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Formulation and In-Vitro Evaluation of Oro-Dispersible Tablets of Olanzapine by Direct Compression

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ABSTRACT

The present research work was to design and develop an optimized oro-dispersible tablet dosage form of an anti-psychotic drug, Olanzapine by using direct compression technology. Total number of nine formulations were prepared as per the standard experimental design protocol using Design Expert Software (Version 8.0.5, Stat-Ease, Inc.). Independent variables such as the amount of the amount of Crospovidone XL 10 (A) and the amount of Avicel PH 102 (B) were optimized by application of Response surface methodology using Central Composite Design. The dependent variables selected were in-vitro dispersion time and wetting time of the tablets. All the evaluated physical parameters of the oro-dispersible tablets were practically within control. The direct compression method used to prepare the oro-dispersible tablets in this study is relatively simple, safe and economic. A stable, effective and pleasant tasting mouth dissolving tablet, which has a good balance over all the physical parameters was formulated.

Keywords: Oro-dispersible, Superdisintegrants, Crospovidone, Response Surface Methodology.

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INTRODUCTION

The oral cavity is an attractive site for the administration of drugs because of ease of administration. Various dosage forms like Tablets, Capsules, Liquid preparations are administered by oral route. During the last decade, Rapid Disintegrating tablet (RDT) technologies make the tablets to disintegrate in the mouth without chewing and there is no need of water. The RDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet. All RDTs which are approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in the mouth in less than 3 minutes before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth to a gel-like structure and allow easy swallowing by patients.[(1)]

Olanzapine is an atypical antipsychotic drug which is classified as a thiobenzodiazepines, used in the treatment of schizophrenia. Olanzapine undergoes extensive first pass metabolism. Some schizophrenic patients with dysphagia can not swallow the conventional olanzapine tablets. To overcome these problems an attempt was made to formulate ODTs.[(2)] An orally disintegrating tablet (ODT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT.[(3)] The basic approach used in development of ODT was the use of superdisintegrant which provide instantaneous disintegration of tablet after placing on tongue, thereby releasing the drug in saliva.

MATERIALS AND METHOD

Olanzapine was procured from Jubilant Organosys LTD. Avicel PH 102 were procured from FMC Biopolymer, Crospovidone from ISP Sales, and Pearlitol and Peppermint flavor were procured from Roquette Freres, Magnesium stearate was procured from S-Kant Health Care and and Aspartame was procured from Nutrasweet LTD. All chemicals and reagents used were of analytical grade.

Method

Preparation of olanzapine Tablets[4]

Olanzapine orodispersible tablets were prepared by Direct Compression Technique using varying concentrations of Crospovidone XL 10. Olanzapine, pearlitol , Crospovidone X L 10, Avicel PH 102 and aspartame were sifted through # 40.The blend of previous step was added in 2 litre bin blender and mixed for 15 minutes at 14 rpm. Then the blend was lubricated with magnesium

stearate (which was previously sifted through # 60) for 5 min. at 14 rpm. The lubricated blends ready for compression were compressed into tablets using flat face 7 mm size punch to get tablet of 120 mg using Cadmach Tablet compression machine. The composition of batches as per the factorial design are shown in Table 1.

Formulation batches as per Design Expert Software

A. Formulation variables (Independent variables)

a. Concentration of Crospovidone (Polyplasdone XL 10)

b. Concentration of Microcrystalline Cellulose (Avicel PH 102)

B. Response variables (Dependent variables)

a. In vitro Dispersion Time

b. Wetting Time

Table 1: Formulation Batches of orodispersible tablets as per Response surface methodology by applying Central composite design

Formulation Batches									
Sr. No.	**Ingredients**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
1	Pearlitol	92.7	85.7	84.3	91.3	88.5	93.5	83.5	87.5	89.5
2	Crospovidone XL 10	10.0	12.8	10.0	7.2	10.0	8.0	12.0	8.0	12.0
3	Avicel PH 102	10.8	15.0	19.2	15.0	15.0	12.0	18.0	18.0	12.0
4	Olanzapine	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
5	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
6	Aspartame	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
7	Flavour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
8	Total	120.0	120.0	120.0	120.0	120.0	120.0	120.0	120.0	120.0

Identification of olanzapine

Identification of drug was carried out using melting point determination by SRS Optimelt system, infrared spectroscopy (IR) by using Schimadzu FTIR 8400S over the wave number range of 4000 to 400 cm^{-1}, Differential scanning calorimetry (DSC) by STAR SW 7.01 software (METLER Toledo GmbH, Switzerland).

