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Design and Evaluation of Mouth Dissolving Tablet of Zopiclone using Different Superdisintegrants

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Abstract:
In the present work, Mouth dissolving tablet of Zopicolon were designed with a view to Enhance patient compliance. A combination of super-disintegrants i.e.Ac-di-sol (Croscarmellose sodium), Polyplasdone XL-10, Microcrystalline Cellulose pH 102 was Used along with directly compressible dextrose to enhance mouth feel. The prepared Batches of tablet were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and in vitro dispersion time. Based on in vitro dispersion time, two formulation were tested for in vitro drug release pattern (in pH7.4phosphatebuffer), short – term stability at 25^0C ± 2^0C/60% RH, 30^0C ± 2^0C/65% RH, 40^0C ± 2^0C/75% RH for 3 month and drug –excipient interaction (IR Spectroscopy) among the two formulation, the formulation prepared by direct Compression method using Ac-di-sol (croscarmellose sodium) 50mg, Polyplasdone XL- 10 -25mg, Microcrystalline Cellulose pH 102- 25mg was found tobe better formulation T80% = 5 min. based on in- vitro drug release characteristics. Short term stability studies on the formulation indicated that there is no significant change in drug content and in vitro dispersion time

Keywords: *Mouth dissolvings tablet, Zopicolon, Direct compression,*

Introduction:

Zopicolon is a (atypical antipsychotic) psychotropic agent that belongs to the thienobenzodiazepine class [1]. The firstgenerationand second-generation antipsychotic drugs are US-FDA approved first-line treatment for schizophrenia. However, Patients who receive antipsychotic drugs differ with respect to treatment response and drug induced adverse events [2]. Although antipsychotic drugs relieve the positive symptoms of schizophrenia, these drugs have limited utility in the treatment of the negative symptoms and cognitive deficits associated with this disorder [3]. Conventional (typical) antipsychotics cause a variety of side effects both acutely [e.g., extra pyramidal side effects (EPS)] [4], and with long-term exposure [e.g., tardive dyskinesia (TD)] [5]. Such adverse effects may reduce compliance and represent a major drawback of these drugs. Hence, introduction of atypical antipsychotics like clozapine [6], produced for the first time effective control of positive symptoms with a low incidence of EPS and TD and an effective on negative symptoms [7]. Olanzapine has affinity for numerous neurotransmitter receptors [8-10]. The binding affinity for dopamine D2, D3 and D4 subtypes is somewhat greater than that for dopamine D1 and D5. Olanzapine has very

high affinity for all serotonin 5-HT2 receptorsubtypes [11]. Olanzapine has high affinity for all five muscarinic (M) receptor subtypes. Olanzapine has lower affinity for α1 and ß adrenergic receptors and higher affinity for histaminergic H1 receptors, as compare to other atypical antipsychotics [11]. The receptor binding affinity profiles of the atypical and typical antipsychotic agents differ from each other [12]. The pharmacokinetics of olanzapine is linear and dose-proportional throughout the clinical dosage range17 for these reasons; tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted great deal of attention. This mouth dissolving tablet of Zopipolon will disintegrate rapidly in the patient mouth without need of water or chewing and released its drug content instaneously so this dosage form is more comfortable for pediatric, geriatric patients. Thus, mouth dissolving tablets of Zopipolon truly serve as Orodispersible drug delivery system because of its convenient nature. The statistical magnificence of difference between the predicted & observed responses by 2^3 factorial designs not only validated the design for optimization but also confirms the usefulness of the

Table 1: Composition of different batches of Mouth dissolving tablet of Zopicolon

Sr.No.	Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8
1	Zopicolon	100	100	100	100	100	100	100	100
2	Dextrose	100	100	100	100	100	100	100	100
3	Ac-di-sol (croscarmellose sodium)	25	50	25	50	25	50	25	50
4	Polyplasdone XL-10	25	25	50	50	25	25	50	50
5	Microcrystalline Cellulose p H 102	25	25	25	25	50	50	50	50
6	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Sodium saccharine	10	10	10	10	10	10	10	10
8	Vanillin	5	5	5	5	5	5	5	5
9	Menthol	6	6	6	6	6	6	6	6
10	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

polynomial equation in predicting *in-vitro* kinetic parameters.

Materials and Methods:

Zopicolon, Ac-di-sol (croscarmellose sodium) Polyplasdone XL-10 Microcrystalline Cellulose pH 1.02 obtained as a gift sample from Kairav chemical Ltd. Mumbai. Dextrose, Magnesium stearate sodium Saccharin, Vanillin, Menthol, Talc from swstik chemical, vadodara. All other materials used were of Analytical grade.

