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OPTIMIZATION OF OLANZAPINE MOUTH DISSOLVING TABLETS USING MICRONIZATION

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ABSTRACT

Formulation of Olanzapine mouth dissolving tablets (MDT) is a challenging approach, since it is practically insoluble in water. Attempts were made by use of different super disintegrants, different level of surfactant and use of micronized drug for the design of the formulation. Initially the batches were started with normal active and super disintegrants alone, after included solubilizing agent for same composition. Due to its insoluble nature of the drug substance, the tablets were not meeting the targeted drug release rate. Further trials were attempted with three different particles of active. The particle size having less than 10µm was showed improved rate and extent of drug release. Flavor and sweetener optimization was also done to have better organoleptic properties. All batches of tablets were evaluated for pre-compression and post-compression parameters and results were found satisfactory. The optimized formulation (F15) was stable for a period of 6 months at accelerated stability study.

KEY WORDS

Direct compression, Dissolution, Micronization, Olanzapine, Stability.

INTRODUCTION

Oral route is the most preferred route for administration of therapeutic agents because of ease of administration, accurate dose, self medication and patient compliance. In this concern tablets and capsules are most preferred dosage forms for oral route. But these dosage forms are difficult to administer to psychic as well as elderly patients. So the present authors focused on mouth dissolving tablets due to increasingly aged and development of appropriate dosage form for the elderly is most desirable. Because of change in the physiological functions in the elderly persons is difficult to swallow the normal conventional tablets. So MDTs are most preferable for its ease of administration and improve the therapeutic efficacy of dosage forms (1-3).

Mouth dissolving tablets (MDT's) are disintegrates and dissolves in the mouth (in saliva) within few seconds without need of any liquid. Mouth dissolving tablets are also called as fast dissolving, oro dispersible, orally disintegrating and fast melting tablets. MDT's combines the advantage of both conventional and liquid formulations (4-5).

In this study, the present authors developed Olanzapine mouth dissolving tablets by direct compression technique due to its lower cost, savings time and energy (6). Olanzapine is used to treat schizophrenia and bipolar disorders and it comes under the category of an atypical antipsychotic drug.

EXPERIMENTAL DETAILS

Olanzapine was obtained as gift sample from Vasudha Pharmaceuticals, Hyderabad and other excipients used in this work was obtained as gift samples from Micro labs, Bangalore.

Preparation of mouth dissolving tablets

Olanzapine mouth dissolving tablets were prepared by direct compression technique. The materials like Olanzapine, MCC PH 101, mannitol SD 200, sorbitol, sodium lauryl sulfate, crospovidone and

croscarmellose sodium was sifted through # 40mesh and colloidal silicon dioxide, magnesium stearate, tutti frutti, lemon flavor, neotame was sifted through # 60mesh and collected separately in poly ethylene bag.

According to formula, loaded sifted Olanzapine, mannitol SD 200, MCC PH 101/sorbitol, sodium lauryl sulfate, crospovidone, and croscarmellose sodium into the blender and blended for 10 minutes and finally added sifted neotame, tutti frutti/lemon flavor, colloidal silicon dioxide and magnesium stearate to the blender and blended for 5 minutes. Finally lubricated blend is compressed into tablets by using rotary compression machine. The process is same for all batches except the concentration change in the formulation.

Initially the batches F1-F6 were prepared with two super disintegrants alone i.e. crospovidone and croscarmellose sodium in different concentrations. Same like F5 formulation, three more batches i.e. F7-F9 was formulated by including SLS (sodium lauryl sulfate) as solubilizing agent. The composition details were given in **Table 1**.

Table 1: Composition of batches F1-F9

Composition	Unit formula (mg/tablet)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Olanzapine	10	10	10	10	10	10	10	10	10
Mannitol SD 200	120	120	120	120	115	115	114.6	114	113
Sorbitol	50	50	---	---	---	---	---	---	---
MCC PH 101	---	---	47	47	49	49	49	49	49
Crospovidone	8.0	---	10	---	12	---	12	12	12
Croscarmellose sodium	---	8.0	---	10	---	12	---	---	---
Sodium lauryl sulfate	---	---	---	---	---	---	0.4	1.0	2.0
Colloidal silicon dioxide	10	10	10	10	10	10	10	10	10
Magnesium stearate	2.0	2.0	3.0	3.0	4.0	4.0	4.0	4.0	4.0
Total tablet weight	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**

Same like F9 formulation further three more batches i.e. F10-F12 was formulated by replacing the normal active with micronized actives (60µ, 25µ, and 8µ). Further four more batches i.e. F13-F16 was formulated with tutti frutti and lemon as flavors alone and neotame as sweetener in different concentrations to optimize the formulation. The composition details were given in **Table 2**.

