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Research Article

FORMULATION AND EVALUATION OF ORALLY DISINTEGRATING FILM OF TRAZODONE HYDROCHOLRIDE

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ABSTRACT

Trazodone Hydrochloride, an serotonin reuptake inhibitor antidepressant. Trazodone Hydrochloride undergoes first pass metabolism on oral administration resulting in reduced bioavailability (60%). Thus the objective of the present study was to formulate and evaluate orally disintegrating film of Trazodone hydrochloride to overcome the limitation of bioavailability and increase patient's compliance. In the present study orally disintegrating film were prepared by solvent-casting method using hydrophilic polymer HPMC K-15, CMC, PEG 6000 as plasticizer. The eight formulations were prepared by the application of freeze drying technology to four formulation and heat drying technique for remaining four formulation and evaluated for the comparative study between heat dried and freeze dried films. It was found that, the freeze drying technology has potential to modify drug release rate and posses good stability and less fragile property. The F4 batch of Freeze dried orally disintegrating film has shown promising drug release within 10 min (88.17) and folding endurance (274.33) good stability than heat dried orally disintegrating film.

Keywords: Trazodone Hydrochloride, Orally disintegrating film and Freeze drying technology.

1. INTRODUCTION

The oral route for drug delivery is most compatible and convenient due to its variety of advantages. It includes typical oral solid as well as liquid dosage forms like Tablets, capsule, pills, syrup, expectorants, gargals etc. The Fast dissolving drug delivery came into existence in 1970's as modification for typical oral dosage forms for patients like geriatric and pediatric who experience difficulties in swallowing traditional oral solid dosage forms. This dosage form consist of quick disintegration and dissolving properties without water in oral cavity[1-5].

Orally dissolving films serve as an alternative to orally disintegrating tablet to provide quick release of an active pharmaceutical ingredient (API) when placed on the tongue. When wet by saliva, the film rapidly hydrates and disintegrates to release the drug. Advantages of ODFs over the conventional solid dosage forms are improved portability, ease of administration, accurate dosing, cost-effectiveness and improved patient compliance. Moreover, ODF has advantage over ODT to eliminate completely the fear of choking because it appears in thin film form, rather than tablet shape form. The formulation of fast disintegrating oral film involves the intricate application of aesthetic and performance characteristics like fast disintegrating, taste-masking, physical appearance and mouth feel. The common adjuvants are film forming polymers, thickening agent, plasticizer, suitable solvent and organoleptic improving agents. The manufacturing methods of ODF are solvent casting, semisolid casting, hot-melt extrusion (HME), solid-dispersion extrusion and rolling. However, solvent casting and hot melt extrusion are reported as the most common method due to the simplicity. In solvent casting method, the water-soluble ingredients are dissolved in a suitable solvent to form a viscous solution. The drug and other smaller quantity ingredients are dissolved in another

portion of smaller volume solvent and combined with the bulk drug later on. The entrapped air is removed by vacuum and the resulting solution is cast as a film and allowed to dry. Oven or heat is commonly applied due to faster removal of solvent and forming of film. The ODF is then cut into pieces to the desired size. The drying temperature plays an important role. In the HME process, the drug and other excipients are mixed in a dry state. The mixture is then subjected to heating process to melt the mixture and the molten mass is then extruded out of the hot-melt extruder. The advantage of this process is the complete elimination of the solvent. The films are allowed to cool and are cut to the desired size. The major limitation for both methods is their unsuitability for drug candidates which are heat-sensitive. Freeze drying (lyophilization) is a process in which solvent is removed from a frozen drug solution or a suspension containing structure-forming excipients. This technology was used to manufacture ODT in 1970 and patented as Zydis Technology. Zydis ODT is very light and has highly porous structures that allow rapid disintegration, within seconds. The entire freeze drying process is done at non-elevated temperatures to eliminate adverse thermal effects that may affect drug stability during processing.

Another property of the freeze-drying process is that it may result in a glassy amorphous structure of excipients as well as the drug substance, leading to the enhanced dissolution rate. However, this technology has not been maximized and reported in formulating ODF. The objective of this study is to investigate the potential of an alternative method for solvent removal in solvent casting method. Instead of using heat to remove the solvent, this study explores the freeze-drying technology. The ODF prepared using heat-drying and freeze-drying methods was compared and characterized afterward[8,16-19].

