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FORMULATION DEVELOPMENT AND OPTIMIZATION OF RAPID DISSOLVING FILM OF OLANZAPINE

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Abstract: As the psychotic, pediatric and geriatric patients are unable to swallow the medicine mouth dissolving drug delivery systems are designed to provide rapid action within minutes without the need of water, chewing or swallowing. Olanzapine rapid dissolving films were prepared by solvent casting technique. The 3^2 factorial design was applied for optimization of concentration of polymer PVA and plasticizer PEG 400. The prepared films were evaluated for various parameters related to delivery system like tensile strength, % elongation, folding endurance, disintegration time, drug content, *In vitro* release study and stability study. Optimised formulation F5 with PVA (3%) and plasticizer PEG 400 (35%) was giving low disintegration time (19.46 sec), sufficient strength, % elongation and high drug release (98.46%). Thus, Olanzapine film was formulated giving rapid release and immediate action for schizophrenic patients.

Keywords: Rapid dissolving film, Olanzapine, Schizophrenia, *Invitro* drug release, Disintegration time

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INTRODUCTION

Oral route of drug administration has been one of the most convenient and accepted route of drug delivery and amongst it the intraoral route is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules and liquid preparations. Various types of intraoral dosage forms used to deliver drug systemically or locally include- Liquids (solution sprays, syrups) Semi-solids (ointments, pastes) Solid dosage forms (quick dissolve and slow dissolve tablets, sublingual tablets, lozenges, films, filaments, gums, patches, lollipops).New dosage forms such as sprays, mucoadhesive patches or rapid dissolving solid matrices using advanced manufacturing processes (i.e. lyophilized wafers, solvent cast films) have been introduced recently. Of the intraoral dosage forms, rapid dissolving dosage forms have gained much attention due to improved patient compliance and ease of administration. Rapid dissolving dosage forms include orally disintegrating tablets (ODTs),oral thin films.[1,2]

RAPID DISSOLVING DRUG DELIVERY SYSTEM[2,3]

These dosage forms are intended to disintegrate, dissolve or release the drug in the oral cavity, where it has opportunity to be locally absorbed, in part or whole and alternatively may be swallowed and subsequently absorbed along the gastro-intestinal tract. Rapid dissolving drug delivery system are designed to meet the needs of special patients like geriatric, paediatric, mentally ill patients and dysphasic patients having difficulty in swallowing or chewing solid dosage forms.[2]

RAPID DISSOLVING FILMS[4]

Rapid dissolving film consists of fast dissolving polymer film embedded with drug. Which Quickly hydrated and dissolves when placed on the tongue or in the oral cavity(i.e., ducal, Palatal, gingival, lingualor sublingual)to provide rapid local or systemic drug delivery without need of water. The rapid dissolving film is also known as fast dissolving film, quick dissolving film, mouth dissolving film or oral thin film. Basically the rapid dissolving film can be consider as an ultra thin film of postage stamp size with an active agent or active pharmaceutical ingredient (API) and other excipients. The advantages of convenience of dosing and portability of rapid dissolving film have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

The film reportedly incorporates soluble, insoluble or taste masked drug substance. The film is manufactured as a large sheet and then cut into individual dosage unit for packaging in a range of pharmaceutical acceptable formats.

These films generally dissolve rapidly (within seconds), to release the active agents, but can be tailored to release the drug more slowly as well, depending upon their thickness, and selection of the polymer matrix.

Advantages of Rapid dissolving film.[5,6]

This dosage form enjoys some distinct advantages over other oral formulations such as-

➤ Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.

➤ The disadvantage of most ODTs is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.

➤ As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the Films.

➤ Pharmaceutical companies and consumers alike have embraced rapid dissolving film as a practical and accepted alternative to traditional over the counter (OTC) medicine forms such as liquids, tablets, and capsules.Fast dissolving film offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices.

➤ The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter into the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.

➤ Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.

➤ Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.