Table 2: Composition of batches F10-F16

Composition	Unit formula (mg/tablet)						
	F10	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
Olanzapine	10^a	10^b	10^c	10^c	10^c	10^c	10^c
Mannitol SD 200	113	113	113	108.8	108.8	106.6	106.6
MCC PH 101	49	49	49	49	49	49	49
Crospovidone	12	12	12	12	12	12	12
Sodium lauryl sulfate	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Colloidal silicon dioxide	10	10	10	10	10	10	10
Neotame	---	---	---	4.0	4.0	6.0	6.0
Tutti frutti flavor	---	---	---	0.2	---	0.4	---
Lemon flavor	---	---	---	---	0.2	---	0.4
Magnesium stearate	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Total tablet weight	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**

a: particle size of active substance is 60µm; b: particle size of active substance is 25µm ; c: particle size of active substance is 8µm

Blend parameters

The blend parameters like bulk density, tapped density and compressibility index was performed for all batches of blend (7).

Physical parameters of compressed tablets

The physical parameters like resistant to crushing, friability, weight variation and disintegration time was performed for all batches of the tablets (8-9). Next dispersion time and water absorption ratio was performed for optimized formulation (F15) to study the dispersion time and water absorption capacity of MDT (10-11).

***In-vitro* drug release studies**

The study was conducted with six tablets for each formulation using USP type II dissolution apparatus using 900 ml of 0.1N HCl as dissolution medium at a paddle speed of 50 RPM. As per time points, 10 ml of aliquots were withdrawn through auto sampler and filtered through 0.45µ filters and the same amount of dissolution medium was replaced into dissolution apparatus for maintaining the sink condition. The absorbance of aliquots was measured at 260 nm using UV-spectrophotometer. Comparative *in-vitro* dissolution study was conducted for optimized test formulation with reference product (OLAN MD 10mg manufactured by Micro labs).

Flavor and Sweetener optimization

The batches F13-F16 was formulated with tutti frutti and lemon as flavors and neotame as sweetening agents in different concentrations. All four formulations were given to five human healthy volunteers and evaluated the taste and flavor of the formulations (12).

Assay by HPLC method

The drug content was measured for optimized formulation F15 by HPLC method at 260 nm using 4.6-mm X 15-cm; 5-µm packing L7 column with a injection volume of 20µl at flow rate of 1.5 ml/minute and the run time was about 10 minutes (13).

Stability studies

As per ICH guidelines, the accelerated stability studies were conducted for optimized formulation F15 for a period of six months. The samples were withdrawn from stability at 1st, 2nd, 3rd, 6th months and analyzed for assay, dissolution, friability, disintegration time and dispersion time (14).

RESULTS AND DISCUSSION

Blend evaluation

All batches of blend was evaluated for blend parameters and confirmed that lubricated blend was very much useful for compression and the results were found satisfactory.

Physical parameters of tablets

All batches of tablets were evaluated for physical parameters like resistant to crushing, friability, average weight and disintegration time. The results of all parameters were found within the acceptable limit.

***In-vitro* dissolution studies**

Initial batches i.e. F1-F4 tablets was showed more disintegration time and not found within the targeted range. So the dissolution study was not performed for these batches and next batches were showed improved disintegration time than previous batches. So here after, the dissolution studies were performed for all batches of tablets. The batches F5-F6 tablets was showed very slow rate of drug release. There is no improvement of drug release was observed in further F7-F9 batches even though the solubilizing agent was included in the formulation. Next F10-F12 batches were formulated with micronized active, in that the particles having less than 10µ showed very good drug release rate than other particles (60µ, 25µ) and confirmed that F12 is optimized formulation. The *in-vitro* drug release data of all batches were given in table 3 and the graph of the same was shown in **Figure 1**.

Table 3: *In-vitro* drug release data of all batches F5-F12

Time in minutes	% Cumulative Drug Release (%RSD)							
	F5	F6	F7	F8	F9	F10	F11	F12
05	65 ± 2.62	58 ± 2.86	67 ± 2.35	63 ± 2.15	65 ± 2.02	71 ± 2.64	82 ± 2.68	92 ± 2.05
10	69 ± 2.53	62 ± 2.65	71 ± 2.12	67 ± 2.26	69 ± 1.26	79 ± 2.03	88 ± 2.06	94 ± 1.38
15	76 ± 2.14	69 ± 2.49	74 ± 2.09	78 ± 2.08	74 ± 1.84	83 ± 1.24	90 ± 1.64	97 ± 1.20
30	79 ± 2.39	70 ± 2.58	78 ± 2.15	81 ± 2.19	79 ± 1.38	85 ± 1.62	93 ± 1.06	98 ± 1.08

