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

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ABSTRACT

In case of psychiatric treatment immediate release of drug from the dosage form is required. 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. Olanzapine is a thienobenzodiazepine class of drugs, which has been approved by the FDA, for the treatment of schizophrenia, depressive episodes associated with bipolar disorder, acute manic episodes and maintenance treatment in bipolar disorder. The absolute bioavailability is only approximately 31.5% due to extensive hepatic metabolism. Thus the objective of the present study was to formulate and evaluate fast dissolving oral films of Olanzapine to improve water solubility, dissolution rate, oral bioavailability and reduction of first pass metabolism and increase patient's compliance. Oral fast dissolving films prepared by solvent casting method using water and 95% ethanol as solvents and HPMC as film forming polymer. PEG 400 was the selected plasticizers, Superdisintegrants such as croscarmellose sodium (CCS) and sodium starch glycolate (SSG) alone and also in combinations was incorporated to achieve the aim. The prepared films were evaluated for the drug content, weight variation, film thickness, disintegration time, folding endurance, percentage of moisture content and *in vitro* dissolution studies. Among all, the formulation F4 was found to be best formulation which releases 98.78 % of the drug within 15 min and disintegration time is 42 sec. which was significantly high when compared to other formulation. The data obtained from In-vitro release were fitted into the various kinetic models such as Zero Order, Higuchi, First Order and Korsmeyer–Peppas Model in order to determine the mechanism of drug release. When the regression coefficient values compared, it was observed that 'r' values of formulation F4 was maximum i.e 0.974 hence indicating drug release from formulations was found to follow first order drug release kinetics.

Keywords: Antipsychotic, Olanzapine, Fast dissolving films, Solvent casting method, Superdisintegrants

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INTRODUCTION

Typical antipsychotic drugs are usually classified by their chemical structure and the potency of binding to the dopamine type 2 (D_2) receptors, while new antipsychotic agents differ from selective dopamine antagonist in having a broader receptor affinity and hence called atypical antipsychotics. The atypical antipsychotics are characterized by improved clinical efficacy against schizophrenia and bipolar disorders with fewer side effects such as hallucinations and delusions[1]. These are also better than the typical analogs at relieving the negative symptoms of the illness, such as withdrawal, thinking problems, and lack of energy[2]. Olanzapine is one of the recent atypical antipsychotics that belongs to the thienobenzodiazepine-class (2-methyl-4-(4-methyl-1-piperazinyl)-10Hthieno-[2,3-b][1,5] benzodiazepine). It is widely used in the treatment of schizophrenia and acute mixed or manic episodes. It is highly efficient with no or minimal side effects such as weight gain and agranulocytosis being similar to the first line treatment such as clozapine[3]. However, Olanzapine exhibits very slight solubility in water and suffers from extensive first pass metabolism and therefore, possesses low bioavailability (40%) after oral administration[4]. The pharmacokinetics of Olanzapine is linear and dose proportional within the approved dosage range from 1 mg up to 20 mg. direct glucuronidation and CYP1A2 mediated oxidation are the primary metabolic pathways for Olanzapine. Phenotypic difference for CYP1A2 between races has been reported. Numerous trials were reported in the literature for improving bioavailability of Olanzapine using solid lipid nanoparticles or through formation of solid dispersions with various polymeric carriers[5-7]. For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been

increasing annually. Orally disintegrating films (ODF) have carved a niche amongst the oral drug delivery systems due to their high patient compliance[8-10]. United States Food and Drug Administration (USFDA) defined the fast dissolving oral thin films as a thin, flexible, non-friable polymeric film strip containing one or more dispersed/dissolved active pharmaceutical ingredients, which is intended to be placed on the tongue for rapid *in vitro* disintegration or dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract[11]. The objective of the present research work was to develop fast dissolving oral films of Olanzapine disintegrating within 45s to enhance the convenience of administration to the patients to improve compliance. The formulation developed was simple, easy to prepare and economical with great applicability and also giving faster *in vitro* drug dissolution rate as compared to the commercially available immediate release tablets.