Pre-compression parameters [5,6]

The blend of all formulations were evaluated for bulk and tapped density, Carr's index, Hausner's ratio and angle of repose to evaluate the compressibility and flow properties.

Post compression parameters

Hardness test[7]

The hardness of tablets were determined by using Erweka Hardness Tester. It is expressed in Newton (N).

Friability test [7]

A pre weighed tablets were placed in the Electrolab friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability.

In-vitro Disintegration Time [8]

Disintegration time was measured in 900 ml Phosphate buffer (pH 6.8), according to the USP 24 method without disc at 37 ±0.5℃ .

Drug content[9]

10 tablets from each batch were taken randomly. Tablets were triturated to form the powder. Blend equivalent to 5 mg of drug was taken and dissolved in sufficient quantity of methanol. The solution was then diluted suitably with 0.1N HCL and filtered through 0.45µ membrane filter and assayed at 260 nm which is the λ_{max} of Olanzapine usig UV–Visible double beam spectrophotometer over the wavelength range 200 to 400 nm.

Weight variation test [6, 9]

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly selected from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

In vitro Dispersion Time [10]

In-vitro Dispersion Time was measured by dropping a tablet in a measuring cylinder containing 6 ml of pH 6.8 Phosphate buffer. Three tablets from each formulation were randomly selected and in-vitro dispersion times were determined.

Wetting time[7]

The method was measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (Internal diameter = 6.5 cm) containing 6 ml of Phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured.

In - vitro dissolution studies[11]

Table 2: Summary of general dissolution conditions

Sr. No.	Parameters	Specifications
1	Dissolution apparatus	USP type II (Paddle)
2	Dissolution medium	900ml of 0.1 N HCL
3	Temperature	37 ± 0.5 ^{0C}
4	Rotation speed	50 RPM

5	Volume withdrawn	10 ml
6	λ max	260 nm

Stability studies [12]

Stability studies were carried out on optimized batch (Batch no. A5) at stability conditions 40ºC ± 2ºC and 75 % ± 5% for 3 months as specified in the ICH guidelines. In the present study oro-dispersible tablets were packed and sealed in suitable packing like HDPE white opaque container. The tablets were withdrawn after period of 1, 2 and 3 months and analyzed for various physic-chemical parameters.

RESULTS AND DISCUSSION

Preformulation Studies

A. Melting point

The melting point was found to be 196^{0C} which complies with reported values.