Classification of oral / buccal dosage forms

Orodispersible Tablets

This is an solid dosage form containing API substances which disintegrates rapidly within a few seconds, when come in contact with the saliva on tongue. Orodispersible tablets have main advantages like ease of administration, improved patient compliance, good mouth feel, rapid drug absorption and ability of high drug loading.

Orally disintegrating Films

To overcome disadvantage of orodispersible tablets, Orally disintegrating films were developed. These are the new drug delivery system for the oral delivery of the drugs. It was developed on the basis of the transdermal films. It shows rapid disintegration, it dissolves and release the medication for oromucosal absorption and maintain the quick-dissolving aspects for gastrointestinal absorption to be obtained when swallowed[1-7].

DEFINITION

It is defined as thin strip, when placed on the patient's tongue mucosal tissue, immediately wet by saliva, the film rapidly disintegrates and adheres onto the site of application.

2 MATERIALS AND METHODS

2.1 MATERIAL

Trazodone Hydrochloride was gifted by Taj Pharma, Mumbai. The HPMC, CMC, PEG 6000 were purchased from local market.

2.2 Compatibility Studies

A compatibility study for Trazodone Hydrochloride was carried out with potential formulation excipients. PEG, HPMC K-15, CMC complex. These samples were subjected to compatibility studies and stored for 30 days at elevated temperature and humidity conditions of 40 ± 2 ^{0}C / 75 ± 5 % RH. After 30days

1) IR spectra of these stored samples was obtained.

2) The assay of drug was performed using U.V. Spectrophotometer.

2.3 Formulation of orally disintegrating film of Trazodone Hydrochloride

The composition of Trazodone HCl orally disintegrating films is given in **Table 1.**

2.4 Preparation of orally disintegrating films

Solvent casting technique

The orally disintegrating films prepared by solvent casting technique are of matrix diffusion controlled systems[5].

1. Heat Drying

- ✓ HPMC K-15 and CMC (Film former) polymers were weighed and transfered in small beaker (A) containing 10 ml of Distilled Water. Then kept to soaking for 24 hrs.
- ✓ Then weighed amount of excipients were taken and transfered into beaker (B) containing 10 ml distilled water.
- ✓ Contents of beaker A (HPMC K-15+ CMC) were stirred by magnetic stirrer at 40rpm/min and solution of beaker B (Excipient) was added Drop wise in the rate as one drop/sec.

- ✓ Then Polyethylene Glycol (Plasticizer) was added to this mixture.
- ✓ The resulting solution was poured in neat and clean glass tray having size of 10cm length and 4cm width.
- ✓ The glass trays were placed in the oven for 6 hrs at 60^{o} C.
- ✓ Films were cut into the pieces of 2 cm x 2cm after drying.

2. Freeze Drying

- ✓ HPMC K-15 and CMC (Film former) polymers were weighed and transfered in small beaker (A) containing 10 ml of Distilled Water. Then kept to soaking for 24 hrs.
- ✓ Then weighed amount of excipients were taken and transfered into beaker (B) containing 10 ml distilled water.
- ✓ Contents of beaker A (HPMC K-15+ CMC) were stirred by magnetic stirrer at 40rpm/min and solution of beaker B (Excipient) was added Drop wise in the rate as one drop/sec.
- ✓ Then Polyethylene Glycol (Plasticizer) was added to this mixture.
- ✓ The resulting solution was poured in neat and clean glass tray having size of 10cm length and 4cm width.

The glass trays were stored in a freezer at -20^{o}C for 2 h to freeze the sample. The frozen samples with the glass tray were then transferred into the freeze dryer(Martin Christ, Alpha 2-4 LD plus) to freeze dry under vacuum suction for 6 h. The film was removed from the glass tray, cut the film into the pieces of 2 cm x 2cm and stored in a desiccator[8,16-19]. The Freeze drying techniqe of orally disintegrating film was shown in **Figure 1**.

2.5 Physicochemical Evaluation of Orally Disintegrating Films

The orally disintegrating films were evaluated for.

1. Weight Variation

Ten different films were weighed from individual batch and the average weight was calculated.

