility and comfort. MDFs are strip type preparations with active molecules dissolved or dispersed in film forming materials[2]. It gives quick dissolution, absorption and instant bioavailability of drugs due to high blood flow and permeability of buccal mucosa of 4-1000 times greater than that of skin[3]. Tadalafil is a potent and selective phosphodiesterase-5 inhibitor used for the treatment of erectile dysfunction which was approved by the FDA. Tadalafil achieves its maximum concentration in plasma after 2-3 hours of administration[4].

MATERIAL AND METHODS

Materials:

Tadalafil was obtained as a gift sample from Shagun Pharma, Indore (M.P.). HPMC-E5, Methyl cellulose and microcrystalline cellulose was obtained from Signet chemicals pvt. Ltd., Mumbai. All other chemicals were purchased from Loba chemicals, Mumbai.

Methods:

UV Analysis:

Absorption maxima of Tadalafil were determined by scanning its solution on spectrum mode of UV visible spectrophotometer. Calibration curve of Tadalafil was

prepared in methanolic distilled water (2:8) and phosphate buffer pH 6.8 separately at 281.5 nm by double beam UV visible spectrophotometer (Shimadzu, 1800, Japan). Linearity was observed over a concentration range of 10–50 µg/ml, with R^2 value of 0.998.

Solubility determination: (n=3)

Sufficient excess amount of Tadalafil was added to 5 ml glass vials containing distilled water and phosphate buffer (pH 6.8) separately. The content of vials was stirred for 12 h on magnetic stirrer at 37 ± 2°C. The solution was transferred into eppendorf tubes and centrifuged for 5 min at 2000 rpm. The content of vial were filtered through 0.45µ membrane filter and analyzed for drug content by UV visible spectrophotometer (Shimadzu, 1800, Japan) at 281.5nm after appropriate dilutions.

Formulation of MDFs of Tadalafil:

MDF of Tadalafil was prepared using solvent casting method. Required amount Tadalafil, HPMC-E5, Propylene glycol, Methyl cellulose, Microcrystalline cellulose, Tween-80, Sucrose, disodium EDTA, Citric acid were dissolved in 10ml distilled water under constant stirring at 1100 rpm on magnetic stirrer (Remi labs, Mumbai) at room temperature until a clear solution had been obtained. Subsequently, mixture was stirred at room temperature for overnight at 100 rpm to allow entrapped air bubbles to disappear. The solution was then casted onto a fabricated glass mould previously lubricated with glycerin. The film layer was dried at room temperature and removed from the mould and cut in squares of 2×2 cm yielding four stamp shaped MDFs [5]. Formulation of MDFs was optimized by two factors, three level (2^3) full factorial design as shown in table-1 using concentration of Plasticizer (X1) and concentration of film forming agent (X2) as independent variables.

Table-1 Formulation optimization of MDFs of Tadalafil (n=3)

	Batch Number								
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Tadalafil (mg)	20	20	20	20	20	20	20	20	20
HPMC-E5 (mg) X1	700	700	700	500	500	500	300	300	300
Propylene glycol (ml) X2	0.025	0.05	0.075	0.025	0.05	0.075	0.025	0.05	0.075
Methyl cellulose (mg)	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose (mg)	100	100	100	100	100	100	100	100	100
Tween-80 (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Sucrose (mg)	5	5	5	5	5	5	5	5	5
EDTA disodium (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Citric acid (mg)	20	20	20	20	20	20	20	20	20
Vanillin (mg)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25

Evaluation of MDFs:

Uniformity of mass:

Uniformity of mass was determined according to the European Pharmacopoeia. Twenty randomly chosen MDF were weighed individually on digital balance (Shimadzu, Japan). Subsequently the average mass was calculated.

Thickness:

The thickness of the film was measured by micrometer screw gauge (Acculab) at three different places and averages of three values were calculated. The uniformity in the thickness of the film is directly related to the accuracy of dose in the film.

Folding endurance:

This test is important to check the ability of the sample to withstand folding. This also gives an indication of brittleness. Folding endurance of the MDF was determined by folding repetitively one film at the same place till it broken.

Drug Content uniformity:

The drug content uniformity of each film was determined by dissolving the film in 10 ml of phosphate buffer pH 6.8, followed by filtering through 0.45 µm membrane filter. The filtrate was appropriately diluted and the content of Tadalafil was determined at 281.5 nm using UV spectroscopy.

In-vitro disintegration test:

Disintegration time of MDF was determined by drop method. Five randomly chosen MDFs from each run were tested. The MDF was placed onto a small glass petridish and subsequently a volume of 0.2 ml distilled water was placed repetitively onto the film until the film disintegrates and time was noted.