B. Compatibility Studies

FTIR analysis

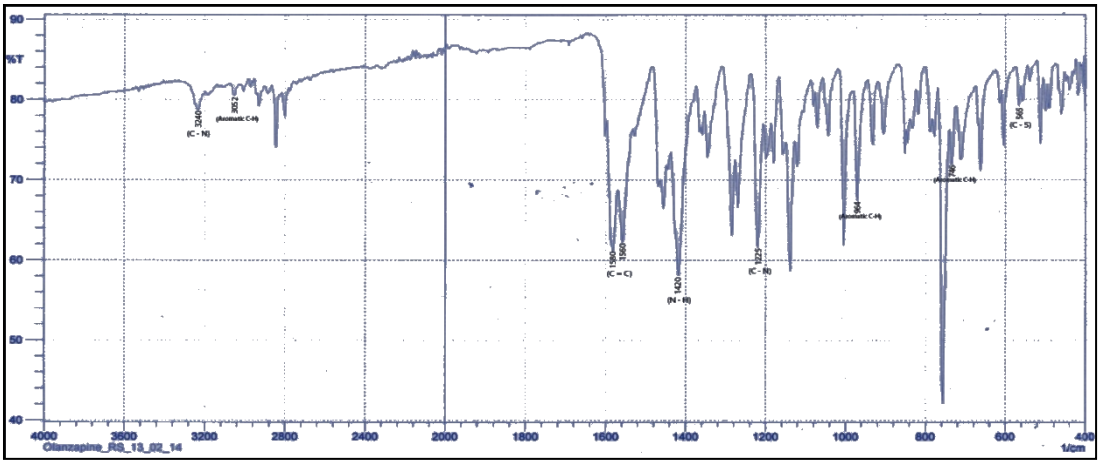


Figure.1 : FTIR spectrum of Olanzapine

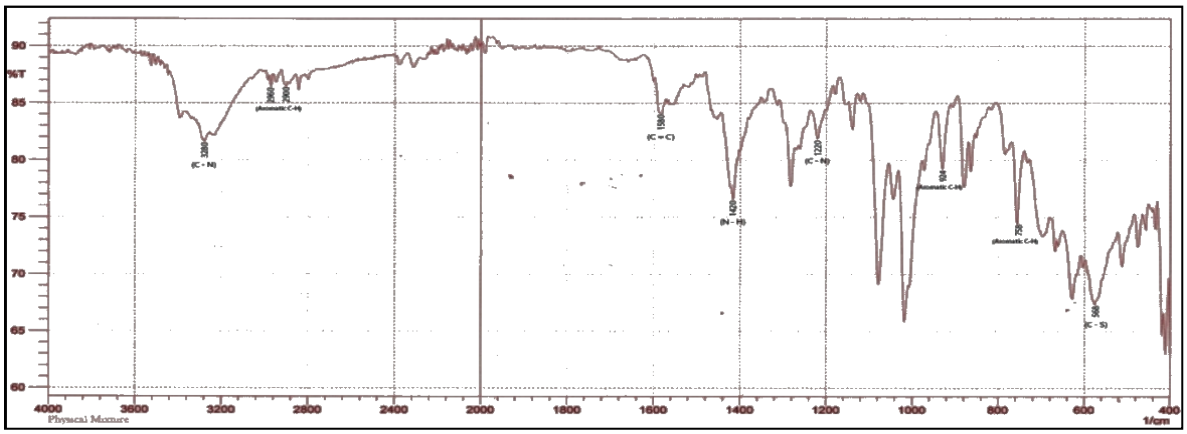


Figure.2 : FTIR spectrum of Physical Mixture

The FTIR spectrum of Olanzapine and Physical Mixture are depicted in the figure 1and 2 respectively. FTIR spectrum of pure drug and drug with excipients were studied. Olanzapine showed characteristic peaks at 1225 cm^{-1} (C-N stretching vibration), 3240 $cm^{-1,}$ 1420 cm^{-1} (N-H stretching and bending vibrations), 1580 and 1560 cm^{-1}(C=C stretching vibration), 3052 cm^{-1}, 964 cm^{-1} and 746 cm^{-1}(aromatic C-H stretching and bending vibrations) and 565 cm^{-1} (C-H bending vibrations) respectively. The peaks obtained in the spectra of physical mixture correlates with peaks of drug spectrum. This indicates that drug was compatible with formulation components.

