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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF OLANZAPINE

Md. Shabuddin*, T. Praveen Kumar, Ch. Sowjanya, Dr. P. Suresh Kumar, Syed Yasmin Sulthana and Dr. V. Jagannath Patro

Department of Pharmaceutics, Browns College of Pharmacy, Khammam, Telangana, Pin – 507 305.

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***Corresponding Author**
Md. Shabuddin
Department of Pharmaceutics, Browns College of Pharmacy, Khammam, Telangana, Pin – 507 305.

ABSTRACT

The objective of this study was to prepare the orally dissolving films of Olanzapine which can be used as Anti emetic, Antipsychotic Agent, Serotonin Uptake Inhibitors. The orally disintegrating films (ODF) of Olanzapine were prepared by solvent casting method using different water soluble low viscosity grades of polymers such as HPMC E3, HPMC E6 and HPMC E15. The films were characterized for various physicochemical properties such as thickness measurement, weight variation, % drug content, folding endurance, In vitro disintegration time, In vitro dissolution time. The experimental results indicated that polymer concentration; plasticizer concentration had complex effects on % drug release. In this study best formulation was chosen from each polymer based on release parameters. It was found that with HPMC E3, F1 was found to be best formulations, with HPMC E6, F5 and F6 was found to be best formulation and with HPMC E15, F9 were found to be best formulations. The prepared film was clear, transparent and had a smooth surface. The DSC and FTIR study revealed no drug polymer interactions. The prepared orally dissolving films have good commercial success after performing the stability study.

KEYWORDS: Olanzapine, orally disintegrating films, Serotonin Uptake Inhibitor, solvent casting.

INTRODUCTION

Fast dissolving oral films are the most advanced form of oral solid dosage form due to their flexibility and comfort.[1] It improves the efficacy of the drug by dissolving within a minute

in oral cavity after the contact with saliva. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa i.e 4-1000 times greater than that of skin.[2,3] Oral films are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active life style.[4] 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 high patient compliance.[5,6]

Olanzapine is an antipsychotic agent used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia. It may also be used for the treatment of obsessive-compulsive disorder and severe behavioral disorders in autism in near future. Its antipsychotic activity is due to a combination of antagonism at D2 receptors in the mesolimbic pathway and 5HT2A receptors in the frontal cortex. Antagonism at D2 receptors relieves positive symptoms while antagonism at 5HT2A receptors relieves negative symptoms of schizophrenia. It is well absorbed but it is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.[7,11]

MATERIALS AND METHOD

Materials

Pure drug Olanzapine was obtained from Aurobindo Pharma Labs, HPMC was obtained from Colorcon Asia Pvt. Ltd, Methanol, Dichloro methane, Poly ethylene glycol was obtained from S.D. Fine Chem Ltd, Acesulfame k, Aspartame, Menthol was obtained from Himedia Lab Pvt Ltd, Orange flavor, Banana flavor was obtained from Pentagon trading company.

Method

The ODFs of Olanzapine were prepared using different grades of HPMC, E6 and HPMC E15 in the ratios of 1:2.5, 1:5, 1:7.5 and 1:10 drug to polymer ratio. The polymeric solution was prepared by using dichloromethane and methanol in the ratio of 1:0.5 and kept aside for complete swelling of polymer. Olanzapine was dissolved in measured quantity of solvents and this drug solution was added to the above polymeric solution. This step was followed by the addition of plasticizers such as PEG 400, Sweetener and flavor was also added. Uniformity of drug content is achieved by mixing in cyclo mixer for 15-20 minutes. The solution was cast on a prepared mould and air dried for 45 minutes. The film was carefully

removed from the mould, checked for imperfections. Film samples with air bubbles, cuts, or imperfections were excluded from the study.

Table no. 1: Formulation development of Olanzapine ODF prepared with different grades of HPMC.

