Available online on 15.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Formulation, Development and Evaluation of Fast Dissolving Oral Film of Antidepressant Drug

Rahul Kumar Sahu*, Shailesh Jain, Vishal Kapoor, Naveen Gupta

Patel College of Pharmacy, Bhopal (M.P.)

ABSTRACT

Fast dissolving dosage forms are gaining popularity in recent time, as this dosage forms requires no water for administration. Oral films dissolve rapidly along with drug in mouth and majority of the drug is absorbed through buccal/oral mucosa in to systemic circulation avoiding first pass metabolism. Trazodone Hydrochloride (TRZ), an serotonin reuptake inhibitor antidepressant. TRZ undergoes first pass metabolism on oral administration resulting in reduced bioavailability (60%). Thus the objective of the present study was to formulate and evaluate fast dissolving oral films of TRZ to overcome the limitation of bioavailability and increase patient's compliance. In the present study oral films were prepared by solvent casting method using HPMC K15 as a film formers and PEG 400, glycerine as plasticizers and evaluated for mechanical properties, disintegration and *in vitro* dissolution. All formulations showed good mechanical properties and *in vitro* drug release. The optimized (F5) Formulation (HPMC K15, CCS and PEG 400) Exhibited drug release of 92.12% in 15 minutes which was significantly high when compared to other formulation.

Keywords: Trazodone hydrochloride, Fast dissolving oral film, Bioavailability, Mechanical properties

Article Info: Received 16 June 2019; Review Completed 29 July 2019; Accepted 04 Aug 2019; Available online 15 August 2019

Cite this article as:

Sahu RK, Jain S, Kapoor V, Gupta N, Formulation, Development and Evaluation of Fast Dissolving Oral Film of Antidepressant Drug, Journal of Drug Delivery and Therapeutics. 2019; 9(4-s):404-407

http://dx.doi.org/10.22270/jddt.v9i4-s.3346

***Address for Correspondence:**

Rahul Sahu, Patel College of Pharmacy, Bhopal (M.P.)

INTRODUCTION

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages[1, 2]. These systems either dissolve or disintegrate within a minute, on contact little quantity of water or by chewing. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption [3,4]. The major portion of the active ingredient is swallowed orally along the saliva and absorption takes place in the gastrointestinal tract subsequently making them particularly suitable for pediatrics and geriatric patients. The fast dissolving films were introduced in 1970's as an alternative to the conventional tablet and capsule which require swallowing of the dosage form. The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms[5,6]. These dosage forms offer specific advantages including no need of water for disintegration, accurate dosing, ease of transport, handling, acceptable taste, rapid onset of action and patient compliance[7]. The trans mucosal deliveries of metformin, dexamethasone and levocetrizine hydrochloride have proved their enhanced bioavailability over the conventional formulations[8-10]. Solvent casting was proved to be reliable technique for the manufacturing of fast dissolving films. The film strips prepared by this method undergo instantaneous disintegration upon placing in buccal/oral cavity. The plasticizers present in fast dissolving films formulation, reduce the glass transition temperature and thereby enabling desired film qualities[10]. TRZ is chemically 2-{3-[4-(3-chlorophenyl) piperazin-1-yl] propyl}-2H, 3H-[1, 2, 4] triazolo[4,3-a]pyridin-3-one. It is a serotonin antagonist and reuptake inhibitor (SARI), which is a second generation antidepressant compound belonging to the class of phenyl piperazine. It acts as a serotonin agonist at high doses and low doses. The drug showing antidepressant activity is due to the blockage of serotonin reuptake by inhibiting serotonin reuptake pump at the presynaptic neuronal membrane. TRZ shows its therapeutic actions through 5-HT_2A receptors. TRZ also induces anti-anxiety and sleep inducing effects[11]. It does not have similar properties to selective serotonin reuptake inhibitors (SSRIs) since its inhibitory effect on serotonin reuptake and 5-HT_2C receptors are relatively weak[12]. The