Formulation of Orodispersible tablet of Zopipolon:

Mouth dissolving tablet of Zopicolon were prepared by Direct compression according to formula given in (Table 1) A total number of Eight formulations were prepared. All the ingredients were passed through 60-mesh sieve separately and collected, finally compressed into tablets after lubrication with talc (2%) and magnesium stearate (1%) by using 8.5mm flat beveled edged punch set, on 16 station Rotatory Tablet compressing Machine (RIMEK MUMBAI) weight and at approximately equal hardness. Tablets were compressed at equal compression force. The composition is given in table 1.

Before tablet preparation, the mixture blend subjected for compatibility studies (IR) by using Shimadzu FTIR spectrophotometer and pre-compression parameters like angle of repose , Compressibility index , and bulk density , Tapped density , Hausner ratio(Table no.2) .The prepared Mouth dissolving tablet of Zopicolon were subjected for post-compression parameters like uniformity of thickness, hardness, friability, weight variation, drug content uniformity, wetting time, and *in vitro* disintegration time.

Evaluation Parameters:

Water uptake of water absorption Ratio:

The water uptake characteristic of the loose disintegrant powder allows and evaluation of both the intrinsic swelling and the wettability of the superdisintegrants water uptake were performed at room temperature. A piece of tissue paper folded twice was placed in small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was 0.5-2min. The wetted tablet was then weighed. Water absorption ratio, R, was determined by using following equation.

Table 2: Evaluation of the Prepared Mouth dissolving tablet of Zopicolon

Batch code	Angle of repose	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index (%)	Hausner ratio
A1	30.14	0.47	0.59	20.30	1.25
A2	32.00	0.49	0.75	15.80	1.53
A3	32.47	0.59	0.68	13.04	1.15
A4	35.47	0.56	0.75	25.33	1.33
A5	32.86	0.53	0.63	34.60	1.18
A6	30.69	0.38	0.48	20.00	1.26
A7	34.41	0.35	0.50	30.00	1.42
A8	31.00	0.46	0.55	16.36	1.19

$R = 10 \times W_a - W_b / W_b$

Where, W_b =weight of tablet before water absorption and W_a = Weight of tablet after water absorption

In-vitro Release studies:

Dissolution profiles of Zopicolon tablets wee determined using the Dissolution Test apparatus USP (Lab India Disso 2000) set with a paddle speed of 50rpm. Dissolution was tested in 7.4pH phosphate buffer, Dissolution was performed in 900 ml, at 37 ± 0.5^0C, 5 ml aliquot was withdrawn, at the 5, 10, 15, 20 up to 60 min with 5minutes interval, and filtered through whatmann filter paper. From these samples, 1ml taken into test tube volume made up with the same buffer up to 10 ml and the drug solution absorbance was analyzed at 275 nm in 1cm cuvettes using UV-Visible spectrophotometer (Systronics UV-VIS spectrophotometer 117). An equal volume of fresh medium, which was prewarmed at 37^0C replaced into the dissolution medium after each sampling to maintain the constant volume through out the test.

Stability studies of the tablets

Stability studies for the present work carried out at 25^0C ± 2^0C/60% RH, 30^0C ± 2^0C/65% RH, 40^0C ± 2^0C/75% RH for the selected formulation for 3 months.

Results and Discussion:

The present work was aimed to find out the effect of various super-disintegrants on the dissolution profile & various properties of Mouth dissolving tablet of Zopicolon Eight formulation of Zopicolon were prepared with different level addition of superdisintegrants, Ac-di-sol (croscarmellose sodium), Polyplasdone XL-10, & Microcrystalline cellulose pH 1.02 .For each designed formulation powder mixed blend of drug and excipient was prepared and evaluated for various pre-compression parameters. There was no appearance or disappearance of peaks in the polymer-drug mixture, which confirmed the absence of any chemical interaction between the drug and polymers. Pre-compression parameters result indicated good flow ability. The results are as follows.

Post-compression studies

In this work for the ease of analysis & to study the impact of various super-disintegrants on enhancing the dissolution of Zopicolon the experiment was design with eight formulations, which were categories into four groups's based on the level and number of variables. The groups are listed below and the results are given in Table no.3.

Group-1; Formulation containing all variables at low level (A1)

Group-2; Formulation containing any one of three variables at high level (A2, A3, A5)

Group-3; Formulation containing any two of the three variables at high level (A4, A6, A7)

Group-4; Formulation containing all three variables at high level (A8).