Ingredients	Formulation codes											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
Olanzapine (mg)	10	10	10	10	10	10	10	10	10	10	10	10
HPMC E3 (mg)	25	50	75	100	--	--	--	--	--	--	--	--
HPMC E6 (mg)	--	--	--	--	25	50	75	100	--	--	--	--
HPMC E15 (mg)	--	--	--	--	--	--	--	--	25	50	75	100
Dichloromethane(ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Methanol (ml)	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
PEG 400 (ml)	10	10	10	10	10	10	10	10	10	10	10	10
Asusulfame Potassium (mg)	1	1	1	1	1	1	1	1	1	1	1	1
FDC Yello colour (mg)	1	1	1	1	1	1	1	1	1	1	1	1
Banana flavor (mg)	1	1	1	1	1	1	1	1	1	1	1	1

Evaluation of Films

Weight variation[12]

The films were weighed individually from the randomly selected batches. The average of five readings from each batch was calculated and reported.

Thickness[13]

The thickness of the films was measured using digital Vernier caliper. Three Readings from all the batches were taken and mean thickness was calculated and reported.

Folding endurance[14]

A strip of film was folded repeatedly at the same place until it was broken. The number of times the film could be folded at the same place without breaking was recorded as the value of folding endurance.

Drug Content[15]

The films are placed in a volumetric flask containing 100 ml of 0.1N HCl. The medium was sonicated for 15 min and filtered using Whatman filter paper. The filtrate was suitably diluted and analyzed using UV spectrophotometer against 0.1N HCl as blank at λ max 252 nm.

In vitro disintegration time[16]

In vitro disintegration time of the films was determined visually in a petridish with 25 ml 0.01N HCl and swirling was done for every 10 sec. The time taken by the film to disintegrate was taken as disintegration time.

In-vitro dissolution studies[17]

In vitro Dissolution study was carried out using USP type II (basket type) apparatus with 0.01N HCl as a dissolution medium. The temperature was maintained at 37±0.5^{0}C with 50 rotations per minute. 5ml of aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were diluted suitably and analyzed for drug content at λ max 252 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported.

Drug Excipient Compatibility Study

Fourier Transform Infrared spectroscopy (FT-IR)[18]

The FT-IR spectra acquired were taken from dried samples. A FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400 cm^{-1}, and 4 cm^{-1} resolution. The results were the means of 6 determinations. A quantity equivalent to 2 mg of pure drug and drug HPMC films were selected separately.

Differential scanning colorimetric study (DSC)[19]

Differential scanning calorimetry (DSC) study of pure drug and prepard films was performed using a Diamond DSC (Mettler Star SW 8.10) to determine the drug excipient compatibility study. The analysis was performed at a rate 5^{0}C min -1 from 50^{0}C to 200^{0}C temperature range under nitrogen flow of 25 ml min -1.

Scanning electron microscopy (SEM)[20]

The surface morphology of the optimized formulations was observed by scanning electron microscopy. The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at 200X, 500X and 1000X magnification.

RESULTS AND DISCUSSION

Formulation development of ODF of Olanzapine prepared With different grades of HPMC

Orally disintegrating films of Olanzapine were prepared using HPMC E 3 polymer, which was dissolved in the methanol and dichloromethane. The drug was then soaked in the above polymer mixture. The films were prepared by using solvent casting method. Good films were formed with the adopted method. The prepared films were characterized for various Physico chemical properties.

Table no 2: Physico chemical Properties and In Vitro drug release profile of Olanzapine ODF prepared with HPMC.