2. Thickness of the films

Thickness was measured by using vernier caliper at different points and average value was calculated.

3. Percentage Moisture loss

It was calculated for three different films from individual batches by storing them in desiccators containing calcium chloride at 37°c for 24 hrs.

4. Folding Endurance

This was determined by repeatedly folding one film at the same place till it broke.

5. Drug content determination

It was determined by cutting films of size 1cm^2 diameter and adding it to a beaker containing 100ml of Phosphate buffer of pH 7.4. The medium was stirred, filtered and analyzed for drug content at 247nm spectrophotometrically.

6. Disintegration time

This test is carried out using the disintegration test apparatus. Three films from each formulation were taken and performed disintegration test by placing the films in the cylindrical glass tube of disintegration apparatus containing phosphate buffer pH 6.8.

7. Percent elongation

Three films of each formulation were taken for the test. Initial length of film was noted and then the stress was applied to find out the increase in length of film. By using the both values % elongation were calculated.

8. Tensile Strength

Tensile strength of the three films of each formulation were determined. Basically, this test is performed to measure the mechanical strength of films.

Tensile strength=
(Load at failure / Cross sectional area of film in mm^2) x 100

9. Dissolution test

Dissolution test was performed in phosphate buffer pH 6.8 (dissolution media) using the standard basket apparatus at 37 ± 0.5°C and 50 rpm. A single film was placed in 900 ml dissolution media. 5 ml of samples were withdrawn at suitable time intervals and replaced with fresh dissolution medium. Then samples were determined using UV visible spectrophotometer at 247 nm and cumulative drug release was calculated.

10. Scanning Electron Microscopy (SEM)

The SEM analysis were performed for the optimized batches of both the heat drying and freeze drying techniques. SEM images were obtained using the scanning electron microscope [1-5, 8].

3 RESULTS AND DISCUSSION

3.1 Drug-Polymers Compatibility Studies

Infrared Spectroscopy

Drug-excipients interaction study shown no interaction between Trazodone Hydrochloride

and selected polymers as there was no significant shift of peaks in IR spectrum.
Thus the Trazodone Hydrochloride was found to be compatible with the selected excipients.

3.2 Evaluation of orally disintegrating films

1. Physical appearance

All films from F1-F4 of Both Heat Dried and Freeze Dried technique were found to be smooth in nature and had good appearance.

2. Weight Uniformity

For weight variation test, 10 films of every formulation were randomly selected and weighed individually to determine the average weight and the standard deviation. Weight variation for heat dried film's batches varies from 48.8±0.04mg to 90±0.08mg, and for freeze dried film's varies from 50±0.09mg to 88±0.04mg. The results are given in the **Table 2.**

3. Thickness

The thickness of the drug loaded films F-1 to F-4 formulations of both of heat dried and freeze dried films was measured with the help of micrometre screw gauge at different strategic locations i.e. four corners and centre of the each films. Mean SD were calculated. Thickness of a single film varies from 0.10±0.01 to 0.14±0.005 mm for heat dried films and 0.21±0.006 to 0.30±0.005 mmfor freeze dried films. The results are reported in the **Table 2.**

4. % Moisture loss

For moisture content test, three films of each formulation were taken. Initially, these selected films were weighed accurately and kept in desiccator containing fused silica. After 3 days, films were removed, weighed and percentage moisture loss was calculated. The amount of moisture loss by films found to be very less (Less than 0.04%) shown in **Table 2.**

5. Drug content uniformity

Drug content of all batches were calculated by using film containing 25 mg of Trazodone HCl. Three trials from each formulation were analysed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content ranges from 84.12±0.74 to 92.17±3.19 %. The results indicated that in all the formulations the drug content is uniform. The studies also show that uniformity of content is within the specifications range 85-115%.The results are as shown in **Table 2.**

6. Folding endurance

The number of times the films were folded until it breaks is reported. The studies shows the influence of concentration of HPMC K15 in the formulation. As the concentration of polymer is increased, the folding endurance were also increased. Formulation F4 of both heat dried and freeze dried films batches have shown the better folding endurance than that of others. Folding endurance of all films are reported in **Table 2.**

7. Disintegration time

Three films from each formulation were taken and disintegration test was performed. *In-vitro* disintegration time is determined visually in a disintegration apparatus containing phosphate buffer pH 6.8 solution. The disintegration is the time when film breaks or disintegrates. Super disintegrants should be incorporated in the film formulation to improve disintegration rate. CMC is incorporated as a super disintegrant. In Indian pharmacopoeia limits for disintegration films are 1-3 min. The *In-vitro* disintegration time of all films are reported in **Table 3.** Results show that the increase in concentration of CMC were decreases the disintegration time.