DSC study

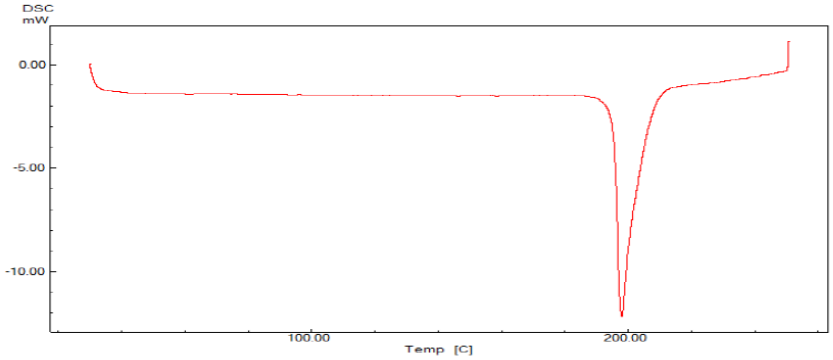


Figure.3 : DSC Thermogram of Olanzapine

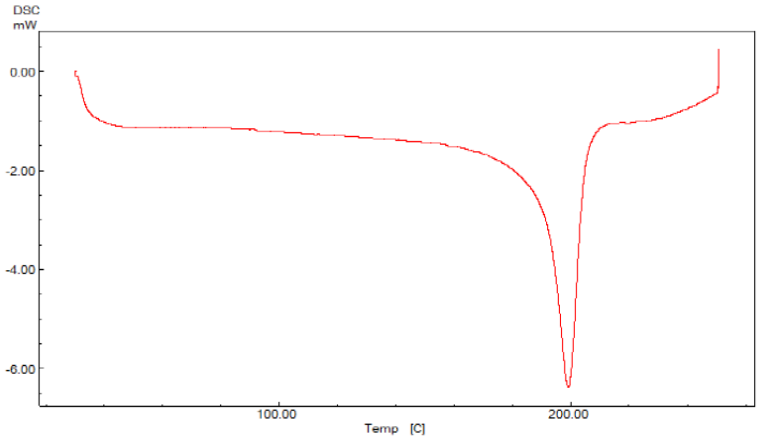


Figure 4 : DSC Thermogram of Physical mixture

The DSC analysis of pure Olanzapine showed a sharp endothermic peak at 196°C corresponding to its melting point (Figure 3). The DSC analysis of physical mixture showed endothermic peak at 195°C which revealed negligible change in the melting point of Olanzapine in the presence of other excipients (Figure 4). Thus both the DSC graphs confirmed that there is no any interactions between drug and the excipients selected for formulation.

Physicochemical characterization

Pre-compression parameters

Table 3: Evaluation of Pre-compression parameters of different formulations of Olanzapine

Batches	Angle of Repose (θ)*	Bulk Density(g/ml)*	Tapped Density(g/ml)*	Carr's Index (%)	Hausner's Ratio
A1	20.93 ± 0.7	0.62 ± 0.01	0.72 ± 0.01	13.89	1.16
A2	22.10 ± 0.3	0.63 ± 0.01	0.69 ± 0.01	8.70	1.10
A3	22.63 ± 0.6	0.58 ± 0.00	0.68 ± 0.01	14.71	1.17
A4	22.20 ± 0.7	0.58 ± 0.01	0.69 ± 0.02	15.94	1.19
A5	**20.73 ± 0.4**	**0.59 ± 0.01**	**0.69 ± 0.01**	**14.49**	**1.17**
A6	20.93 ± 0.3	0.63 ± 0.01	0.73 ± 0.01	13.70	1.16
A7	22.53 ± 0.7	0.64 ± 0.01	0.71 ± 0.01	9.86	1.11
A8	21.17 ± 0.4	0.60 ±0.02	0.71 ± 0.01	16.67	1.20
A9	23.70 ± 0.4	0.64 ± 0.01	0.73 ± 0.02	12.33	1.14

* : Mean ± SD. n = 3 (All values are average of three determinations.)

Angle of repose was found in range of 20.73- 23.70 $^{\theta.}$ Bulk density was found in range of 0.58-0.64 g/ml, tapped density of all formulation blend was found in range of 0.68-0.73 g/ml. Compressibility index was found in between 8.70-16.67 % and Hausner's ratio in the range of 1.10-1.20 indicating excellent flow properties and compressibility of all blends. Pearlitol along with Microcrystalline cellulose improved flow properties of other materials in formulations.

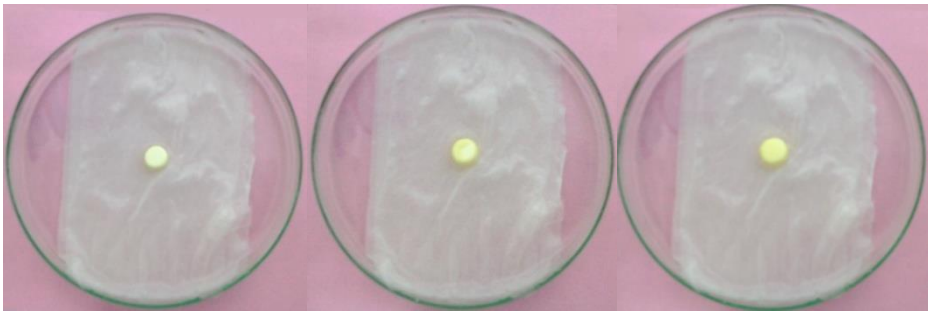
Post compression parameters

Table 4: Evaluation of Post compression parameters of different formulations of Olanzapine