Parameter	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F=12
Thickness (mm)	0.11± 0.03	0.12± 0.04	0.14± 0.02	0.17± 0.03	0.14± 0.03	0.16± 0.04	0.17± 0.02	0.19± 0.03	0.15± 0.02	0.17± 0.03	0.18± 0.02	0.20± 0.03
Disintegration time (Sec)	11± 2.0	19± 2.0	28± 2.0	40± 3.0	19± 2.0	26± 2.0	38± 2.0	44± 3.0	24± 3.0	32± 3.0	48± 2.0	60± 4.0
Assay (%)	99	98	99	99	97	98	98	99	99	98	98	99
Folding Endurance	>300	>300	>300	>300	>300	>300	>300	>300	>300	>300	>300	>300
Dissolution Time(min)	**% Drug release**											
0	0	0	0	0	0	0	0	0	0	0	0	0
5	90	85	75	70	87	80	72	68	84	75	70	65
10	96	90	88	85	90	85	80	75	89	83	78	72
15	99	99	94	92	97	92	90	88	93	90	87	80
30	99	99	99	99	100	99	99	96	98	97	94	91

Physicochemical Properties and In Vitro drug release profile of Olanzapine ODF prepared with HPMC E3

The thickness of the prepared films was found to be 0.11 to 0.17. The disintegration time was found to be 11 to 40 sec. The disintegration time was mainly depends on the polymer concentration. The disintegration time was more for the ODF prepared with 1:10 ratio of the HPMC E3. The assay of the prepared films was found to be 98 to 99 which were within the pharmacopoeia limits. The folding endurance of all the formulations was found to be more than 300.

In vitro dissolution of the prepared ODF of Olanzapine were performed in 900 ml of 0.1 N HCl. In vitro dissolution was faster in the ODF prepared with low polymer content and the dissolution rate was retarded with increase in the polymer concentration. All the formulations were released the complete drug in 30 minutes but in case of Oral disintegration formulations the release of initial time point is important for the rapid absorption. Initial rapid release was

observed up to 1:2.5 ratio of the formulations. Almost 96% of drug was released in formulation F1 with in 10 mins. Initial delayed release was observed in the formulation prepared with 1: 10 ratio. This may be due to the increased polymer concentration. This can directly correlate with the disintegration time which was found around 40 sec.

Physicochemical Properties and In Vitro drug release profile of Olanzapine ODF prepared with HPMC E6

The thickness of the prepared films was found to be 0.14 to 0.19. The disintegration time was found to be 19 to 44 sec. The disintegration time was mainly depends on the polymer concentration. The disintegration time was more than 30 sec for the ODF prepared with 1:7.5 and 1:10 ratio of the HPMC E6. The assay of the prepared films was found to be 97 to 99 which were within the pharmacopoeia limits. The folding endurance of all the formulations was found to be more than 300.

In vitro dissolution was faster in the ODF prepared with low polymer content and the dissolution rate was retarded with increase in the polymer concentration. All the formulations were released the complete drug in 30 minutes except the formulation prepared at 1: 10 ratio. Initial rapid release was observed up to 1:2.5 ratio of the formulations. 97% of drug was found to be released in F5 within 15 mins. Initial delayed release was observed in the formulation prepared with 1: 7.5 and 1: 10 ratio. This may be due to the increased polymer concentration. This can directly correlate with the disintegration time which was found around 38 and 40 sec respectively.

Physicochemical Properties and In Vitro drug release profile of Olanzapine ODF prepared with HPMC E15

The thickness of the prepared films was found to be 0.15 to 0.20. The thickness was increased with increase in the polymer concentration. The disintegration time was found to be 24 to 60 sec. Only the formulation prepared at 1:2.5 ration show the good disintegration and found below 30 sec. The disintegration time was mainly depends on the polymer concentration. The disintegration time was more than 30 sec for the ODF prepared with 1:5 1:7.5 and 1:10 ratio of the HPMC E15. The assay of the prepared films was found to be 98 to 99 which were within the pharmacopoeia limits. The folding endurance of all the formulations was found to be more than 300.

All the formulations were released the complete drug in 30 minutes except the formulation prepared at 1: 10 ratio. But in case of Oral disintegration formulations the release of initial time point is important for the rapid absorption. Initial rapid release was observed for the formulation prepared at 1:2.5 ratio. Initial delayed release was observed in the formulation prepared with 1: 5, 1: 7.5 and 1: 10 ratio. This may be due to the increased polymer concentration. This can directly correlate with the disintegration time which was found around 32, 48 and 60 sec respectively.