MATERIALS AND METHODS

Materials

Olanzapine was obtained as gift sample from Bioplus life science, Bangalore India. HPMC was procured from Qualikems fine chem. Pvt Ltd Vadodhara. PEG400, sodium starch glycolate, croscarmellose sodium was obtained from S.D fine chemicals limited, Mumbai. Citric acid, ethanol was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid, KH_2PO_4, NaoH 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 the chemicals used in this work were of analytical grade.

Preformulation studies

Standardization of Olanzapine by UV-Visible spectrophotometry

Preparation of stock solution: Stock solution 1000µg/ml Olanzapine was prepared in phosphate buffer pH 6.8 solutions. This solution was suitably diluted with buffer solution to obtain a concentration of 15µg/ml. The resultant solution was scanned in the range of 200-400 nm using UV double beam spectrophotometer (Labindia 3000+, Mumbai).

Standard calibration of Olanzapine: From stock solutions of Olanzapine 1 ml was taken and diluted up to 10 ml. from this solution 0.5, 1.0, 1.5, 2.0 and 2.5 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with Phosphate buffer pH 6.8, gives standard drug solution of 5, 10, 15, 20, 25µg/ ml concentration, absorbance was measured at 226nm.

FTIR Spectroscopy

Identification of Olanzapine was done by FTIR spectroscopy with respect to marker compound. Olanzapine was obtained as Yellow crystalline powder. It was identified from the result of IR spectrum as per specification.

Formulation development of oral film of Olanzapine

Solvent casting technique

Drug (Olanzapine) containing fast dissolving films were fabricated by the solvent casting method[12].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 olanzapine oral fast dissolving films

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6
Olanzapine	60	60	60	60	60	60
HPMC	250	500	750	250	500	750
PEG-400	150	150	150	150	150	150
SSG	150	200	250	-	-	-
CCS	-	-	-	150	200	250
Citric acid	100	100	100	100	100	100
Glycerin	-	-	-	-	-	-
DM water qs to (ml)	-	-	-	-	-	-

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm2 films present whole plate = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug? = 5×12 = 60mg
- The amount of drug added in each plate was approximately equal to 60mg.

Evaluation

The formulations were evaluated by the following tests[13-16].

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.

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 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 at 226nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work. The film of (4.15cm2) 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.

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 Olanzapine was determined using UV-Visible spectrophotometer at 226nm. 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.

RESULTS AND DISCUSSION

Identification of Olanzapine was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification fig. 1. Solubility of Olanzapine was freely soluble in ethanol and methanol, sparingly soluble in 0.1N HCL and chloroform, soluble in 6.8 pH phosphate buffers, insoluble in water. λ_{max} of Olanzapine was found to be 226 nm by using U.V. spectrophotometer (Labindia-3000+). The calibration curve of Olanzapine was found to be linear in the concentration range of 5-25µg/ml at 226 nm fig. 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 and % of moisture were shown in table 3. Tensile strength value of optimized formulation (F4) was 1.236±0.045 kg/cm^2 and folding endurance was 145± 8.55. The formulations containing CCS were showing good results compared to SSG. The assay values of all the formulations were ranging from 97.65 to 99.05 %. The disintegration time was ranging between 42 to more than 73 sec. The final formulation shows better drug release (98.78%) compared to other formulation within 15 m (Table 4). The cumulative percentage (%) drug release profile and the assay of the F4 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. The kinetic data of optimized formulation F4 was given in table 5and fig 3, 4. It was fallow first order drug release.