8. Percent elongation

The three films from each batch were taken for the determination of % elongation. The initial length and final length at failure were noted and the % of Elongation were calculated. Percentage elongation was found to be increased as increase in concentration of polymer in the film. Data is reported in **Table 3.**

9. Tensile Strength

The Tensile strength were performed for the three films from each batches. The results of the tensile strength for each of batch were shown in **Table 3.** From the results it was observed that as the concentration of the polymer increases, the tensile strength of the film increases. The formulation F2 shows the maximum tensile strength. Presence of HPMC K15 as a plasticizer imparts the flexibility to the Polymers. Tensile strength measures the ability of the film to withstand rupture. The Formulation F2 of both heat dried and freeze dried films shows the maximum strength 0.35±0.2 and 0.33±, shown in **Table 3.** This might be due to formation of strong hydrogen bonds between polymer and plasticizer thereby imparting flexibility to withstand rupture, but also formulation F4 batches of both heat dried and freeze dried films shows comparable tensile strength as compared to F2 formulation.

10. Surface pH

The orally disintegrating film formulations will be administred in the oral cavity, pH of saliva ranges from pH 5.5-7.5. Hence, to dissolve and solubilize the drug in the saliva in the oral cavity the pH of the film should be kept near 5.5-7.5. If it is acidic it can lead to irritation of the buccal mucosa. Surface pH of all films are reported in **Table 3.**

11. Dissolution test

Dissolution test was performed in phosphate buffer pH 6.8 (dissolution media) using the standard basket apparatus at 37±0.5°C and 50 rpm. A single film was placed in 900 ml dissolution media. Then samples were analysed by UV visible spectrophotometer at 247 nm and cumulative drug release was calculated. 80-90% drug release were found at 10min by the dissolution. *In-vitro* dissolution study of both heat dried and freeze dried films batches were shown maximum release i.e. 85.79% and 88.15% respectively. For F4 formulation this could be attributed to higher concentration of HPMC K15 and lower concentration of CMC in the formulation. *In-vitro* drug release data is shown in **Table 4.** The comparative % drug release study of F1 – F4 batches of Trazodone HCl Heat Dried Films and Comparative % drug release study of F1 – F4 Batches of Trazodone HCl Freeze Dried Films were shown in **Figure 2 and 3** respectively.

Kinetics of Drug Release

The kinetic Drug release study was performed for all batches of orally disintegrating films. From this, drug release profile of optimised batch F4 is given below.

The release data of formulation F4 was fitted into release rate equations such as zero order, first order, Higuchi's, Hixon Crowell, square root time dependent dissolution and Korsmeyer- peppas exponential equation. It was found it follows Zero order with diffusion controlled mechanism. The kinetics of drug release data were shown in **Table 5.**

12. Scanning Electron Microscopy (SEM)

The F4 formulation batches of both heat dried and freeze dried films were analyzed by SEM. The results of SEM of both F4 formulations have shown difference in surface nature i.e. the freeze dried films were found to possess greater porous nature than that of heat dried film, which can be correlated with its disintegration rate, as more porous nature have high disintegration rate and lower disintegration time relative to plane surface nature[1,8]. The Scanning Electron Microscopic view of Heat Dried Film and Freeze Dried Film were shown in **Figure 4 and 5** respectively.