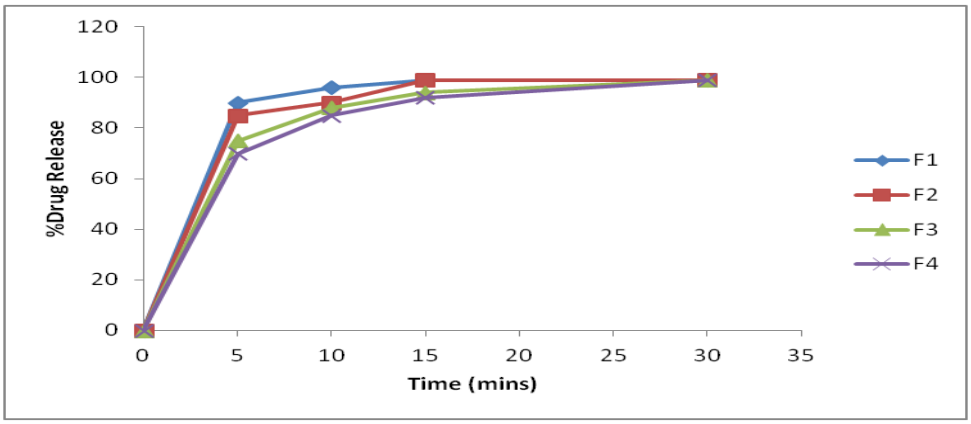

Fig. 1: Dissolution profiles of the Olanzapine ODF prepared with HPMC E 3.

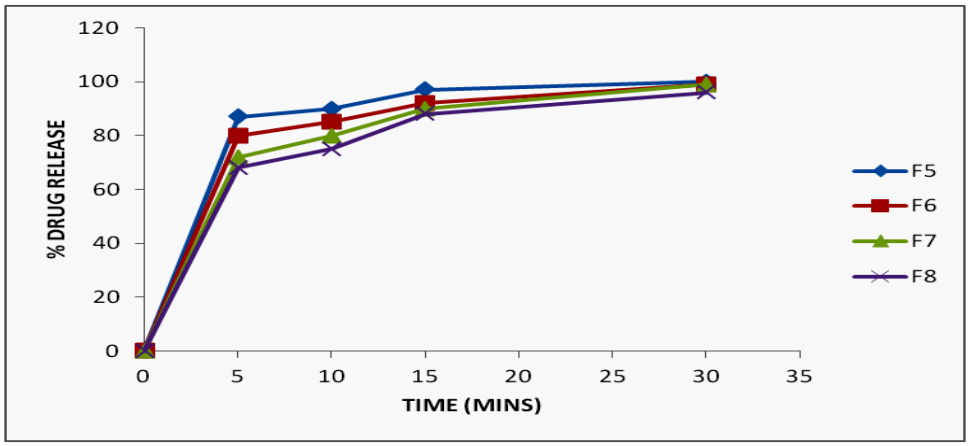

Fig. 2: Dissolution profiles of the Olanzapine ODF prepared with HPMC E 6.

