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 Trazodone Hydrochloride

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ABSTRACT

The concept of fast dissolving dosage form has become popular as new delivery system. This system will provide maximum therapeutic efficacy, increased bioavailability and maximum stability by reducing the frequency of dosage. It will also avoid first pass metabolism of the drugs. This system provides more rapid drug absorption from the pre gastric area which may provide quick onset of action. Trazodone hydrochloride an serotonin reuptake inhibitor, antidepressant. Trazodone 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 Trazodone 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 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 (F3) formulation exhibited drug release of 92.12% in 5 minutes which was significantly high when compared to other formulation. It is evident from the above results that the developed formulation can be an innovative dosage form to improve the drug delivery, onset of action as well as improve patient compliance.

Keywords: Trazodone hydrochloride, HPMC K15, Plasticizers, Mechanical properties

Article Info: Received 09 June 2019; Review Completed 19 July 2019; Accepted 20 July 2019; Available online 15 August 2019

Cite this article as:

Jaiswal M, Dubey BK, Pandey GK, Yadav SK, Parkhe G, Formulation Development and Evaluation of Fast Dissolving Oral Film of Trazodone Hydrochloride, Journal of Drug Delivery and Therapeutics. 2019; 9(4-s):394-397

http://dx.doi.org/10.22270/jddt.v9i4-s.3343

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INTRODUCTION

Trazodone 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. Trazodone shows its therapeutic actions through 5-HT_2A receptors. Trazodone also induces anti-anxiety and sleep inducing effects[1]. 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[2]. The result of α-adrenergic action blocking and modest histamine blockade at H receptor due to sedative effect of trazodone. It weakly blocks presynaptic α_2-adrenergic receptors and strongly inhibits postsynaptic α_1 receptors. Trazodone 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. Trazodone metabolizes to its primary m-chlorophenyl piperazine (mCPP) which is a non selective serotonin receptor agonist which might outweigh the benefits of trazodone[3-6]. There has been significant interest in the development of modified release oral dosage forms because oral delivery market holds approximately 52% of the market in the overall drug delivery market. But there are some commonly associated problems with oral administration of drugs like minimizing the risk of partial loss of active ingredients due to tablet or capsule crushing or imprecise liquid administration which leads to dosage inaccuracy and drug therapy overdosing or inefficiency[7-9]. In order to overcome these issues, fast dissolving drug delivery systems are gaining considerable attention. Among them oral film strips have hit the mainstream in the last few years as a new way of freshening the breath. These gel-like wafers slip into the mouth and

dissolve quickly to release the flavor[10-12]. Recent technological advancements have diverted many drug companies to explore new prospective in this technology to provides fast, accurate dosing that is expected to increase compliance, particularly among children[13-15]. Nowadays, there has been significant development in transmucosal routes of drug administration because this route has a potential to fathom such problems associated with oral administration of the drugs[15]. There is no need for water or measuring and upon melting; the dose of medicine is swallowed. Absorption of drug by oral mucosa into systemic circulation is an attractive approach because it is highly vascularized and hence highly permeable. Therefore fast dissolving films have become a popular oral dosage form for various medicaments which provide rapid disintegration due to large surface area and hence improve patient compliance. The aim of present investigation was to develop and formulate fast dissolving films of trazodone by solvent casting method for the direct absorption of drug via transmucosal lining to the systemic circulation. The proposed formulation has the potential to improve compliance and presents multiple competitive advantages over its marketed oral dosage forms used to treat depression.

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. Mannital 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.

Procedure for the determination of λ_{max}

Accurately weighed 10 mg of trazodone hydrochloride separately and dissolved in 10 ml of phosphate buffer pH 6.8 in 10 ml of volumetric flask and prepared suitable dilution to make it to a concentration of 100µg/ml make adequate of sample with concentration range of 5-25 µg/ml. Trazodone hydrochloride calculate the spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer. (Labindia UV 3000 +).

Preparation of oral films

Solvent casting technique

Drug (Trazodone hydrochloride) containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of HPMC was dissolved in 5ml of water and stirrered continuously for 1 hour, optimized amount of Plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept on sonication for proper dispersion. 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 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.

Selection and optimization of film forming agents

Two film forming agents and one co-film forming were selected for this research work. The concentration of film forming was important to form a proper thickness for appropriate packaging and handling of oral films. Concentration of film forming agent is optimized on the basis of thickness and appearance of film Table 1.

Table 1 Formulation of trazodone hydrochloride oral fast dissolving films

Name of ingredients (mg) (mg for 12 strips)	Trazodone Hydrochloride	HPMC	PEG-400	SSG	CCS	Mannitol	Citric acid	DM water qs to (ml)
F1	300	150	100	50	-	100	100	30
F2	300	200	100	100	-	100	100	30
F3	300	250	100	150	-	100	100	30
F4	300	300	100	-	50	100	100	30
F5	300	350	100	-	100	100	100	30
F6	300	400	100	-	150	100	100	30

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 films present whole plate = 25
- Each film contains 10 mg of drug.
- 12 no. of films contains mg of drug? = 25×12 = 300mg
- The amount of Trazodone added in each plate was approximately equal to 25mg.

Evaluation of prepared film

Thickness

The thickness of patches was measured at three different places using a vernier caliper.

Weight uniformity

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.

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 with respect to final weight.

Drug content analysis

The film 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 reacted by UV spectrophotometer at 246nm.