Batches	Uniformity of Thickness (mm)	Hardness (N)	Friability (%)	In-vitro Disintegration Time (Sec.)	Drug Content (%)	Weight Variation (mg)	In -vitro Dispersion Time(Sec.)	Wetting Time (Sec.)
A1	2.54± 0.00	36 ± 1.25	0.20 ± 0.02	11± 0.94	98.6 ± 1.30	122.1±0.54	11.0 ± 0.47	12.0 ± 1.70
A2	2.54± 0.01	37 ±0.94	0.21 ± 0.02	10± 1.25	97.3 ± 0.66	122.3±0.61	10.0 ± 1.25	9.0 ± 0.47
A3	2.55± 0.01	37 ± 0.94	0.22 ± 0.03	14± 1.25	97.5 ± 0.49	123.0±0.83	10.0 ± 1.25	15.0± 0.82
A4	2.55± 0.01	36 ±0.82	0.20 ± 0.02	11± 1.25	99.5 ± 1.65	123.2±0.65	22.0 ± 1.25	9.0 ± 0.82
A5	**2.56± 0.02**	**36 ± 0.47**	**0.20 ± 0.02**	**7 ± 0.47**	**99.7± 0.09**	**120.8±1.28**	**10.0 ± 1.25**	**8.0 ± 1.25**
A6	2.57± 0.01	35 ± 0.47	0.22 ±0.02	13±1.70	99.2± 0.71	121.7±1.53	18.0 ± 1.63	14.0± 1.25
A7	2.56± 0.01	3 7± 0.82	0.22 ±0.01	14±1.41	98.6± 1.63	120.2±1.23	15.0 ± 0.94	14.0± 1.70
A8	2.57± 0.01	35 ± 0.47	0.22 ± 0.01	15± 1.63	99.5 ± 0.31	120.4±1.36	18.0 ± 1.25	16.0 ± 0.94
A9	2.57± 0.02	36 ±0.82	0.21 ± 0.02	10± 1.63	99.0 ± 0.60	122.1±1.47	15.0 ± 0.94	13.0 ± 1.70

Mean ± SD. n = 3 (All values are average of three determinations.)

Tablets of all batches showed round flat faced, yellowish in colour with thickness 2.54 – 2.57mm. The hardness and friability values indicated good handling properties of the prepared tablets. The batch A5 showed least disintegration time (7 sec.). All the batches showed drug content and weight variation within acceptance value. In-vitro disintegration time for all formulation batches were found in the range of 7-15 sec. It was observed that wetting time of tablets were found in the range of 8-15 sec. The batch A5 showed least in- vitro dispersion time (10 sec.) and least wetting time (8 sec.).



0 second **5 seconds** **8 seconds**

Figure. 5: Wetting Time determination of optimized formulation (A5)

Table 5: ANOVA for selected statistics model

Response model	Sum of Squares	Mean square	F value	P value	R^2	Adjusted R^2
In vitro dispersion time (Sec.)	106	11.78	*36*	<0.0001	0.9992	0.9990
Wetting time (Sec.)	53.67	5.96	35.78	<0.0001	0.9938	0.9960