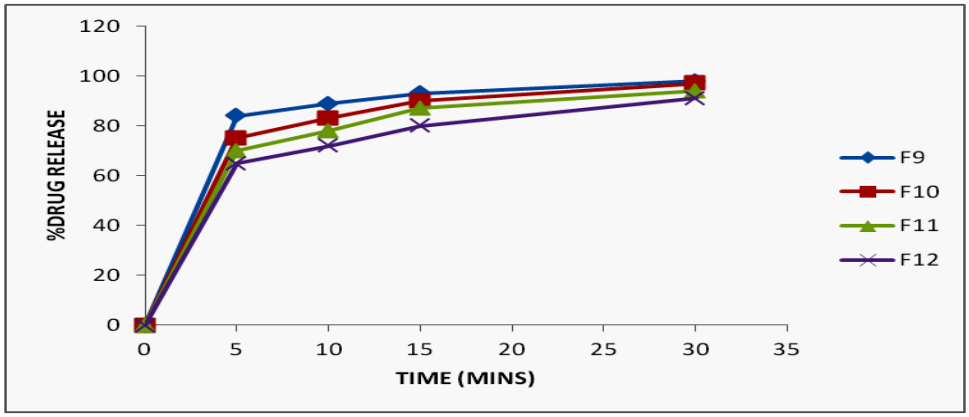

Fig. 3: Dissolution profiles of Olanzapine ODF prepared with HPMC E15.

Drug Excepient Compatibility Study

Differential scanning calorimetric study

DSC thermograms of pure Olanzapine showed sharp endothermic peak at 196.9^{0}C. Similar sharp endothermic peaks were observed in the formulations prepared with the HPMC. This clearly indicated no drug polymer interaction. Fig showed the DSC thermograms of pure drug and the prepared Olanzapine ODF.

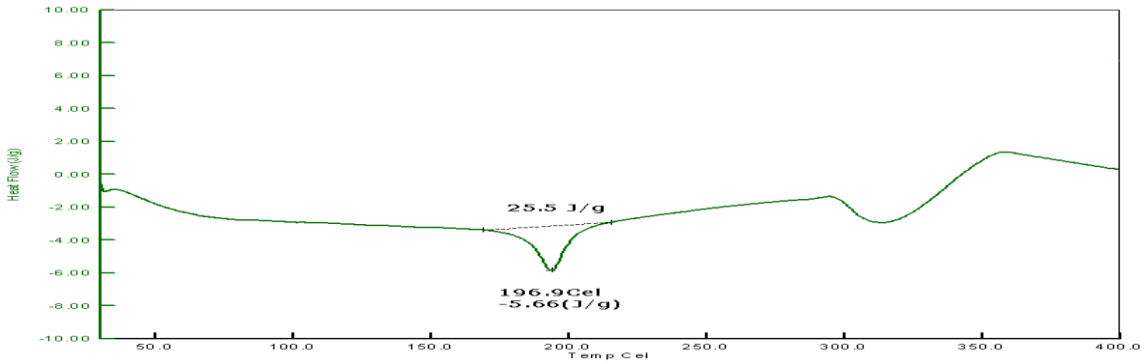

Fig. 4: DSC thermogram of Pure Olanzapine.

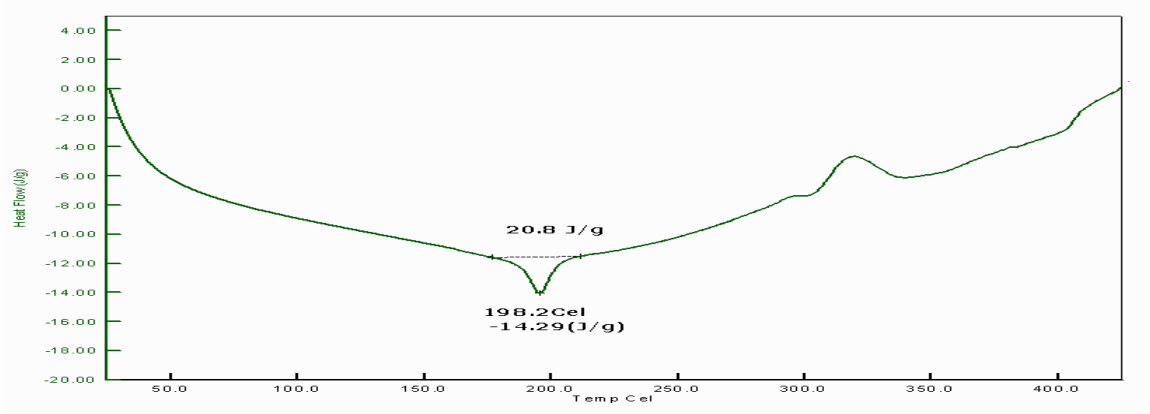

Fig. 5: DSC thermogram of Olanzapine Orally disintegrating films.