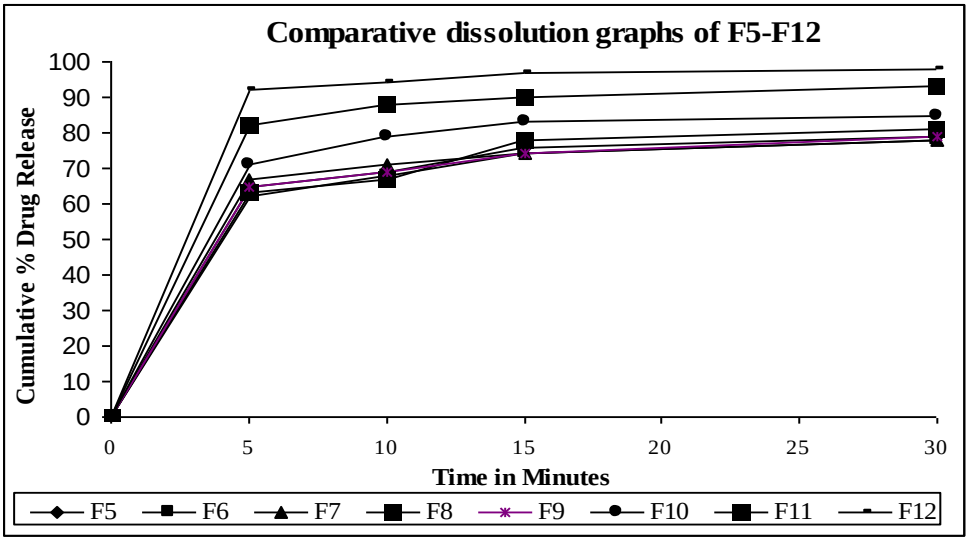

Figure 1: Comparative dissolution graphs of F5-F12

Flavor and sweetener optimization

The formulation prepared with neotame and tutti frutti flavor i.e.F15 batch was showed very good taste and flavor than other formulations and confirmed as optimized formulation in concern of disintegration time, dispersion time, dissolution and organoleptics.

Stability studies

From the stability data it was observed that all parameters were found within the limit and the drug was stable for a period of 6 months at accelerated condition without any noticeable change and confirmed that F15 batch is optimized formulation. The results of the same were given in table 4 and the comparative dissolution graph of initial with after stability was showed in **Figure 2**.

Table 4: Comparative stability data with initial at accelerated condition

Name of Test	Initial	1st month	2nd month	3rd month	6th month
Appearance	*	Complies	Complies	Complies	Complies
Dissolution					
05 minutes	91	91	90	90	91
10 minutes	93	94	93	93	94
15 minutes	96	96	97	96	97
30 minutes	99	99	99	98	98
Assay	99.8	99.7	99.6	99.7	99.5
Friability	0.12 ± 0.03	0.11 ± 0.02	0.13 ± 0.04	0.12 ± 0.02	0.13 ± 0.05
Disintegration test	14 ± 0.36	15 ± 0.52	14 ± 0.45	16 ± 0.28	15 ± 0.31
Dispersion time	12 ± 0.38	12.5 ± 0.45	12.1 ± 0.29	13 ± 0.24	12.4 ± 0.15

***Yellow coloured round, biconvex uncoated tablets plain on both sides**

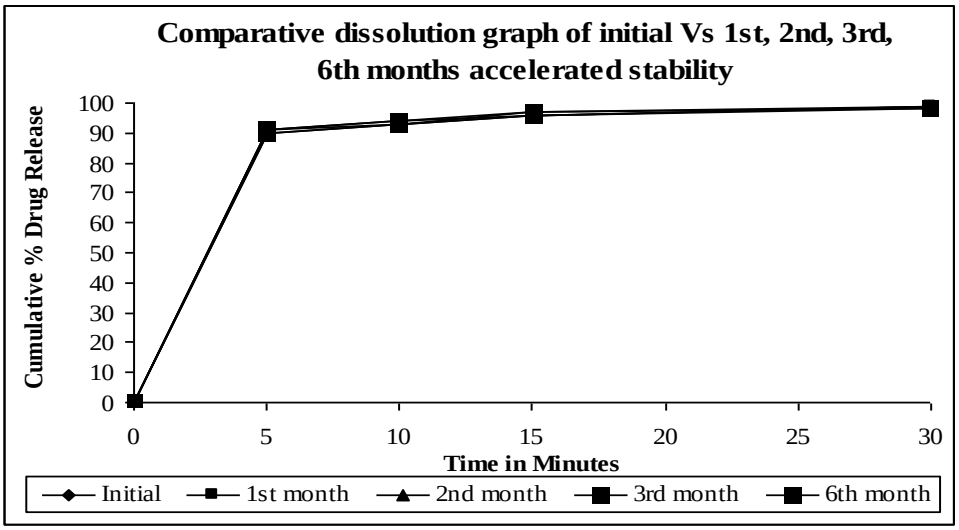

Figure 2: Comparative dissolution graph of Initial Vs Stability

CONCLUSION

From the above results it revealed that the tablets prepared with micronized active i.e. less than 10µ (F15) is the optimized formulation of Olanzapine mouth dissolving tablets and all parameters of tablets were found satisfactory. The optimized test formulation F15 was showed similar drug release compared to the reference product and also passes accelerated stability study for a period of 6 months without any noticeable change.

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