The drug selected for present work is Olanzapine. The drug is used as an atypical antipsychotic, approved by the FDA. It is a yellow crystalline solid, which is practically insoluble in water, used to treat schizophrenia and acute manic episodes associated with bipolar disorder.[7]

Olanzapine's half life is about 21-54 hours, thus effective as single daily dose medication. The usual oral dose of olanzapine for treating schizophrenia is 5-20 mg once daily.

It undergoes hepatic first pass metabolism after oral administration,40% of the dose is metabolized before reaching the systemic circulation. Therefore the drug satisfies the criteria for the dosage form films.

Schizophrenia is a mental disorder characterized by an breakdown of thought processes and by a deficit of typical emotional responses. The major problem of this disease relies with patients unwillingness to take or swallow tablets due to risk of choking.Thus an attractive dosage form like rapid dissolving films can be formulated to increase the patient compliance of schizophrenic patients.[8]

MATERIALS AND METHODS

Olanzapine was received as a gift sample from Nosch labortary Ltd, Hyderabad. PVA, PEG-400, Aspartame were received from S.D Fine Chemicals, Mumbai. The materials and reagents used in the study were of analytical grade.

Drug Excipient Compatibility Study

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm-1 by KBr disc method using FTIR spectrophotometer. FTIR study was carried out individually for drug and polymers and physical mixture of drug with all polymers. FTIR spectra of physical mixture of drug with all polymers were compared with FTIR spectra of pure drug and polymers.[9]

Preparation of Rapid dissolving film of Olanzapine

The composition of rapid dissolving film was optimized by using 3^2 full factorial design (table 1). In this study, two factors were evaluated each at three levels and experimental trials were performed at all nine possible combinations. The amounts of PVA (X1) and PEG-400 (X2) were selected as independent variables. These nine formulations were studied and optimized for Disintegration time and % Drug release.

Solvent Casting Method

Polymer PVA (2%,3%,4%) were weighed accurately and dispersed in water .Then calculated quantity of plasticizer(30%,35%,40%) was added and mixed well till clear solution was obtained. Then the drug was added to the polymeric solution. Then solution was poured into a clean and dry glass petri dish and allowed to dry. The dried films were carefully removed from the petri dish, checked for any imperfections or air bubbles and cut in to pieces of 4 cm^2.[6]

Evaluation of Rapid dissolving film of Olanzapine

Thickness

The thickness of the film was determined using a vernier calliper at three separate points of each film. From each formulation, three randomly selected films were tested for their thickness.[10]

Tensile Strength and % Elongation

A tensile strength of film is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of iron. The 4 cm^2 film equivalent to 25 mg drug from each formulation was taken. One end of the film was sandwiched between the iron plates and fixed. Other end was connected to a freely movable thread over a pulley. The weights were added gradually to the pan attached with the hanging end of the thread. The force needed to fracture the film was determined by measuring the total weight loaded in the pan. The weight corresponds to break the films were taken as tensile strength.[10]

The following equation was used to calculate the tensile strength (TS)

Load * 100/ Thickness * Width

For determination of % elongation, the initial length of the film was measured on scale and a pointer is attached to freely movable thread. Increase in length at the time of break of the film was recorded and % elongation was calculated by following formula.[10]

Initial length- Final length/ Initial length*100

Experiments were performed in triplicate and average value was reported.

Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.[11]

In vitro disintegration studies

Disintegration time gives an indication about the disintegration characteristics and dissolution Characteristics of the film. The film as per the dimensions (4 cm^2) required for dose delivery was placed on a stainless steel wire mesh placed in a petridish containing 10 ml distilled water. Time required for the film to break was noted as *in vitro* disintegration time.[11]

Drug Content

Three films were taken from each formulation and dissolved in 100ml isotonic phosphate buffer pH6.8. Then the solution was filter through whatman filter paper (0.45 µm). From the filtrate 1ml solution was taken and suitably diluted with isotonic phosphate buffer pH 6.8 and analyzed at 252 nm using a UV visible spectrophotometer. The experiments were performed in triplicate and average values were reported.[11]