Fourier Transforms Infrared Radiation measurement (FT-IR)

The FTIR spectrum of pure Olanzapine and Olanzapine ODF showed similar spectrum peak points clearly indicating no drug polymer interaction.

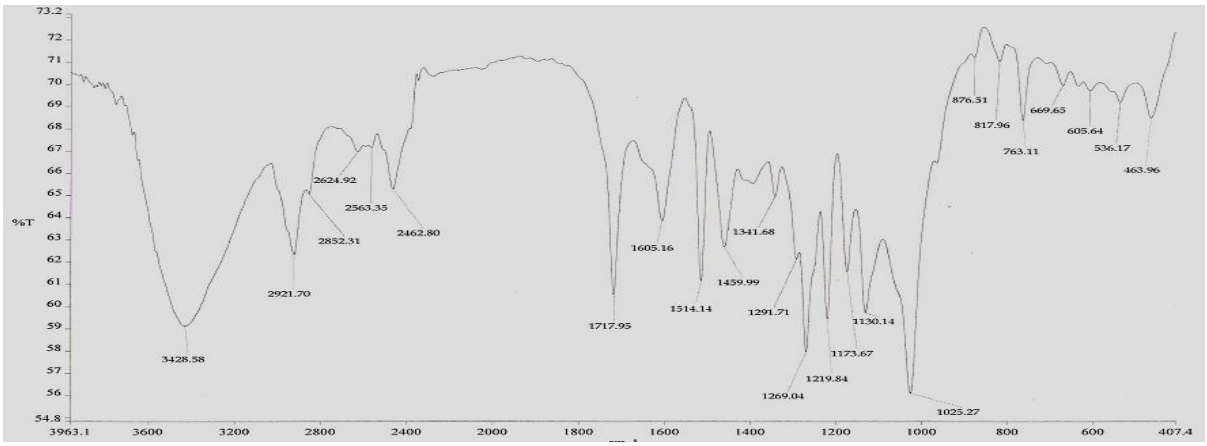

Fig. 6: FTIR Spectrum of Pure Olanzapine.