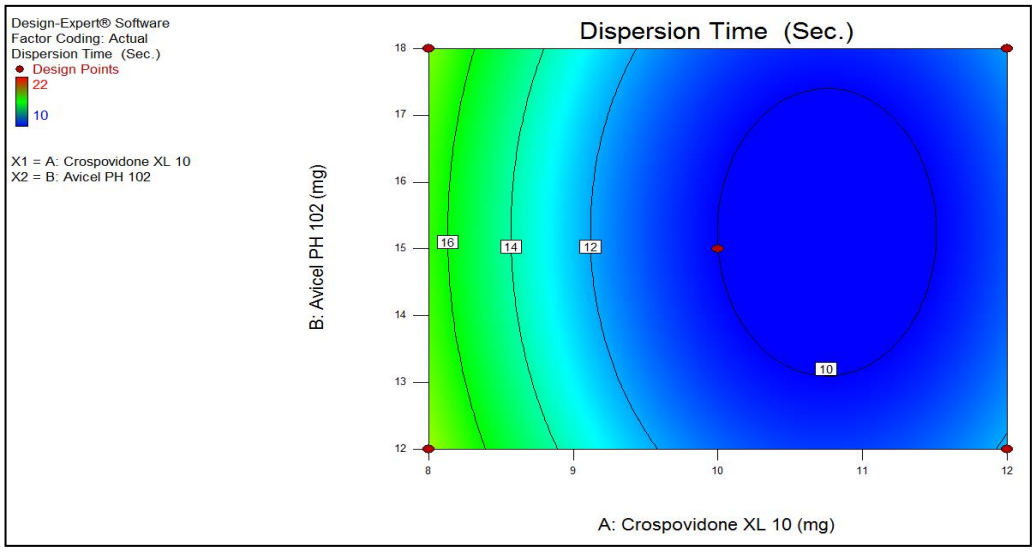


Figure.6:Plot of In-vitro dispersion time

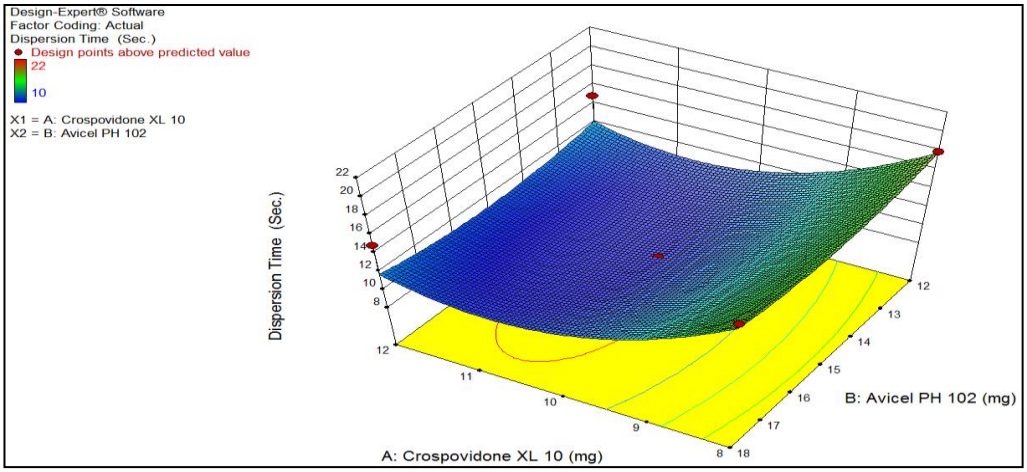


Figure.7: 3DPlot of In-vitro dispersion time

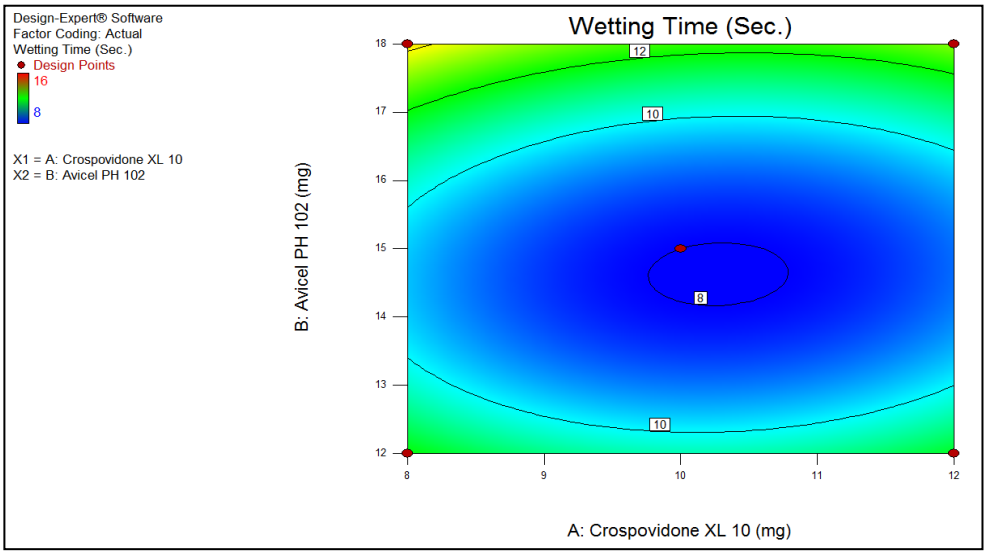


Figure.8:Plot of wetting time

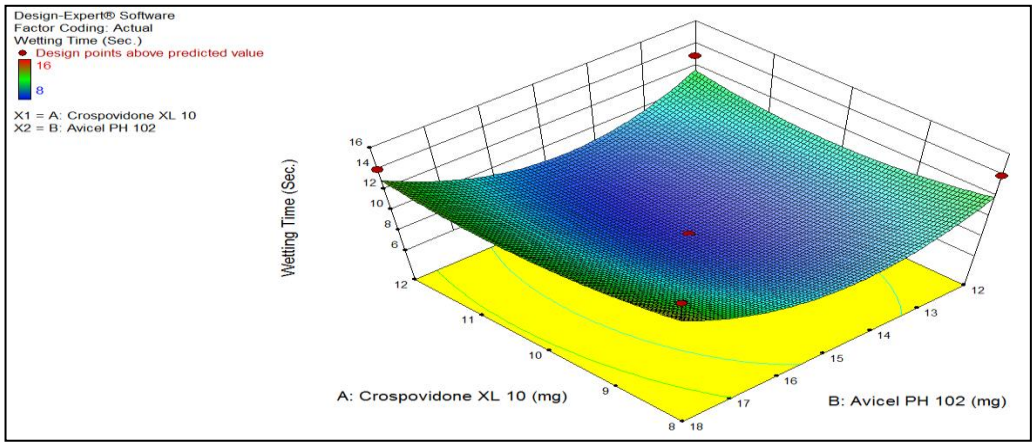


Figure.9: 3D Plot of wetting time

Table 6:Cumulative % drug release of tablet from formulations in 0.1 N HCl

Cumulative % drug release of tablet from formulations in 0.1 N HCl									
Time(min)	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
0	0	0	0	0	**0**	0	0	0	0
5	82 ± 0.21	78 ± 0.68	80 ± 0.39	78 ± 0.92	**92 ± 0.21**	89 ± 1.20	80 ± 0.35	75 ± 0.93	80 ± 1.29
