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Manufacturing of new formulation of olanzepine + fluoxetine capsules 6mg/25mg

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Abstract

Olanzapine and fluoxetine HCl are used to treat the episodes of depression, in the present study manufactured the new combined formulations of Olanzapine and fluoxetine HCl by using Pregelatinized starch, Sodium lauryl sulphate, Aerosil-200 and Magnesium stearate. This study is divided into two phases. In the first phase of the study new formulation of Olanzapine and fluoxetine HCl capsules were prepared. In the 2nd phase of study new combined formulation is evaluated for their physical parameters like average weight, weight variation, disintegration time and also evaluated the chemical analysis like dissolution behaviour and assay. All quality control parameters: average weight, weight variation test, disintegration test, dissolution test and assay were carried out specified by BP/USP (British and United state Pharmacopoeia) for capsules. The results showed that all parameters of new formulations are in accordance with the BP/USP limits.

1. Introduction

Now Depression is a real world-wide problem. Olanzapine (OZP) or 2-methyl-4- (4-methyl-1-piperazinyl)-10H-thieno-[2, 3b] [1, 5] benzodiazepine (Figure 1) is an atypical antipsychotic drug used in the treatment of schizophrenia and other psychotic syndromes [1]. It is a yellow crystalline solid, which is practically insoluble in water. It has lower incidences of extra pyramidal side effects than typical antipsychotics because they are potent antagonists of serotonin type 2A and type 2 dopamine (D2) receptors [2]. The mode of action of Olanzapine's antipsychotic activity is unknown [3].

Fluoxetine (FLT) or (±)-N-methyl-3-phenyl-3-[α,α,α-trifluoro-p-tolyl]oxy] propylamine (Figure 2) is an antidepressant agent, selective serotonin re-uptake inhibitor [4]. It is a white to off-white crystalline solid with a solubility of 14 mg/mL in water. It acts by increasing the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the cell [5].

Among persons with major depression, 75–85% has recurrent episodes [6]; 10–30% recovers incompletely and has persistent, residual depressive symptoms [7]. Several combinations of effective treatments have been used in the search for higher response rate or more rapid responses than monotherapy to diminish treatment resistant depression [8]. One strategy is to combine of the antipsychotic drug olanzapine plus antidepressant drugs [9]. Accordingly, olanzapine plus fluoxetine is an approved therapy for treating human depression [10]. In addition, a fixed combination of olanzapine and fluoxetine has been introduced for the treatment of bipolar depression [11]. The literature confirms that

the combined formulation of Olanzapine and fluoxetine HCl (OFC) is an effective treatment for bipolar I depressive episodes, as well as major depressive episodes that have not responded to several adequate courses of antidepressant therapy. Its use as a first-line treatment for bipolar I depressive episodes. [12]. Caryo et al. demonstrate that the combination of OZP and FLT is beneficial for treatment-resistant depression [13]

The manufacturing of Pharmaceutical drug, from formulation development to finished product, is very difficult process. This includes interactions of various kinds between process conditions and raw materials. These interactions are of great importance for the process ability and quality of the finished product, so these interactions should be taken into account earlier, such that to save later loss of time and money. [14]

In our present study we developed a new formulation of olanzapine and fluoxetine HCl and all of the following parameters were analyzed i.e. average weight, weight variation, disintegration, dissolution and assay as per USP [15].

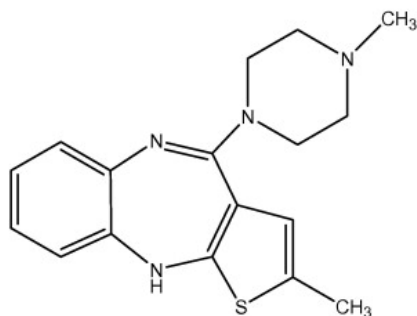


Figure 1. Structure of Olanzapine

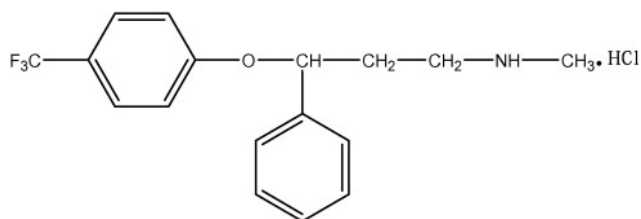


Figure 2. Structure of Fluoxetine HCl

2. Methodology

2.1. Materials

The API and excipients used in the formulation were Olanzapine, Fluoxetine HCl, pregelatinized starch, sodium lauryl sulphate, aerosol 200 and magnesium stearate. All of them were of analytical grade. For quantitative analysis, the standards used were Olanzapine, Fluoxetine HCl (Potency 98-101%).

2.2. Manufacturing of New Formulations

Accurately weigh all the ingredients of capsules. Pass the olanzapine, fluoxetine HCl, pregeletenized starch and sodium lauryl sulphate through mesh 0.5 mm than transferred them

into suitable food grade polyethylene bag. Ingredients were mixed by tumbling action in a large size poly bag for 5 minutes. Add the aerosil 200 and magnesium stearate in the premix and finally blend for 2 minutes. Finally adjust the capsules shell into the capsules filling machine carefully so the body adjust in the lower hole. The head of capsules were unlocked by adjusting the lever. Fill the blended powder in the body of capsule. Place the upper plate carrying head of the capsules and locked them on the body with the help of the lever.