result of α-adrenergic action blocking and modest histamine blockade at H receptor due to sedative effect of TRZ. It weakly blocks presynaptic α_2-adrenergic receptors and strongly inhibits postsynaptic α_1 receptors. TRZ does not show any action on the reuptake of norepinephrine or dopamine within the CNS. It has fewer anticholinergic side effects than most of the tricyclic antidepressants such as dry mouth, constipation and tachycardia. TRZ metabolizes to its primary m-chlorophenyl piperazine (mCPP) which is a non selective serotonin receptor agonist which might outweigh the benefits of TRZ[13-16]. Initial investigations were focused on the development of placebo fast dissolving films with good peelability, appearance and a quick disintegration time. After choosing the components for the placebo film, TRZ loaded films were formulated. Although, fast dissolving film is an attractive dosage form for the delivery of TRZ. Finally fast dissolving films using HPMC and CCS were formulated and evaluated.

MATERIALS AND METHODS

Trazodone HCl were obtained as pure sample from Sun Pharmaceutical Industries Ltd. Dewas, as gift samples along with their analytical reports. HPMC K15M, PEG-400, SSG, CCS was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Aspartame, citric acid was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Drug-excipient compatibility study

FTIR spectra of pure drugs, polymers used, and blends were recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Preparation of oral films

Drug (TRZ) containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of HPMC was dissolved in 5mL of water and stirrer continuously for 1 hour, optimized amount of Plasticizer and drug were dissolved in 95 % ethanol and then added to the polymeric solution, Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm, 10 films area and was dried at controlled room temperature (25-30°C, 45 % RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use. Formulations were prepared using HPMC K15, PEG-400, SSG and CCS at different drug: polymer ratios. The compositions of the formulations were shown in table 1.

Table 1 Formulation of trazodone hydrochloride oral fast dissolving films

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
TRZ (mg)	600	600	600	600	600	600
HPMC K15 (mg)	800	100	1200	800	100	1200
Glycerin (mg)	-	-	-	-	-	-
PEG-400 (mg)	100	100	100	100	100	100
SSG (mg)	200	300	400	-	-	-
CCS (mg)	-	-	-	200	300	400
Aspartame (mg)	60	60	60	60	60	60
Citric acid (mg)	120	120	120	120	120	120
DM water qs to (ml)	-	-	-	-	-	-

Evaluation

The formulations were evaluated by the following tests.

Thickness

Randomly 10 films were selected and thickness was measured using vernier calliper at three different places.

Weight variation

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Drug content analysis

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight.

In vitro dissolution study

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5°C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was

used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved TRZ was determined using UV-Visible spectrophotometer at 246nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2°C temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature.

Physical appearance and texture analysis of the films

These parameters were checked simply with visual infection of films and by feel or touch.

***In vitro* disintegration**

The film of (4.15cm^2) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.

Measurement of mechanical properties

Microprocessor based advanced force gauge tensiometer (DS 2 series) equipped with a 50 kg

load cell was used to determine the mechanical properties of OFDFs. Film of 60x10 mm2 was fixed between two clamps separated by a distance of 3 cm[17]. The lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke. The force and elongation of the film at the point when the strip broke was recorded. The tensile strength and percent elongation values were calculated using the following formula.