Percentage Moisture Absorption (PMA)

The PMA test was carried out to check the physical stability of the mouth dissolving film at high humid conditions. Three films were taken, weighed accurately and placed in a desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccators at 79.5 %. After 72 hours the films were removed, weighed and percentage moisture absorption was calculated by using the following formula.[12]

PMA = (Final weight-Initial weight)/Initial weight *100

Percentage Moisture Loss (PML)

Percentage moisture loss was calculated to check the integrity of films at dry condition. Three 1cm square films was cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. The percentage moisture loss was calculated by using the following formula.**[12]**

PML=(Initial weight-Final weight)/Initial weight *100

In vitro dissolution studies

The in-vitro dissolution studies were conducted using dissolution media phosphate buffer (500 ml). The dissolution studies (n=3) were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at 37 ± 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 2 cm^2) was placed on a stainless steel wire mesh (700 µm). The film sample was placed on the sieve and submerged into dissolution media. Samples containing 5 ml volume were withdrawn at 0, 2, 5, 10, 15, 20, 25 and 30 min time intervals and filtered through 0.45 µm Whatman filter paper and were analyzed spectrophotometrically at 222.86 nm and at 270.62 nm respectively. To maintain the volume, an equal volume of fresh dissolution medium, maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment.[13]

Stability study

Stability testing of promising formulation was done by subjecting the films from optimized formulation at 40 °C temperature and 75% RH for one month. After 1 month samples were withdrawn and evaluated for physical appearance, drug content, tensile strength, % elongation, folding endurance, % drug release study as discussed earlier.[14]

RESULT AND DISCUSSION

Drug Excipient Compatibility

Drug- Excipient interaction study Infrared spectroscopy was used as means of studying drug-excipients interactions. It was found that there was no chemical interaction between Olanzapine and excipients used because there were no changes in the characteristic peaks of Olanzapine in the IR spectra of mixture of drug and excipients as compared to IR spectra of pure drug.(Figure no.1 and 2)

EVALUATION OF FACTORIAL DESIGN FORMULATIONS (F1 TO F9)

Thickness

The results of thickness from various formulations (F1 to F9) are given in table 2. Thickness of all the films was in the range of 0.098±0.06 to 0.22±0.004 gm/cm^2 with very low values of standard deviation suggesting all films have appropriate thickness.

Tensile Strength

The results of tensile strength from various formulations (F1 to F9) are given in table 2. Tensile strength of all the films was in the range of 314±4.53 to 508±4.22 gm/cm^2 with very low values of standard deviation suggesting all films were having good mechanical strengths to withstand mechanical damage during, production and application.

% Elongation

The results of % elongation from various formulations (F1 to F9) are given in table 2.The results revealed that % elongation was in the range of 6.8±2.09 to 8.7±3.12. This represents the elasticity of the film. Increase in concentration of PVA results in enhancement of elasticity of films.

Folding Endurance

The results of folding endurance of various formulations (F1 to F9) are given in table 2. All the films were showing folding endurance in the range of 120±2.08 to 163±0.12. Results revealed that as the concentration of polymers increases folding endurance increases.

Disintegration Time

The results of disintegration time of various formulations (F1 to F9) are given in table 2.All the films were showing disintegration time in the range of 16.03±0.24 to 28.87±0.30. Results revealed that as the concentration of polymers increases disintegration time increases.

Drug content

The results of drug content of various films are given in table 3. The results indicate that drug content of films were in the range of 91.33 ± 0.41 to 98.91 ± 0.30%. The standard deviation values were very less suggesting that the drug was uniformly dispersed and the method adopted was accurate and reproducible.

% moisture absorption

The results of % moisture absorption of various films are given in table 3. The results indicate that % moisture absorption of films were in the range of 1.52 ± 0.549 to 2.04 ± 0.528. The standard deviation values were very less suggesting that the drug absorbed low moisture content.