In-vitro dissolution study:

In vitro dissolution test was carried out for Tadalafil MDF and marketed Tadalafil tablet for comparative study in a paddle type dissolution testing apparatus (Electrolab). Each film was fixed to a piece of metal wire slab and placed at the bottom of the dissolution vessel. The dissolution medium was 250 ml of phosphate buffer pH 6.8, maintained at 37±0.5°C and stirred at 50 rpm. Samples of 5 ml were withdrawn at 30, 60, 90, 120,150 and 180 seconds and were filtered

through a 0.45-µm membrane filter and analyzed by UV-spectroscopy at 281.5 nm.

Stability Studies

Stability studies were conducted for optimized MDF formulation (F5) to assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing them at 40° C/75 % RH for 3 months. Samples were withdrawn at 0, 30, 60 and 90 days.

RESULTS AND DISCUSSION

Solubility determination:

The saturated solubility of Tadalafil was found to be 0.243±0.042 mg/ml in distilled water and 0.312±0.025 mg/ml in phosphate buffer pH 6.8 and it confirms the low aqueous solubility of Tadalafil.

Evaluations of MDF:

The results of various evaluation parameters are shown in Table-2. Thickness and uniformity of mass for films were noted to increase by increasing the fraction of polymer as expected. The maximum force and the tensile strength were higher for the HPMC-E5 films in general which clearly justified in results of folding endurance and was found to be more than 195 times for all the formulations, which showed that the prepared films were robust in nature. In general all formulations were found to be fast disintegrating and showed different disintegration time because of different polymer concentration. The result of in vitro dissolution study showed almost complete (upto 96%) drug release within 3 minutes time. This indicated fast drug release from the thin MDF delivery system. Furthermore, in comparison with Tadalafil tablet, MDF showed 2 fold fast dissolution rate upto 3 minutes as shown in figure-1. Almost all batches met the criteria regarding the content uniformity and the observed results of drug content in the films were found to be in the range 89-97% which indicated that the drug was uniformly dispersed in the film. Formulation F5 was rated as the best formulation with respect to the drug release and content uniformity.

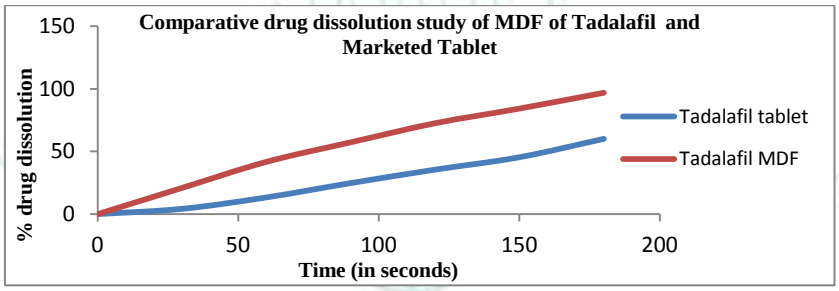

Figure 1: Comparative in-vitro drug dissolution study of MDF of Tadalafil and Marketed Tablet

Table 2: Evaluation data of mouth dissolving film of Tadalafil (n=3)

Batch No.	Uniformity of mass (mg)±SD	Thickness (mm)±SD	Folding endurance (times)	In-vitro disintegration time (Seconds)	% In-vitro dissolution	% Drug Content
F1	213.9±0.02	0.15± 0.04	236 ±1	62±2	85.57±0.78	93.5±0.04
F2	214.5 ±0.05	0.12±0.02	230 ±2	71±2	80.82 ±0.07	89.7±0.08
F3	212.4±0.04	0.14±0.01	227±1	65±1	91.42±0.06	93.4±0.07
F4	160.2±0.06	0.10±0.06	228 ±2	32±2	94.87±0.05	95.0±0.05
F5	162.3±0.04	0.11±0.78	230±2	29 ±1	96.30± 0.04	96.8 ±0.02
F6	162.4±0.09	0.10±0.05	225 ±1	27 ±2	92.23± 0.04	94.4±0.04
F7	113.2±0.08	0.09±0.05	198 ±3	25 ±3	89.56 ±0.02	94.5±0.06
F8	113.8±0.05	0.09±0.07	197 ±2	29 ±2	82.56 0.71	89.8±0.09
F9	112.6±0.07	0.10±0.04	195±2	27 ±3	88.50±0.08	92.5 ±0.07

Stability Studies

The result of stability study indicated that the drug product falls well within the proposed stability specification. The data showed that there is no significant physical or chemical change indicating that the formulation would maintain its efficacy and quality throughout its proposed shelf life.

CONCLUSION

Formulation of MDF of Tadalafil with desirable properties was achieved by optimization approach through 2^3 full factorial designs. The results indicated that formulation F5 showed desired properties as compared to other batches. Results of comparative in-vitro dissolution study of MDF with Tadalafil tablet showed 2 fold fast dissolution rate up to 3 minutes. Stability study also suggested the good shelf life of the MDF. On the basis of above presented experimental work we can conclude that MDF of Tadalafil improve its oral bioavailability and may provide faster onset of action as compared to available tablet dosage form.

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