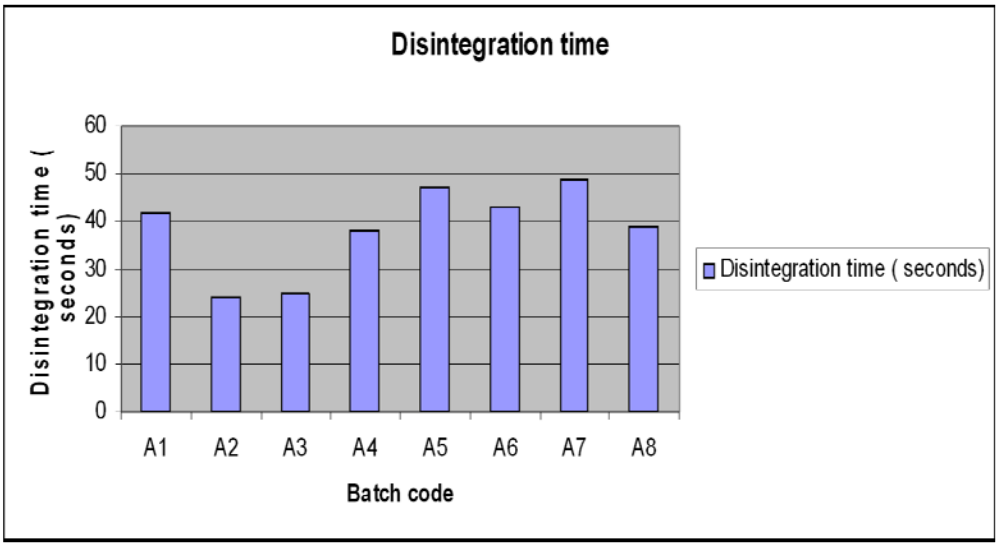

Figure 1: Disintegration studies of Mouth dissolving tablet of Zopicolon

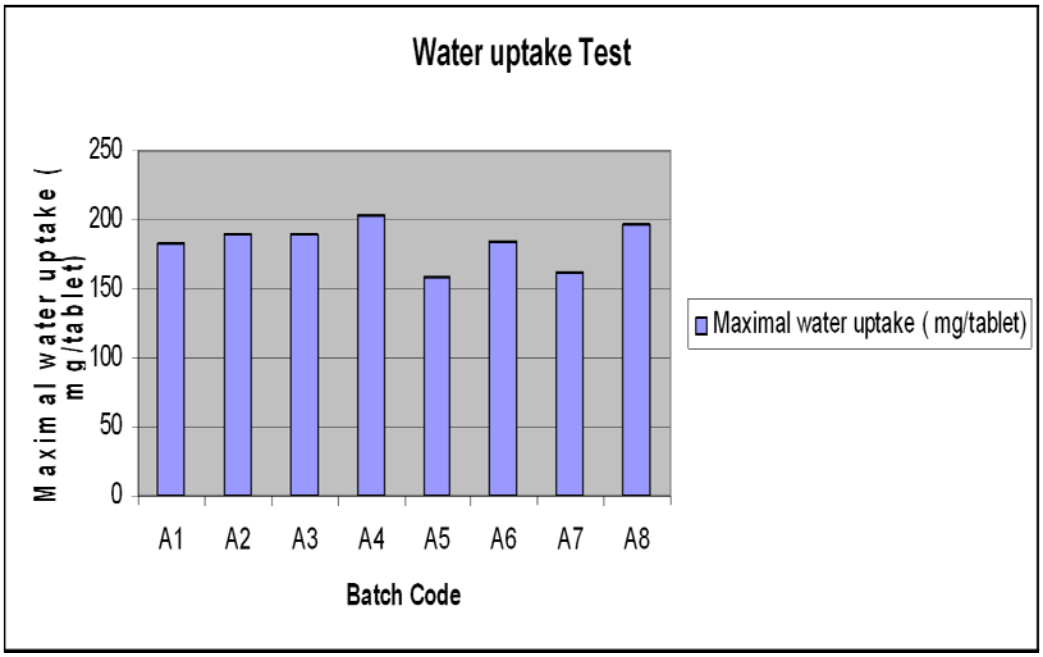

Figure 2: Water Uptake test for Mouth dissolving tablet of Zopicolon

Table 3: Evaluation of Post-compression studies of Mouth dissolving tablet of Zopicolon