% moisture loss

The results of % moisture loss of various films are given in table 3. The results indicate that % moisture loss of films were in the range of 1.01 ± 0.015 to 2.06 ± 0.514. The standard deviation values were very less suggesting that the drug lost low moisture content.

Invitro Drug release

It can be seen from the table 4 and figure 3 that the cumulative % drug release from the formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9 was found to be 96.03 ± 0.96, 94.26 ± 1.09, 96.23 ± 0.89, 97.67 ± 1.09, 98.96 ± 2.31, 97.63 ± 0.99, 95.88 ± 1.10, 95.08 ± 0.83 and 94.30 ± 1.06 at the end of 30 min respectively. The results suggest that PVA plays an important role in the release of drug from the films. Films having lower concentration of PVA showed higher values of drug release as compared to films having higher amount of PVA. Formulation F5 showed the highest value of drug release of 98.96 ± 2.31%.

Stability study

The promising formulation F5 was subjected at 40 ± 0.5 °C temperature and 75 ± 5 % RH for 1 month to check the stability. The results of physical appearance, drug content, disintegration time and other parameters after 1 month storage of prepared fast dissolving films are shown in table 5 and % drug release is shown in table 6.

CONCLUSION

The formulation F5 satisfied all pharmaceutical parameters of rapid dissolving films and appears to be promising would be able to offer benefits such as rapid drug release, good disintegration time, tensile strenght and promising % elongation and thereby may help to improve the bioavailability of drug.

Table 1: Composition of Factorial Design Formulations of Olanzapine

Batch No.	Drug: Inclusion Complex (mg)	PVA (%w/w)	PEG 400 (%w/w of dry polymer)	Citric Acid (mg)	Aspartame (mg)	Orange Flavour (ml)	Water (ml)
F1	418.881	2%	30%	30	20	0.5	10
F2	418.881	3%	30%	30	20	0.5	10
F3	418.881	4%	30%	30	20	0.5	10
F4	418.881	2%	35%	30	20	0.5	10
F5	418.881	3%	35%	30	20	0.5	10
F6	418.881	4%	35%	30	20	0.5	10
F7	418.881	2%	40%	30	20	0.5	10
F8	418.881	3%	40%	30	20	0.5	10
F9	418.881	4%	40%	30	20	0.5	10

Table 2: Physicochemical Evaluation of Fast Dissolving Film of olanzapine

Batch No.	Thickness* (mm)	Tensile* Strength (gm/cm^2)	% Elongation*	Folding Endurance*	Disintegration Time* (sec)
F1	0.098±0.06	314.00±4.53	6.8±2.09	120±1.52	16.03±0.24
F2	0.10±0.002	346.33±3.52	7.4±0.39	129±4.15	18.23±0.28
F3	0.104±0.02	378.41±1.41	7.8±0.52	137±2.52	20.08±0.19
F4	0.102±0.001	400.67±1.74	7.5±3.12	134±3.52	17.33±0.21
F5	0.11±0.003	420.45±3.52	7.8±0.82	139±1.53	19.46±0.52
F6	0.16±0.002	462.66±2.52	8.0±1.11	147±2.08	22.31±1.6
F7	0.12±0.003	449.32±2.43	7.9±0.87	141±2.68	21.16±0.49
F8	0.19±0.001	480.53±3.87	8.2±3.52	150±1.79	24.69±0.29
F9	0.22±0.004	508.92±4.22	8.7±2.12	163±1.53	28.87±0.33

*Values are means ± SD, (n=3).