10	90 ± 0.35	82 ± 0.68	86 ± 0.93	84 ± 0.34	**95 ± 0.34**	92 ± 0.39	88 ± 0.53	80 ± 0.60	84 ± 0.93
15	96 ± 0.69	94 ± 0.91	96 ± 0.61	96 ± 0.36	**99 ± 0.37**	95 ± 1.26	94 ± 1.36	92 ± 0.92	95 ± 0.67
20	99 ± 0.98	100 ± 0.73	99 ± 0.97	99 ± 0.67	**100 ± 0.62**	97 ± 0.63	98 ± 0.92	98 ± 0.97	99 ± 1.90

Mean ± SD. n = 3 (All values are average of three determinations.)

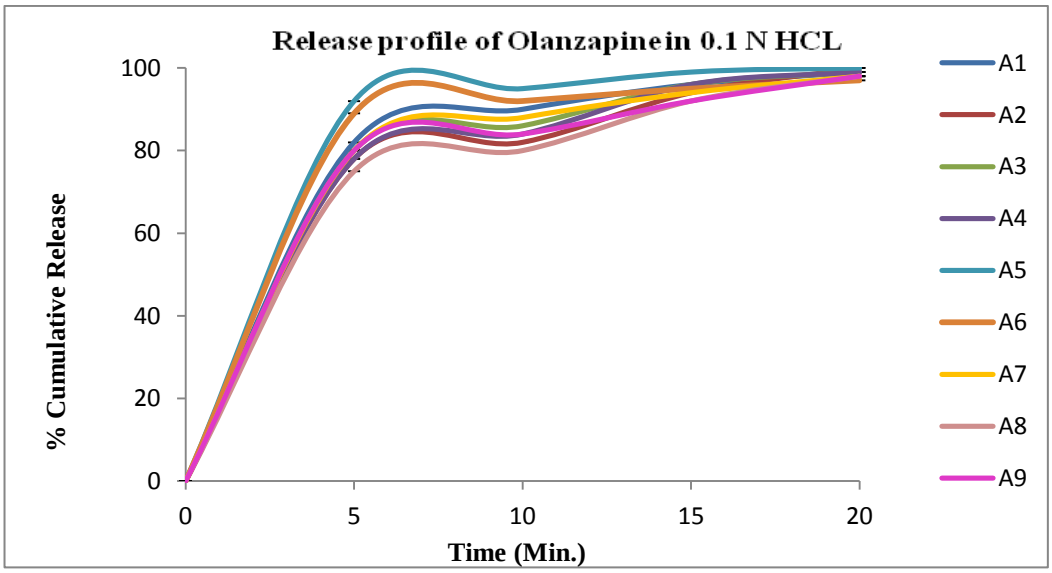


Figure.10: Comparative study of Release Profile of Olanzapine in 0.1 N HCL

Amongst all 9 batches Batch no. A5 Showed faster drug release. About 99% drug released within 15 min. which was faster as compared to other batches indicating best result.