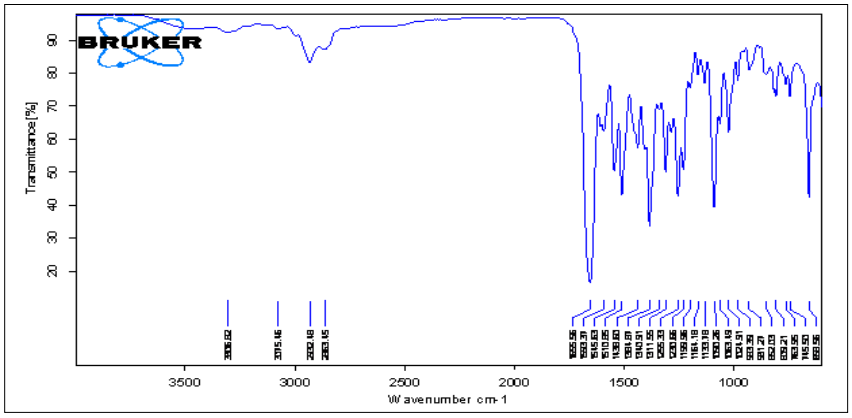

Fig. 1 FT-IR Spectrum of pure drug

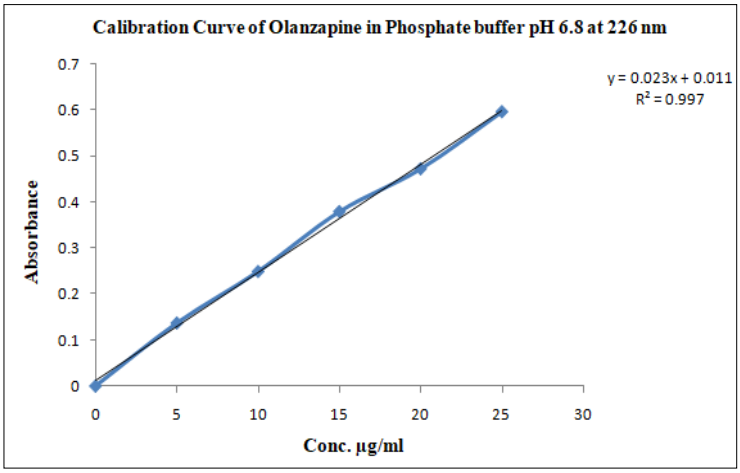

Fig. 2 Calibration curve of olanzapine in phosphate buffer ph 6.8 at 226 nm

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

F. code	General Appearance	Thickness in µm	Weight(mg) Mean ± S.D	% Assay
F1	Translucent	45±5	88±1	98.89±0.13
F2	Translucent	48±3	93±4	97.65±0.22
F3	Translucent	52±1	95±3	98.85±0.31
F4	Translucent	42±4	85±6	99.05±0.25
F5	Translucent	44±2	90±5	98.98±0.15
F6	Translucent	49±3	93±3	98.78±0.13

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

F. code	Folding endurance (Times)	Disintegrating time (Sec)	Tensile strength in kg/cm²	% of moisture content
F1	125± 9.87	69±4	1.105±0.056	2.45±0.111
F2	135± 4.56	73±6	1.241±0.045	2.22±0.101
F3	132± 6.45	65±7	1.265±0.012	1.98±0.142
F4	145± 8.55	42±6	1.236±0.045	1.45±0.156
F5	165± 7.67	55±4	1.165±0.065	2.23±0.136
F6	147± 5.29	63±5	1.145±0.045	2.65±0.145