Table 3: Evaluation of prepared films

Batch No.	Drug content*	% moisture absorption	% moisture loss
F1	91.78 ± 0.30	1.70 ± 0.590	1.37 ± 0.598
F2	91.33 ± 0.41	1.66 ± 0.554	1.01 ± 0.015
F3	95.40 ± 0.45	1.99 ± 0.031	1.34 ± 0.592
F4	97.30 ± 0.34	1.60 ± 0.572	1.29 ± 0.580
F5	98.61 ± 0.41	1.58 ± 0.930	1.25 ± 0.537
F6	92.86 ± 0.16	1.82 ± 0.025	1.22 ± 0.525
F7	98.91 ± 0.30	1.76 ± 0.549	1.53 ± 0.517
F8	94.26 ± 0.18	2.04 ± 0.528	2.06 ± 0.514
F9	95.33 ± 0.38	2.00 ± 0.509	1.44 ± 0.508

*Values are means ± SD, (n=3).

Table 4: In vitro cumulative % drug release in phosphate buffer pH 6.8

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	31.72± 1.121	35.50± 2.871	37.31± 1.034	42.70± 1.341	44.45± 1.345	46.31± 1.234	30.03± 1.034	29.92± 3.104	27.36± 1.364
5	45.54± 0.934	49.63± 2.360	54.20± 2.467	59.98± 2.119	62.51± 1.970	56.60± 0.796	52.77± 1.397	49.32± 2.541	42.43± 2.671
10	56.67± 1.037	58.39± 1.789	62.85± 2.111	69.32± 2.006	71.35± 0.873	68.62± 1.843	64.12± 1.863	61.92± 1.301	59.86± 2.009
15	69.76± 2.047	72.26± 3.214	75.79± 0.687	76.50± 1.943	80.62± 0.931	74.55± 0.873	71.04± 2.548	69.10± 2.037	68.73± 1.942
20	74.39± 1.348	79.44± 0.541	81.41± 0.982	82.86± 1.083	87.28± 1.094	82.00± 0.795	85.83± 2.317	76.01± 0.901	72.81± 0.864
25	86.14± 0.843	88.30± 1.067	85.93± 1.643	91.08± 0.837	93.22± 2.314	90.58± 1.04	91.44± 1.347	87.63± 0.861	85.54± 1.993
30	93.41± 0.701	97.03± 0.961	96.38± 1.092	96.11± 0.899	98.46± 0.613	96.88± 1.107	97.42± 0.937	95.83± 1.672	94.53± 0.991

*Values are means ± SD, (n=3).

Table 5: Stability study of promising batch F5:

Parameter	At 0 day	After 30 days
Appearance	Good	No change
Drug content	98.61± 0.41	97.05 ± 0.27
Disintegration time (min.)	19.46± 0.52	18.69 ± 2.32
Tensile strength (gm/cm^2)	420.45± 3.52	188.67 ± 1.53
% elongation	7.8 ± 0.82	4.44± 2.12
Folding endurance	139± 1.53	109± 3.06

The results of % cumulative drug release of promising formulation (F7) after 1 month of storage is shown in table 6.

Table 6: *In vitro* % drug release of F5 at 0 day and after 30 days

Time	% Cumulative drug release	
	At 0 day*	**After 30 days***
0	0.00 ± 0.000	0.00 ± 0.000
2	44.45±1.345	27.0± 0.137
5	62.51± 1.970	53.23± 0.896
10	71.35± 0.873	63.14± 1.067
15	80.62± 0.931	76.12± 0.936
20	87.28± 1.094	86.56± 1.009
25	93.22± 2.314	92.75± 0.861
30	98.46±0.631	96.21±0.012