Batch code	Weight Variation (5%)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Tensile Strength (kg/cm^2)	Content uniformity (%)	Porosity (%)
A1	Pass	4 ±0.06	3.2±0.31	0.58	12.57	99.35±1.26	20
A2	Pass	4 ± 0.04	3.4±0.45	0.19	13.92	99.08±1.43	35
A3	Pass	5 ± 0.06	3.3±0.34	0.83	10.37	98.86±1.19	25
A4	Pass	5 ± 0.03	3.3±0.64	0.54	9.82	98.14±0.69	14
A5	Pass	5 ± 0.05	3.5±0.54	0.70	13.10	99.42±1.56	16
A6	Pass	6 ± 0.04	3.4±0.15	0.43	12.74	99.88±1.35	30
A7	Pass	5 ± 0.04	3.3±0.71	0.66	12.63	98.10±1.24	22
A8	Pass	6 ± 0.04	3.5±0.45	0.46	13.10	99.23±1.46	16

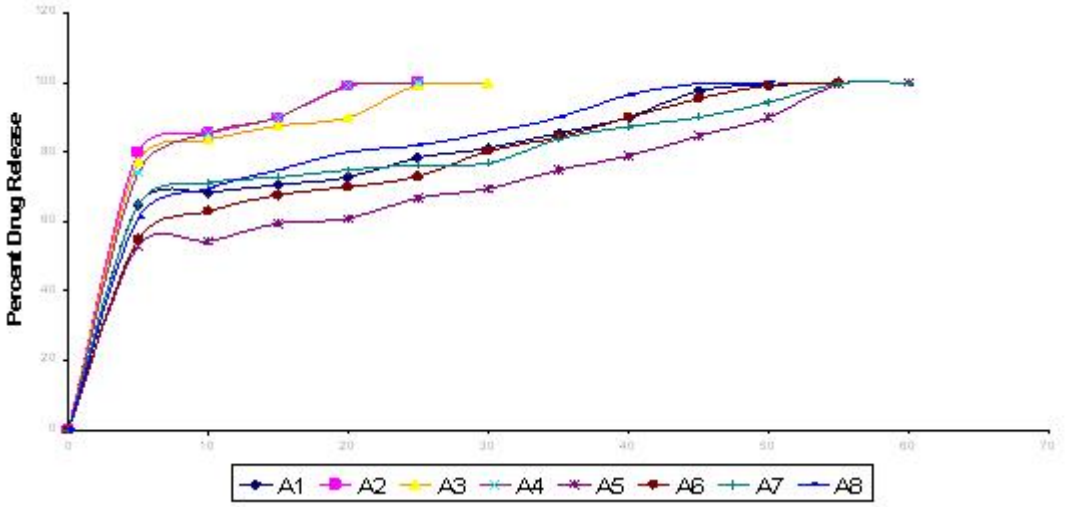

Fig 3: Release profile of formulated batches

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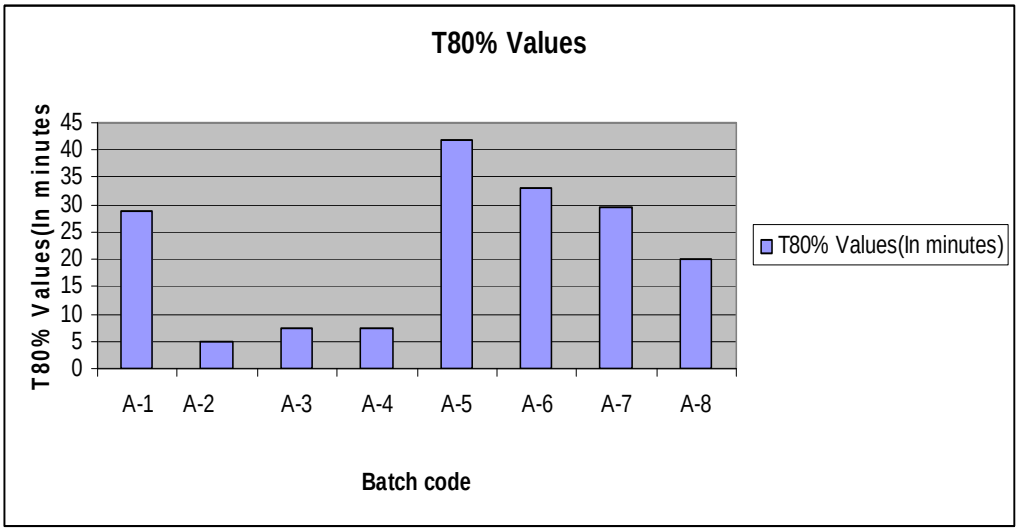

Figure 4:T80% values for Orodispersible tablet of Zopipolon

Disintegration Time: The disintegration time was found in the range 24-50 seconds for all batches. The batch A2 showed fastest disintegration. The result are given in Table 4, Figure 1.