Table 4 Results of *In-Vitro* release study of optimized formulation F4

S. No.	Time (Min.)	Cum % Drug release
1.	1	22.45
2.	2	45.65
3.	5	75.65
4.	10	89.98
5.	15	98.78

Table 5 Kinetics data of optimized formulation F4

Formulation	Regression Coefficient	Zero order	First order
F4	r^2	0.829	0.974

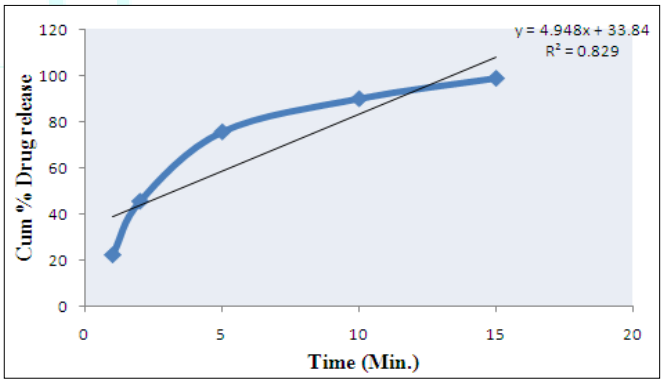

Fig. 3 Zero order release kinetics of optimized formulation F4

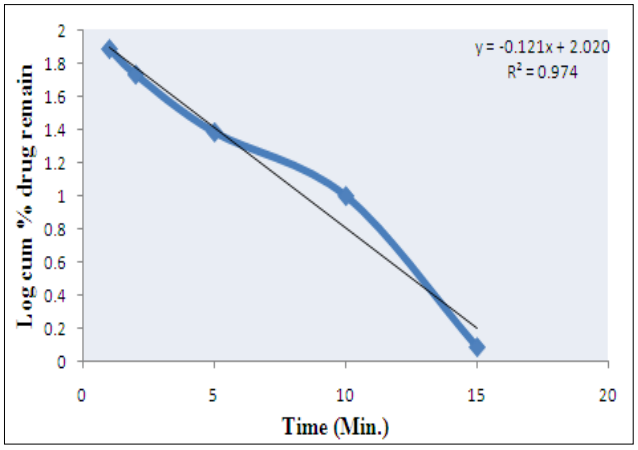

Fig. 4 First order release kinetics of optimized formulation F4

CONCLUSION

From present study 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. F4 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. Olanzapine administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric, psychiatric and also for general population by providing faster release and better patient compliance. Stability studies indicated F4 was stable for 90 days. Hence, there is a lot of scope for future *in vivo* studies.

REFERENCES

1. Worrel JA, Marken PA, Beckman SE, Ruehter VL. Atypical antipsychotic agents: a critical review. Am J Health Syst Pharm 200; 57: 238-55.
2. Ayala AP, Siesler H, Boese R, et al. Solid state characterization of olanzapine polymorphs using vibrational spectroscopy. Int J Pharm 2006; 326:69-79.
3. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Focus 2004; 2:59-67.
4. Sood S, Jawahar N, Jain K, et al. Olanzapine loaded cationic solid lipid nanoparticles for improved oral bioavailability. Curr Nanosci 2003; 9:26-34.
5. Krishnamoorthy V, Nagalingam A, Priya Ranjan Prasad V, et al. Characterization of olanzapine-solid dispersions. Iran J Pharmaceut Resh: IJPR 2009; 10:13-24.
6. Harde H, Das M, Jain S. Solid lipid nanoparticles: an oral bioavailability enhancer vehicle. Expert Opin Drug Deliv 2011; 8: 1407-24.
7. Cavallari C, Fini A, Ceschel G. Design of olanzapine/lutrol solid dispersions of improved stability and performances. Pharmaceutics 2013; 5: 570-90.
8. Aurora J, Pathak V. Oral disintegrating dosage forms, an overview. Drug Del Tech 2005; 5:50-54.
9. Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: a new approach to oral drug delivery system. Int J Pharm Investig 2013; 3:67-76.
10. Kathpalia H, Gupte A. An introduction to fast dissolving oral thin film drug delivery system: a review. Curr Drug Deliv 2013; 10:667-84.
11. http:// www.access data. fda. gov/drugsatfda_docs/ nda/2015/022524orig1s000chemr.pdf.
12. Senthilkumar K, Vijaya C. Formulation development of mouth dissolving film of etoricoxib for pain management. Advances in Pharmaceutics. 2015, Article ID 702963.
13. Kumar GV, Krishna RV, William GJ, Konde A. Formulation and evaluation of buccal films of Salbutamol sulphate. Ind J Pharm Sci 2005; 67: 160-164.
14. Nagar M, Nagar M, Chopra V. Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole, Der Pharm Lett 2012; 4 (4): 1221- 1227.
15. Prabhu P, Malli R, Koland M et al. Formulation and evaluation of fast dissolving films of levocetrizine dihydrochloride, Int J Pharm Inves 2011;1(2): 99-104.
16. Nafee NA, Boraie MA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. ACTA Pharm 2003; 53: 199-212.