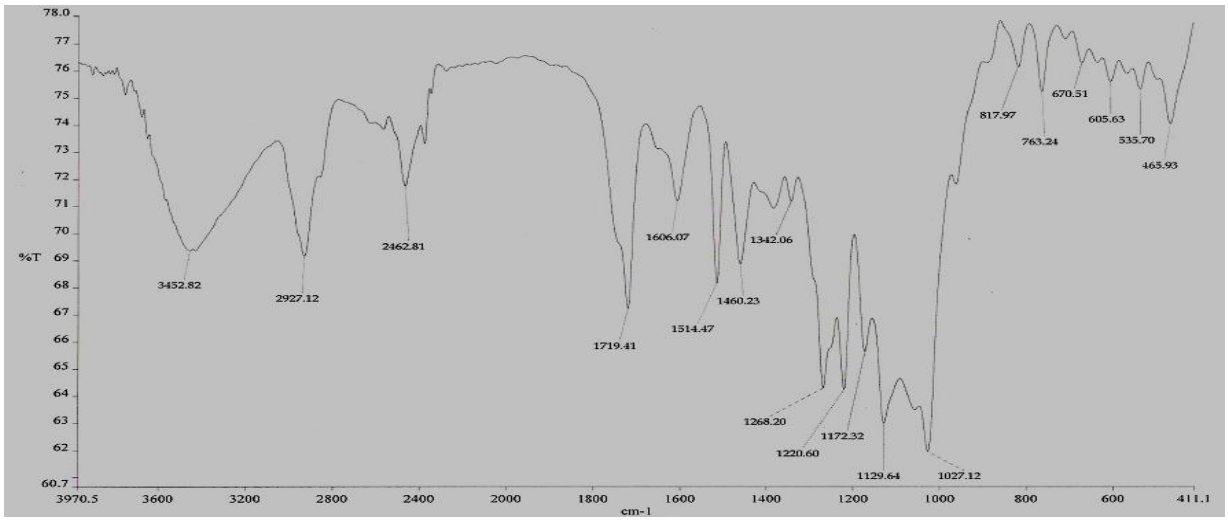

Fig. 7: FTIR Spectrum of Olanzapine ODF.

Scanning Electron Microscopy (SEM) study

SEM determines the surface morphology of the film as they revealed as best formulation. The surface morphology of the optimized formulations was observed with scanning electron microscope. The samples were attached to the slab surfaces with double-sided adhesivetapes and the scanning electron photomicrograph was taken at 200X, 500X and 1000X magnification. The surface of films was found to be smooth and uniform.

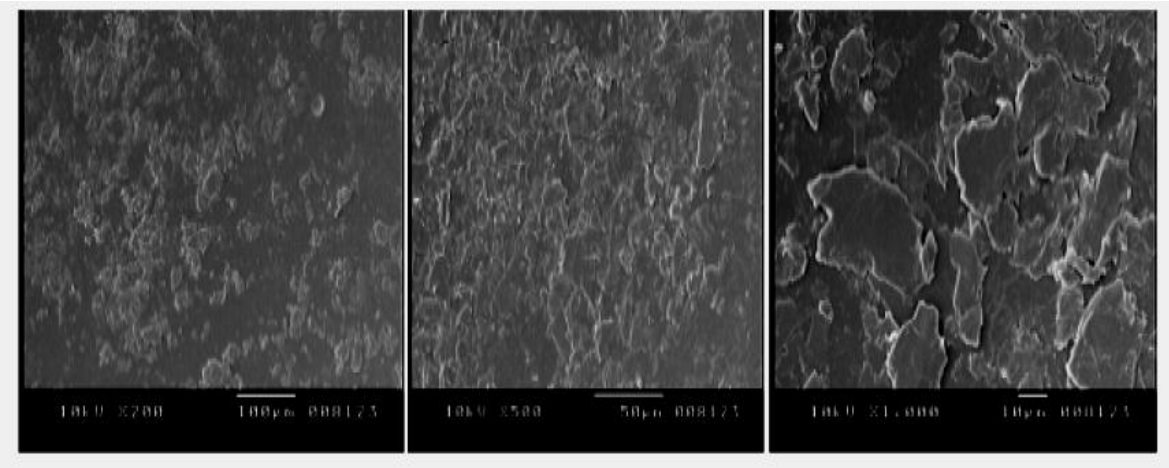

Fig. 8: SEM images of film containing olanzapine prepared with HPMC E3.

CONCLUSION

The orally dissolving films (ODF) were prepared using a solvent casting technique by water soluble polymers like HPMC E3, HPMC E6, HPMC E15 of various concentrations and PEG 400 as a plasticizer and an active ingredient Olanzapine to measure the effect on dissolution profile. The weight of the films prepared were uniform. The disintegration time was found in the range of 11 to 60 sec. The thickness was found in the range of 0.11mm to 0.20mm. The drug content was within the pharmacopoeial limits. The results shown that drug dissolved quickly and had good onset of action. This study indicates the possibility of oral delivery of Olanzapine by orally disintegrating film. The low viscosity polymers were dissolved faster than the high viscosity polymers. The FTIR and DSC studies showed that there is no interaction between the selected polymer and drug. The SEM studies showed that the films prepared where smooth and uniform. Sweetener such as asusulfame potassium, banana flavor was used to improve taste and mouth feel. DSC and FTIR study shows no drug-Excepient interaction.

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