4 CONCLUSION

- ✓ All the prepared formulations i.e. both heat dried and freeze dried batches show satisfied organoleptic properties.
- ✓ Trazodone HCl was initially characterized for its preliminary studies such as organoleptic properties, melting point, solubility, UV Spectroscopy, FTIR, DSC studies and also drug-excipients compatibility was confirmed by FTIR
- ✓ As no unaccountable peaks was observed in FTIR analysis, so it confirmed the purity of developed formulations and no interaction of excipients with drug.
- ✓ Orally disintegrating films were prepared by solvent-casting method using hydrophilic film forming polymer HPMC K-15 and CMC. And PEG 6000 as plasticizer. Films prepared were smooth and elegant in appearance and showed no visible cracks.
- ✓ Optimization of orally disintegrating film was carried out using 2^2 factorial design, with independent variables as concentration of HPMC (X_1) and concentration of CMC (X_2). This design was employed to study the effect of independent variables on various dependent variable i.e. *in vitro* drug release at 10 min.
- ✓ The eight formulations prepared were subjected to evaluation parameters like physical appearance, thickness, weight variation, % moisture loss, surface pH measurement, drug content uniformity, folding endurance, tensile strength, percentage of elongation, morphological study (SEM), disintegration time and *in vitro* dissolution study etc.
- ✓ Films shows satisfactory organoleptic properties.
- ✓ Film also shows uniform properties in Thickness, Weight, %Moisture loss, Disintegration time, Folding Endurance, Drug content uniformity, *in vitro* dissolution, surface pH, tensile strength, % elongation, and morphological study (SEM) etc.
- ✓ From above evaluation parameter F4 Batch of both the heat dried and freeze dried films were selected as optimized batch.
- ✓ For preparation of ODF formulation if comparison is done among heat dried and freeze dried techniques, the

formulations prepared by freeze dried techniques were found to have better drug release pattern and organoleptic properties.

5. ACKNOWLEDGEMENT
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Conflict of Interest
We declare that we have no conflict of interest.

Table 1: Composition of Trazodone Hydrochloride orally disintegrating Films:

Sr. No.	Name of Drug and Excipients	Different batches of mouth dissolving films of Trazodone HCl							
		HEAT DRIED FILMS BATCHES (wt.gm)				FREEZE DRIED FILMS BATCHES (wt.gm)			
		F1	F2	F3	F4	F1	F2	F3	F4
1	Trazodone HCl	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
2	HPMC K15	0.15	0.25	0.15	0.25	0.15	0.25	0.15	0.25
3	CMC	0.03	0.06	0.06	0.03	0.03	0.06	0.06	0.03
4	PEG 6000	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
5	Citric Acid	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
6	SLS	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7	Mannitol	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
8	Flavor and Color	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 2: Results of Evaluation Parameters for Heat Dried and Freeze Dried Films

Batch No.	Evaluation Parameters				
	Thickness (mm) Mean ± SD	Weight Variation (mg) Mean ± SD	% Moisture Loss (%) Mean ± SD	Drug content uniformity (%) Mean ± SD	Folding Endurance Mean ± SD
Heat Dried Films					
F1	0.126±0.0158	48.8±0.0417	0.0208±0.017	85.96±1.29	219.66±2.49
F2	0.138±0.008	89.98±0.0815	0.0111±0.0091	84.12±2.53	246±5.09
F3	0.1086±0.0050	64.47±0.0412	0.0103±0.0072	86.01±3.19	176.33±5.73
F4	0.138±0.0052	83.19±0.0406	0.0039±0.0056	90.10±1.84	261.33±3.68
Freeze Dried Films					
F1	0.2193±0.0061	50±0.0976	0.0261±0.009	84.70±1.26	229.66±1.24
F2	0.2726±0.0041	84.95±0.1080	0.0159±0.014	90.10±0.74	257.66±3.39
F3	0.238±0.0034	63.98±0.0792	0.0364±0.019	84.93±1.29	196.66±4.18
F4	0.2893±0.0050	87.48±0.0469	0.0114±0.009	92.17±0.84	274.33±3.85

Table 3: Results of Evaluation Parameters for Heat Dried and Freeze Dried Films

Batch No.	Evaluation Parameters			
	Disintegration time (Sec) Mean ± SD	Percent elongation (%) Mean ± SD	Tensile Strength Kg/mm^2 ± S.D	Surface pH Mean ± SD
Heat Dried Films				
F1	69.66±1.24	5±0	0.27±2.94	6.1066±0.06
F2	49.66±1.24	11.66±0.04714	0.3516±1.24	6.2513±0.07
F3	86.66±2.62	1.66±0.04714	0.2233±1.24	6.0693±0.04
F4	67.66±2.05	8.33±0.04714	0.32±2.44	6.3873±0.03
Freeze Dried Films				
F1	50.66±2.49	6.66±0.04714	0.2516±	6.225±0.004
F2	39±0.81	11.66±0.04714	0.3383±	6.3996±0.06
F3	60.33±1.24	0	0.2033±	6.082±0.05
F4	51.33±1.24	11.66±0.04714	0.3033±	6.2976±0.01