*Values are means ± SD,(n=3

IR Spectroscopy of pure drug

Fig 1: FT-IR spectrum of Olanzapine
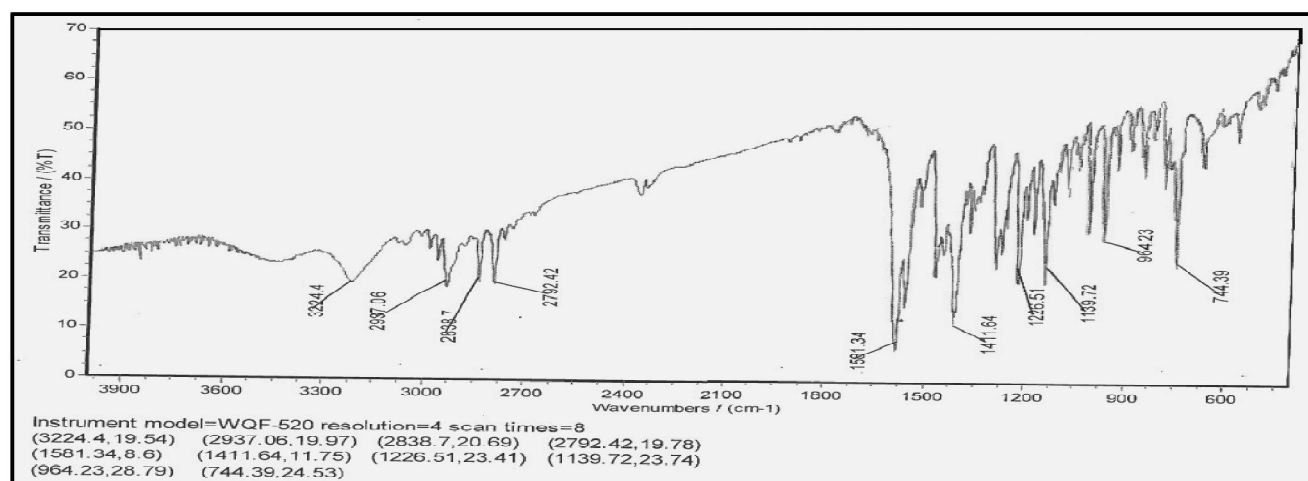
Pure drug + Excipients

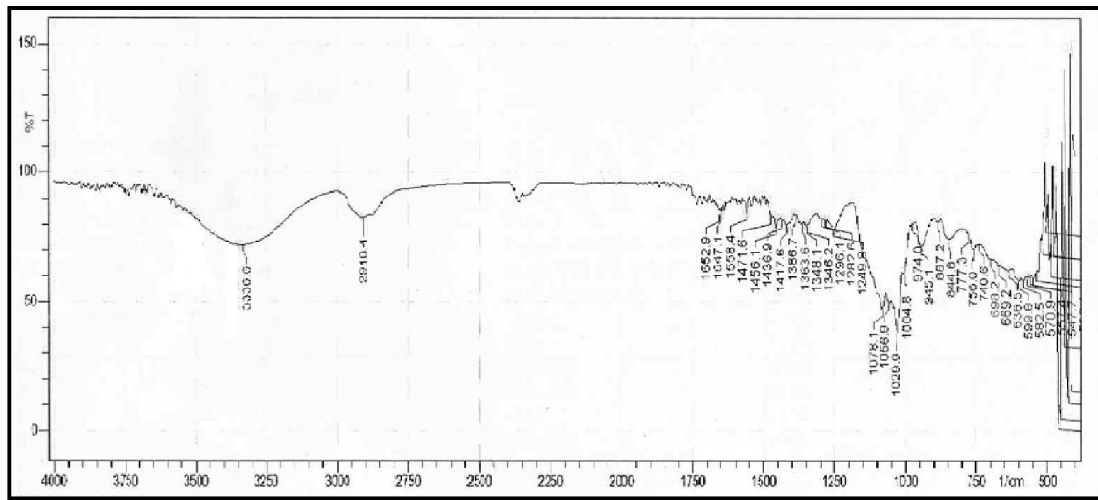**Fig 2: FTIR spectra of physical mixture of olanzapine and excipients**