Disintegrating time

The most important criteria of present work are that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent was done to minimize the disintegrating time. Two super disintegrating agent (Sodium starch glycolate and Croscarmellose sodium) were selected for this work.

***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, and 5 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 drug 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 **F3** 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.

RESULTS AND DISCUSSION

The λ max of trazodone was found to be 246.0 nm by using U.V. spectrophotometer (Labindia-3000+) with concentration range of 5-25µg/ml Fig. 1, 2. 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, % moisture content and folding endurance value of optimized formulation (F3) were 0.658±0.045 kg/cm^2, 14.45±0.25 and198±8 respectively. The assay values of all the formulations (F1 to F6) were ranging from 97.56±0.12to 99.12±0.36%. The disintegration time was ranging between 20±5 to more than 55±6 sec. The final formulation shows better drug release (92.12%) compared to other formulation within 5 min (Fig. 3). The cumulative percentage (%) drug release profile and the assay of the F3 formulation films indicates that the drug remain stable under the ASC without any significant change in its release profile and the drug content. From stability studies minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time.

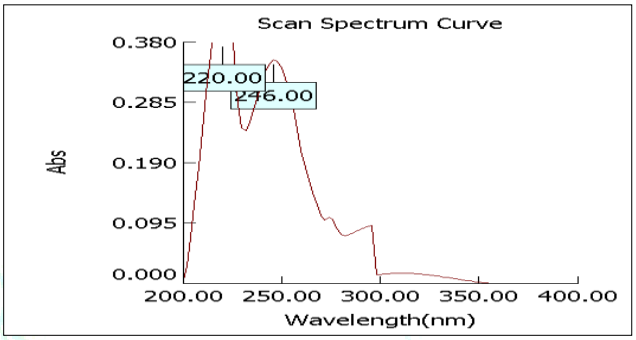

Figure 1 Determination of λ_{max} of trazodone hydrochloride

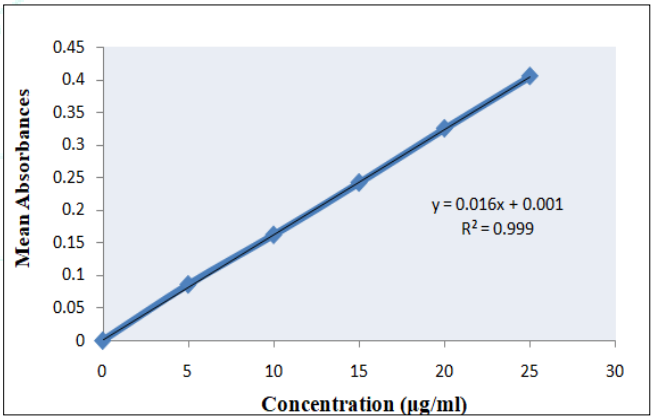

Figure 2 Calibration curve of trazodone hydrochloride at 246 nm

Table 2 Result of general appearance, thickness, weight variation and % assay

F. Code	General Appearance	Thickness* (nm)	Weight* (mg)	% Assay
F1	Approx Transparent	0.08±0.01	150	97.56±0.12
F2	Approx Transparent	0.10±0.02	156	98.25±0.32
F3	Approx Transparent	0.11±0.02	166	99.12±0.36
F4	Approx Transparent	0.08±0.01	170	98.85±0.45
F5	Approx Transparent	0.11±0.02	172	97.56±0.58
F6	Approx Transparent	0.13±0.02	176	98.85±0.52

***Average of three determination (n=3±SD)**

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

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm²	Percentage of Moisture Content
F1	125±4	30±3	0.658±0.012	20.23±0.45
F2	135±6	32±4	0.548±0.032	18.56±0.65
F3	198±8	20±5	0.658±0.045	14.45±0.25
F4	160±5	55±6	0.587±0.023	19.98±0.47
F5	154±4	40±4	0.658±0.032	22.12±0.58
F6	150±2	36±5	0.854±0.014	23.36±0.69

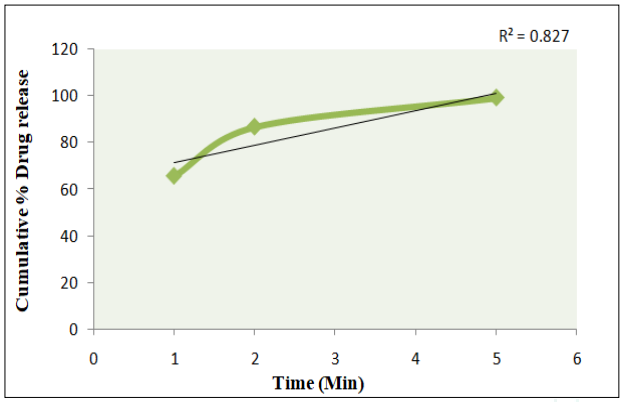

Figure 3 Release kinetics of optimized formulation F3

CONCLUSION

In the present study fast dissolving drug delivery system of Trazodone Hydrochloride were successfully developed in the form of fast dissolving oral films which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increase in patient compliance by avoiding the first pass metabolism and enhance the bioavailability of the drug.

ACKNOWLEDGMENTS

The authors would like to thank the Mr. Prabhat Kumar Jain, Geeta Parkhe and All supporting staff of Scan Research Laboratories, Bhopal (M.P.) who helped in the experiments during research work.

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