Table 4: Dissolution Test of Heat Dried and Freeze Dried Films

Sr.No	Time	% Drug Release							
		Heat Dried Films				Freeze Dried Films			
		F1	F2	F3	F4	F1	F2	F3	F4
1	0.15	21.01	16.92	14.31	24.24	17.78	20.14	19.89	25.73
2	0.3	28.89	22.56	32.00	29.89	21.82	26.78	32.00	31.25
3	1	36.58	39.69	36.41	40.72	33.24	39.15	36.85	38.77
4	2	41.07	47.20	41.03	46.13	42.04	48.77	42.59	47.26
5	3	47.11	50.57	47.69	51.72	46.47	51.66	47.27	50.26
6	4	53.95	54.47	52.79	56.01	55.17	57.18	53.86	56.88
7	5	58.37	60.14	56.96	61.20	58.74	61.89	58.17	62.95
8	6	66.81	65.25	63.40	66.32	64.58	65.65	62.26	66.35
9	7	71.62	70.04	68.42	70.74	72.47	69.57	65.90	71.02
10	8	74.61	76.24	72.61	78.06	74.35	76.14	69.69	76.86
11	9	78.74	80.39	77.34	80.24	79.97	81.52	78.24	80.64
12	10	82.53	83.70	79.76	85.79	83.03	86.46	81.78	88.17

Table 5: Kinetic parameters of Trazodone HCl orally disintegrating film

Batch No	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Hixon Crowell (R^2)	Korsemayer Peppas (R^2)
Heat Dried Films					
F1	0.9732	0.9638	0.9876	0.9891	0.906
F2	0.9345	0.915	0.9856	0.9658	0.9562
F3	0.9404	0.9257	0.9709	0.9695	0.9211
F4	0.9702	0.9597	0.9898	0.986	0.9206
Freeze Dried Films					
F1	0.9638	0.9509	0.9961	0.9854	0.9313
F2	0.9485	0.9325	0.9886	0.9723	0.9465
F3	0.9638	0.9542	0.9769	0.977	0.906
F4	0.9788	0.9711	0.9876	0.987	0.9033