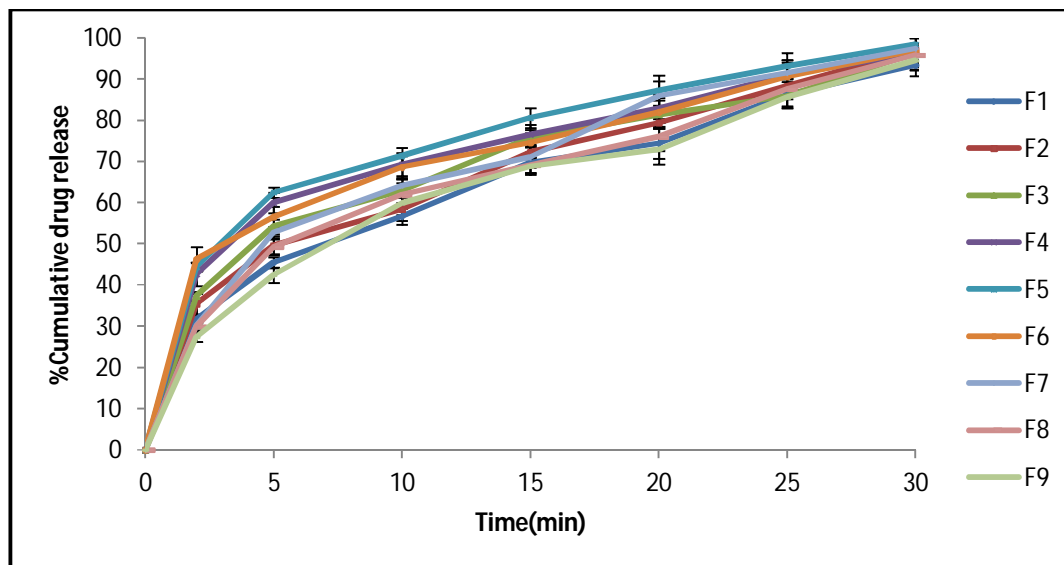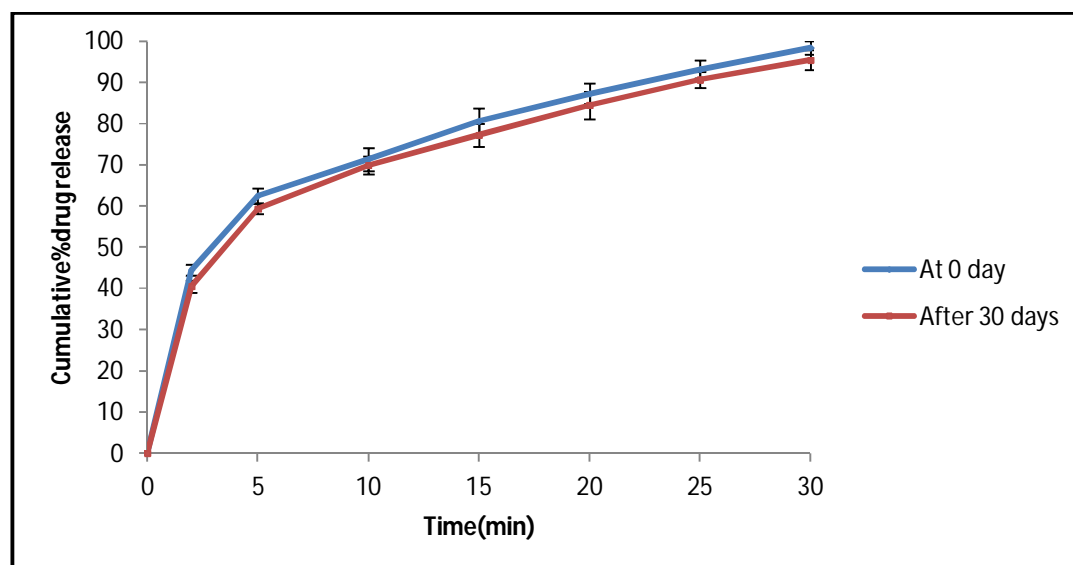**Fig. 3:** *In vitro* **dissolution of olanzapine of formulations F1 to F9**

Fig.4: *In vitro* **% drug release of F5 at 0 day and after 30 days**

REFERENCES

1. Cilurzo F, Cupone IE, MinghettiP, and Montanari L: Fast dissolving films made of maltodextrin. European Journal of Pharmacy & Biopharmaceutics 2008; 70: 895-900.