Table 4: Disintegration studies of Mouth dissolving tablet of Zopicolon

Batch code	Disintegration time (seconds)
A1	42±0.12
A2	24±0.25
A3	25±0.15
A4	38±0.36
A5	47±0.45
A6	43±0.13
A7	49±0.32
A8	39±0.15

Water uptake test: Water uptake test which is important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water was calculated and found in the range of 159.40-203.01. The result are given in table 5, figure 2.

Table 5: Water Uptake test.

Batch code	Maximal water uptake (mg/tablet)
A1	183 ±0.32
A2	190.96±061
A3	190.32 ±0.54
A4	203.01 ±0.38
A5	159.40 ±031
A6	184.20 ±0.19
A7	162.20 ±0.12
A8	196.90 ±0.20

Table 6: *In- vitro* drug release kinetic studies

Time (Min.)	Percent Drug Release							
Batch code	A1	A2	A3	A4	A5	A6	A7	A8
5	64.8	80.1	77.4	74.1	53.1	54.9	64.8	61.2
10	68.3	85.5	83.4	85.5	54.3	63.0	71.2	69.4
15	70.6	90.0	87.7	90.0	59.4	67.6	72.6	74.9
20	72.6	98.9	90.0	99.1	60.9	69.9	74.8	80.1
25	78.3	100.0	99.3	100.0	66.7	73.0	76.3	81.9
30	81.1	-	100.0	-	69.4	80.2	76.7	85.6
35	85.5	-	-	-	74.8	84.2	83.9	90.0
40	90.0	-	-	-	78.8	90.0	87.3	96.5
45	97.7	-	-	-	84.5	95.4	90.0	99.7
50	99.2	-	-	-	90.0	99.3	94.3	100.0
55	100.0	-	-	-	99.5	100.0	99.6	-
60	-	-	-	-	100.0	-	100.0	-

Table 7: Stability studies of formulated of Mouth dissolving tablet of Zopicolon

Sr.No.	Evaluation Parameter	Observation			
		Batch A2		Batch A3	
		Before	After	Before	After
1	Physical Appearance	* *	* *	* *	* *
2	Weight Variation (mg)	* *	* *	* *	* *
3	Hardness(kg/cm^2)	3.4 ±0.4	3.4 ±0.3	3.3 ±0.3	3.4 ±0.4
4	Friability (%)	0.19	0.18	0.83	0.83
5	Drug content (mg/tablet)	99.08 ±1.43	99.52 ±1.19	99.86 ±1.56	99.59 ±1.35
6	T80% (Dissolution in min.)	5.0 ±0.03	5.0 ±0.05	7.5 ±0.04	7.3 ±0.06

* * = No change

In-vitro Release studies:

The comparative analysis of each formulation was based on in-vitro kinetic parameters which elucidated the release profile. The time taken for 80% drug release was taken as a response for comparative interpretation of superdisintegrants. The results are shown in table no .6 and figure .3.

Stability studies: The selected formulations (Batch A2,A3) were stored at 25° C ± 2°C/60% RH, 30°C ± 2°C/65% RH, 40°C ± 2°C/75% RH for 3 month in Humidity chamber(Thermo lab Mumbai) and evaluated for their physical appearance and drug content at specified intervals of time. Tablet were evaluated for Weight Variation, Hardness, Friability, Drug content, T80%, There is no change in these parameters as given in Table no. 7 . Based on the results it can be concluded that the formulated Mouth dissolving tablet of Zopicolon were stable at given conditions. The results are shown in table 7.

Conclusion:

From all the above observations, it was concluded that Batch A2 which containing (Ac-di-sol 50mg, Polyplasdone XL-10 25mg, Micro crystalline cellulose pH 1.02 25mg) gave the promising enhancement in the onset action of Zopicolon. The superdisintegrants Ac-di-sol (cross carmellose sodium) was found to have maximum impact on the enhancement of

dissolution, which was followed by Polyplasdone XL10 while Micro crystalline cellulose pH1.02 had a negative impact on the enhancement of dissolution of Zopicolon

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