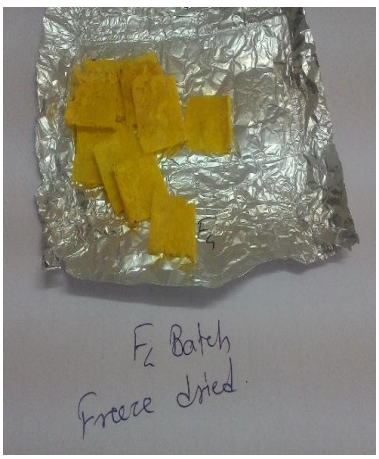

Fig. 1: Preparation of orally disintegrating films by Freeze Drying Method

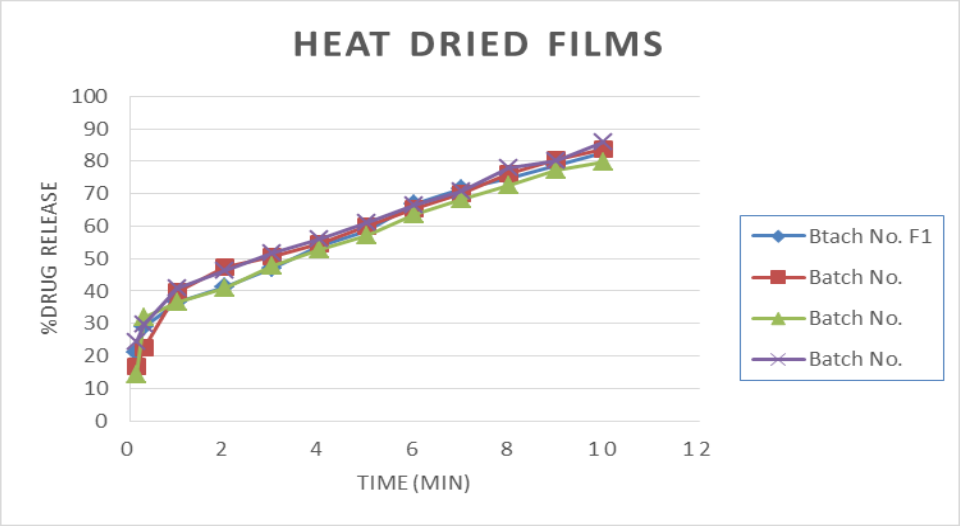

Fig. 2: Comparative %Drug Release study of F1 – F4 batches of Trazodone HCl Heat Dried Films

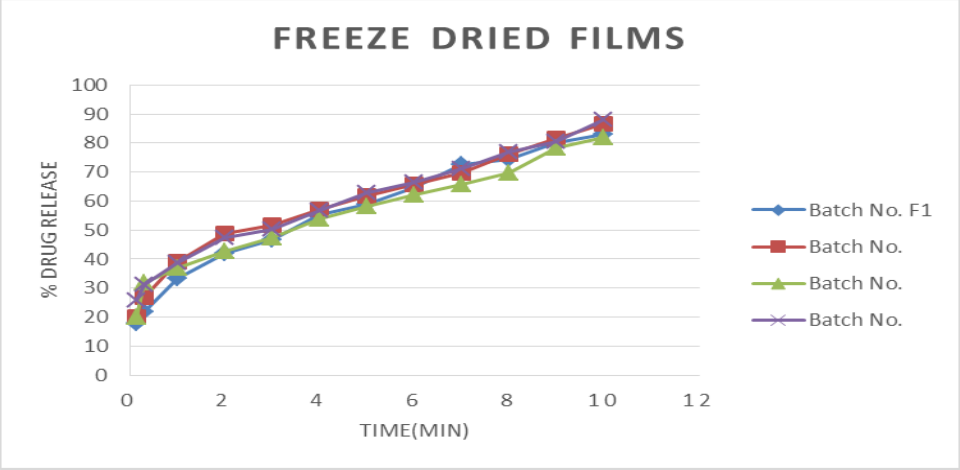

Fig. 3: Comparative %Drug Release study of F1 – F4 Batches of Trazodone HCl Freeze Dried Films

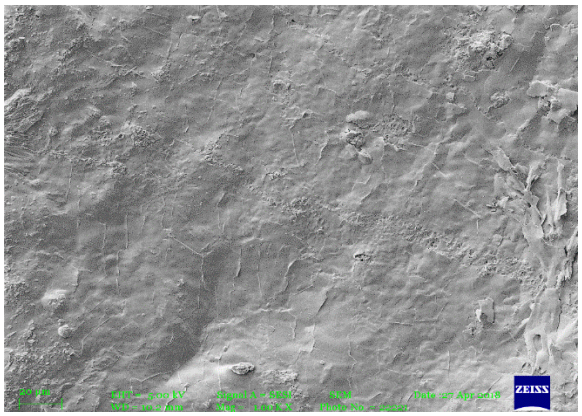

Fig. 4: Scanning Electron Microscopic view of Heat Dried Film

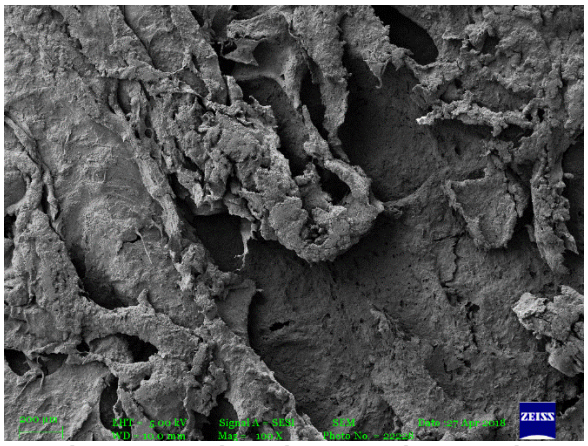

Fig. 5: Scanning Electron Microscopic view of Freeze Dried Film

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