2. Mashru RC, Sutariya VB, Sankalia MG and Parikh PP: Development and evaluation of fast dissolving film of salbutamol sulphate. Drug Development & Industrial Pharmacy 2005; 31: 25-34

3. Prabhu P, Ali RM, Koland M, Naravana KV: Formulation and evaluation of fast dissoving films of levocetrizine dihydrochloride. International Journal of Pharmaceutical Investigation 2011; 1(2): 99-104

4. Doaa Ahmed, Minghetti P and Buratti S: orodispersible film of the antidepressant drug tianeptine. AAPS PharmSciTech 2010; 11(4):1511–1517.

5. Ghorwade kumar Vijay, Patil kumar Ajay: Formulation and evaluation of Montelukast sodium fast dissolving films by using Gelatin as a film base. Research Journal of Pharmaceutical Biological and Chemical Sciences 2011; 2(3):880-888.

6. Seema Saini, A.C.Rana, and Sumit Gupta: Optimization of formulation of fast dissolving films made of pullulan polymer. International Journal of Pharmaceutical Sciences Review and Research 2011; 9(1):128-131.

7. Kulkarni Ajit Shankarrao, Ghadge Dhairysheel Mahadeo and Kokate Pankaj Balavantrao: Formulation and *In-vitro* Evaluation of Orally Disintegrating Tablets of Olanzapine-2-Hydroxypropyl-β-Cyclodextrin Inclusion Complex. Iranian Journal of Pharmaceutical Research 2010; 9 (4): 35-47.

8. Siva Prasad Reddy S, Hindustan Abdul Ahad, Sreenivasulu R, Kishore Kumar Reddy B, Krishna Mahesh CH, Kranthi G, Chandrasekhar A: Designing of Mouth Dissolving Tablets for Bitter Drugs Taking Clozapine as Model Drug. Scholars Research Library 2011; 3(1): 13-20.

9. Sarath Chandiran, V. Narayanan and S. Sushma: Formulation and evaluation of olanzapine as oro-dispersible drug delivery system by using beta cyclodextrin and super disintegrant. International journal of pharmaceutical sciences and research 2011; 2(5): 1212-1216.

10. Shirsand SB, Sarasija Suresh, Swamy PV, Nagendra Kumar D, Rampure MV: Design and evaluation of fast dissolving tablets of clonazepam. Indian J Pharm Sci 2008; 70(6): 91-105.

11. Sudhakar Sekar, V. Malarvizhi and C. Vijaya: Formulation and optimization of fast dissolving tablet of olanzapine using vaccum drying technique by 2^2 factorial design. International journal of pharmaceutical sciences and research 2011; 2(6): 1594-1599.

12. Anil kumar katharya,Rajiv sharma: Development and Optimization of Solid Dispersion of Olanzapine in Poly Ethylene Glycol by D-Optimal Response Surface Factorial Design. International Journal of PharmTech Research 2013; 5(2):700-710.

13. Manjunatha Kattalagere Maheswarappa, Priyankabahen Dineshchandra Desai: Design and *in-vitro* evaluation of mouth dissolving tablets of Olanzapine. Asian journal of pharmaceutics 2011; 5: 17-33.

14. Marcia Rocha de Freitas: Inclusion complex of methyl-cyclodextrin and olanzapine as potential drug delivery system for schizophrenia. Carbohydrate Polymers 2012*;2:*1095– 1100.

15. Mudit Dixit, Ashwini Gopalkrishna Kini, Parthasarthi Keshavarao Kulkarni: Enhancing the aqueous solubility and dissolution of olanzapine using freeze-drying. Brazillian Journal Of Pharmaceutical Sciences 2011;47: 741-751.