2.3. Capsules Specifications

After manufacturing of a new formulation of capsules all of the following parameters were analyzed i.e. average weight, weight variation, disintegration, dissolution and assay [15].

2.3.1. Average Weight and Weight Variation Test

Weight Variation (in process test) ensures that content of each dosage units is uniform during encapsulation. Accurately weigh 20 capsules of new formulation on Electronic Balance Metler AG-245. Calculate the weight of each capsule that must be within official limits. USP/ BP states that the capsules containing less than 300 mg of the total weight may be outside $\pm 10\%$ of the average (NMT two capsules out of the sample) and all must be within 20%.

2.3.2. Disintegration Test

Disintegration apparatus Pharmatest Disintegration Tester Series Type PTZ Auto was used for this test. Place one capsule in each of the six tubes of the basket and add a disc. Using water as the immersion fluid, operate the apparatus by maintaining its temperature at 35- 39 °C. Finally at the specified time, pick up the basket from the fluid and check whether all of the capsules have disintegrated completely. The test is repeated on 12 extra capsules if one or two capsules fail to disintegrate. The requirements are met when out of 18 capsules 16 are disintegrated. According to USP, capsule should disintegrate in not more than thirty minutes.

2.3.3. Dissolution Test

Dissolution test was carried out on Dissolution Tester AT7 Smart dissolution apparatus. Assemble the equipment, pour 900ml of 0.1 HCl in each of the vessel and maintain the temperature of vessels at $37 \pm 0.5^\circ\text{C}$. Place one capsule of new formulation in a each vessel before rotation. The rotation of the basket was set at 50RPM. A sample of 10 ml is withdrawn after 30 minutes. The sample must be taken from a zone midway between the surface of the dissolution medium and the top of the rotating basket, at least 10 mm from the vessel wall and not less than 10 mm below the surface. The quantity of olanzapine and fluoxetine HCl dissolved was determined as specified in USP [15].

2.3.4. Assay

Assay was performed on High Performance Liquid

Chromatography (HPLC) Knauer, with Auto sampler. Sample and standard were prepared as specified in the USP and tested was carried out at UV 227 nm, Column: 4.6-mm × 7.5-cm; 3.5- μ m packing L7, Column temperature: 40°C, Flow rate: 2 mL/min, and Injection volume: 10 μ L as per USP [15].

3. Results and Discussion

3.1. Average Weight and Weight Variation Test

Average weight and Wt. variation test of new formulation capsules proved statistically that all the capsules were in accordance to the BP/USP requirements. (Table 1, 2)

3.2. Disintegration Test

Disintegration test was conducted on newly developed formulation and our results were in accordance to BP/USP (Table 3).

3.3. In Vitro Dissolution Studies

The percentage of the labeled amount of olanzapine and Fluoxetine Hydrochloride dissolved in 30 minutes are shown in Table-4. As per U.S.P official limits for olanzapine and Fluoxetine Hydrochloride capsules, dissolved amount of olanzapine and Fluoxetine Hydrochloride should NLT 80% (Q) of the labeled amount in 30 minutes and new formulation is under the specified limit.

3.4. Pharmaceutical Assay

The assays described are the official methods upon which the standard of the pharmacopoeial depend. By using HPLC

assay was carried out on the newly developed formulation of Olanzapine and Fluoxetine Capsules contain an amount of Olanzapine and Fluoxetine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% each of the labeled amount of olanzapine and fluoxetine during the study. All capsules have potencies in accordance of required specification (Table 5).

4. Discussion

In the present study new of Olanzapine and Fluoxetine Hydrochloride capsule was manufactured. All parameters of (average weight, weight variation, dissolution, disintegration, assay) of new formulation were carried out and results showed that they are in accordance with the BP/USP limits. In our trials Disintegration time was found to be 5 minutes 40 seconds which is within specified BP\USP limit. And the dissolved amount of Olanzapine and Fluoxetine Hydrochloride should NLT 80% (Q) of the labeled amount in 30 min. Potency of the Olanzapine and Fluoxetine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% each of the labeled amount of olanzapine and fluoxetine. Our research group has done these types of formulation studies.

5. Conclusion

All parameters (average weight, weight variation, dissolution, disintegration, and assay) of new formulations were carried out and results showed that average weight, wt. variation, disintegration, dissolution and assay are in accordance with BP/USP limits. The advantage of this formulation is that this formulation is quite simple; less time consuming and economical therefore pharmaceutical industry use this method.

Table 1. Statistical Weight Variation

No. of Capsules	Average (mg)	Standard deviation	Upper limit (X+3S)	Lower limit (X-3S)
20	255.00	0.005	262.32	250.09

Table 2. Weight Variation Test

No. of Capsules	Average (mg)	BP/USP Specification	Deviation from BP/USP Specification
20	255.00	Deviation should be \pm 10%	Within specified limit

Table 3. Disintegration Test

Disintegration time (min:sec)	USP Specification	Deviation from USP Specification
5 min: 40 sec	NMT 30 Min	Passes

Table 4. Dissolution Test

No. of Capsules	Results (%)		USP Spec	Deviation from USP
	Olanzapine	Fluoxetine		
6	95.58	99.85	Not less than 80%(Q) of the labeled amount dissolved in 30 min	Passes

Table 5. Assay Test

No. of Capsules	Results (%)		USP Spec	Deviation from USP
	Olanzapine	Fluoxetine		
20	100.02	99.31	90.0%–110.0%	Passes

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