Table 7:Comparison of dissolution profiles of olanzapine 5mg ODT with Zyprexa 5mg IR Tablet

Time (Min.)	Zyprexa 5mg % CR	A5 % CR
0	0	0
5	45 ± 0.89	97 ± 0.92
10	79 ± 0.96	97 ± 0.85
15	93 ± 0.93	99 ± 0.89
20	99 ± 0.95	100 ± 0.93

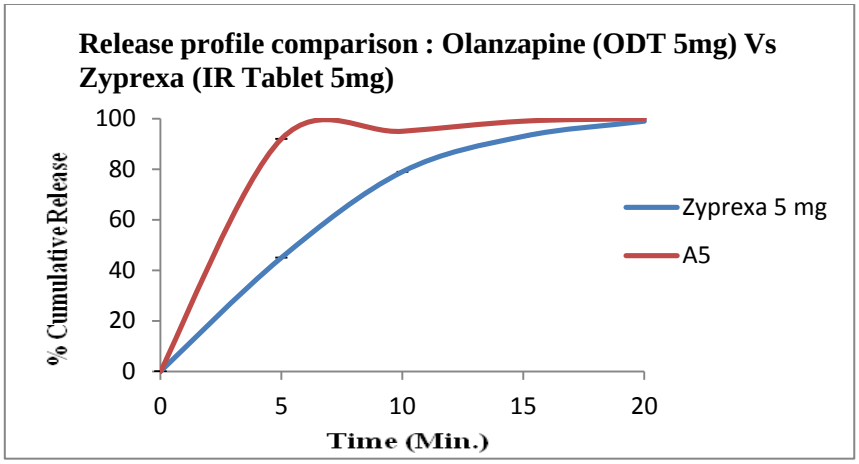


Figure.11 : Dissolution profile comparison-Olanzapine (5mg) ODT vs Zyprexa (5mg) IR Tablet

Commercial product (Zyprexa) released about 93% of drug within 15 minutes in 0.1 N HCl. The optimized formulation A5 showed faster release than the marketed IR product (99% drug released within 15 min.). The formulation A5 was selected as optimized batch because it showed faster in-vitro disintegration time, in- vitro dispersion time and wetting time and also maximum drug release within 15 min.

Table 8: Evaluation of physical parameters of A5 during storage for 3 months at 40^0C/75%RH

Time (Months)	Evaluation Parameters					
	Colour	Hardness (N)	Drug content %	%Drug Release	In-Vitro Dispersion Time (Sec.)	Wetting Time (Sec.)
1	Yellow coloured	33.00±0.82	98.83±0.33	98.67±0.47	11.33±0.47	8.33±0.47
2	Yellow coloured	33.67±1.25	97.87±0.21	97.67±0.47	12.67±0.47	10.00±0.82
3	Yellow coloured	32.67±0.47	97.83±0.21	97.00±0.82	12.33±1.25	10.67±0.47

Mean ± SD. n = 3 (All values are average of three determinations.

No significant changes were found in the physical characteristics of the tablets of optimized formulation A5 indicating the stability of oro-dispersible tablets.

CONCLUSION

In the present work, Mouth dissolving tablets were prepared by Superdisintegrants addition method using Crospovidone XL 10 in different concentrations. Total nine formulations were prepared and evaluated for various parameters. Formulation A5 containing Crospovidone in

concentration of 8.33% showed minimum in–vitro disintegration time, in–vitro dispersion time and wetting time as compared to other formulations. Dissolution studies concluded that the optimized formulation (A5) showed faster release as compared to other formulation batches and marketed formulation Zyprexa IR Tablet. The formulation was also found to be stable under accelerated stability conditions of 40°C ± 2°C/75% ± 5% RH for 3 months. Hence an attempt for development of patient friendly dosage form with the ideal drug candidate could be an alternative to the marketed IR product with good palatability and faster release.

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