Tensile strength = load at breakage/film thickness × film width

% Elongation = increase in length ×100/original length

RESULTS AND DISCUSSION

Solubility of TRZ was freely soluble in methanol and ethanol, slightly soluble in 0.1N NaOH, soluble in water, 0.1N HCL and 6.8 pH phosphate buffers. The melting point of TRZ was 223-226ºC and λ_{max} of TRZ was found to be 246.0 nm by using U.V. spectrophotometer (Labindia-3000+). The general appearance, assay, weight variation and thickness of all the films were within acceptable limits table 2. The results for tensile strength, folding endurance, disintegrating time, % elongation and % of moisture were shown in table 3. Tensile strength value of optimized formulation (F5) was 1.224±0.065 kg/cm^2 and percent elongation 6.67±0.62. The folding endurance of the optimized oral fast dissolving formulation (F5) was 122.35±6.45. The formulations containing CCS were showing good results compared to SSG. The assay values of all the formulations were ranging from 92.25 to 98.89 %. The disintegration time was ranging between 52 to more than 92 sec. The final formulation shows better drug release (92.12%) compared to other formulation within 15 m (Figure 1). The cumulative percentage (%) drug release profile and the assay of the F5 formulation films indicates that the drug remain stable under the ASC without any significant change in its release profile and the drug content. From the stability studies it was clearly observed that the drug showed good stability after subjecting to accelerated stress conditions and the polymers shown significantly compatibility with the drug.

Table 2 Result of thickness and weight variation

F. code	General Appearance	Thickness in µm	Weight(mg) Mean ± S.D	% Assay
F1	Translucent	90±2	158±4	92.25±0.14
F2	Translucent	93±5	155±3	95.45±0.28
F3	Translucent	89±5	160±1	94.65±0.36
F4	Translucent	93±6	162±2	95.65±0.24
F5	Translucent	95±4	159±5	98.89±0.14
F6	Translucent	94±2	160±4	97.45±0.16

Table 3 Result of folding endurance, disintegrating time, tensile strength, % elongation &% of moisture content

F. code	Folding endurance (Times)	Disintegrating time (Sec)	Tensile strength in kg/cm^2	% elongation Mean ± S.D	% of moisture content
F1	103.33 ± 9.87	92±4	0.620±0.056	5.94 ± 0.88	0.698±0.111
F2	105.25 ± 4.56	80±6	0.680±0.045	4.29 ± 0.67	0.647±0.101
F3	99.33 ± 7.67	75±7	1.212±0.012	2.24 ± 0.57	0.897±0.142
F4	111.02 ± 8.55	60±6	1.542±0.045	4.35 ± 0.66	0.998±0.156
F5	122.35 ± 6.45	52±4	1.224±0.065	6.67 ± 0.62	0.898±0.136
F6	120.66 ± 5.29	55±5	1.269±0.045	3.21 ± 0.21	0.956±0.145

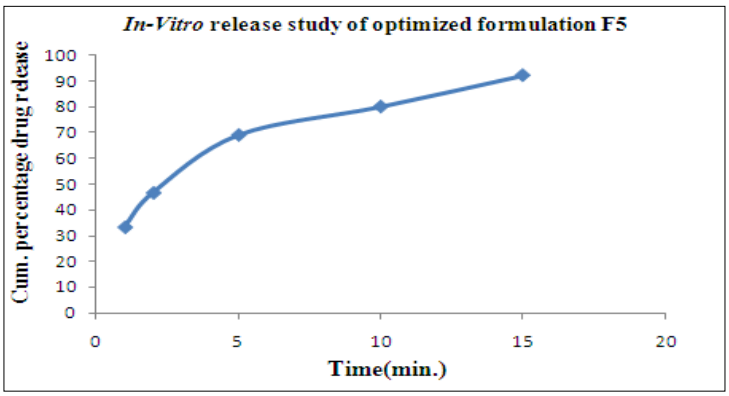

Figure 1 Graph of *In vitro* drug release study of optimized formulation

CONCLUSION

From present investigation it can be concluded that oral fast dissolving films are superior in drug release. The films prepared by HPMC and PEG 400 had shown good mechanical strength, drug release, disintegration time and stability. F5 formulation is considered as the best according to the obtained results with less disintegrating time and complete drug release in 15 min. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. As the concentration of CCS was increased, both the disintegration and the drug release rates increased. The disintegration and release rates were found to be faster for films prepared with lowest concentration of HPMC along with maximum concentration of superdisintegrants. TRZ administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric and also for general population by providing faster release and better patient compliance.

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