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Research Article

FABRICATION & EVALUATION OF FLUOXETINE AND VITAMIN E FAST RELEASE BILAYER TABLETS IN DEPRESSION MANAGEMENT

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ABSTRACT

The aim of the present research is fabrication of fluoxetine and Vitamin E fast release bilayer tablets. This investigation was carried out to achieve multi benefits in depression associated with sexual dysfunction problems .Objectives of this investigation are to wipes away the Depression immediately, to promotes the Fertility and sexual function in depressed patients and to scavenges the free radicals production on long term use. In this study both layers were formulated as immediate release layers with the aim of reaching high serum concentration in a short period of time. Direct compression method was used for formulation of fast release bilayer tablets. The optimized formulation consists of Fluoxetine and Vitamin E fast release layer. Vitamin E was taken as Tocopherol Succinate (tablet grade granules) .It is fat soluble drug. To make fast release of Vitamin E layer, polysorbate 80 (non-ionic surfactant) was added in 2% concentration. Like that half life of Fluoxetine is longer. So it is the suitable drug to formulate the fast release layer. Croscarmellose was used as the Superdisintegrant for fluoxetine and Vitamin E fast release layers. This Bilayer formulated tablets were evaluated for physico-chemical properties such as hardness, thickness, friability, weight variation and drug content uniformity. Invitro dissolution studies were carried out by using USP type II Paddle type apparatus. All the studies revealed that optimized bilayer tablets satisfy all the parameters and have the potency to meet the challenges of dose dependant side effect in depression and it provide quick onset of action in depression.

Keywords: Bilayer, Fluoxetine, Tocopherol Succinate, Fast release layer, Croscarmellose.

INTRODUCTION

Multilayer immediate release tablet dosage forms were designed for various reasons to deliver different medicament in a single dosage forms and for exhibit instant drug release etc. Fluoxetine is one of the Selective Serotonin Reuptake Inhibitor (SSRI) drug approved for the treatment of major depression, obsessive compulsive disorder, bulimia nervosa, Panic disorder[1] and also used for Cataplexy, obesity and alcohol dependence, binge eating disorder[2]. Elimination of half the amount of Fluoxetine takes 1 to 3 days. In long term use, Fluoxetine the half life increases up to 4 to 6 days[3, 4]. But Fluoxetine has some side effects such as erectile dysfunction, and lack of interest in Sex[5].

It possess slower metabolism in Geriatric, Adolescent and black patients. Overdose and long term usage of Anti-depressants are toxic[6], which produces Free radicals. Focused on all side effects this investigation was carried out .Here Vitamin E acts as a peroxyl

radical scavenger preventing the propagation of free radicals[7]. Vitamin E is one of the fat soluble vitamins which play a very special role in the body as a Protector and Fertility Promoter[8]. Tocopherol is an oily liquid at both room and higher temperatures and acids do not affect the stability of Vitamin E[9]. It keeps sperms alive for several days. Some research papers connotes Vitamin E helps the semen quality improvement and sperm motility and also enhance female fertility[10]. Based on this beneficial effect Vitamin E was taken as an antioxidant for second layer.

Half life of Vitamin E in plasma is 2-3 days[11]. It is also called as Anti-sterility vitamin. In this study Croscarmellose was used as a super disintegrant for Fluoxetine and Vitamin E fast release layer.

MATERIALS

Fluoxetine was procured as gift sample from Ranbaxy pharmaceuticals, Mumbai. Vitamin E Succinate was procured as gift samples from Triveni chemicals, Gujarat. Croscarmellose, Talc, and Magnesium Stearate were procured as gift samples from Acumen Pharmaceuticals Private Limited, Pondicherry. Polysorbate 80 was procured from Dhiven chemical industries Thane, India.

Preparation of fast release Bilayer Tablets[12]

The bilayer tablets consist of Fast release Fluoxetine layer and fast release Vitamin E layer. It was prepared by Direct Compression method.

Formulation of Fast Release Fluoxetine Layer

The dose of Fluoxetine in fast release layer is 20 mg as per I.P. Granules were prepared by blending Fluoxetine with Croscarmellose as given in Table I. Finally the granules were mixed with talc and magnesium stearate.

Formulation of fast release Vitamin E layer

Tocopherol Succinate was selected for Vitamin E layer. Here Succinate acts as a carrier. When this nutrient is ingested, the carrier will be removed and it goes back as d-α-Tocopherol in the body. Vitamin E Succinate granules (tablet grade) were blended with microcrystalline cellulose, polysorbate 80 powder as given in the table II and the granules were passed through the sieve and were blended with lubricants.

Characterization of Granules

Prior to compression, granules were evaluated for their parameters such as tapped density, Carr's Index, and angle of repose.

Compression of Bilayer Tablet

The quantity of granules of Vitamin E layer was compressed lightly by slugging process using Single Punch tablet machine equipped with 11mm round flat punches. Over this compressed layer the required quantity of Fluoxetine fast release layer granules were placed and compressed to obtain hardness in the range of 3-4 Kg/cm^2 to form a bilayer matrix. Average weight of tablet was 350mg.

Evaluation of Bilayer Tablets

Weight variation[13]

Twenty tablets were selected and average weight was determined. Then individual tablets were weighed and it was compared with the average weight.

Hardness & Friability[14]

Hardness of tablet is defined as the force required for breaking the tablet. The friability of the tablets was checked by using Roche Friabilator. Friability was calculated using the formulae

$$Percent\ Friability = \frac{W_{in} - W_R}{W_{in}} * 100$$

W_{in} - Initial Weight
W_R - Final Weight

The hardness of the tablets was measured using a Monsanto Hardness Tester.

Wetting Time[15]

A piece of tissue paper folded twice was placed in a small petridish containing 6ml of dissolved water. A tablet having amaranth powder on the upper surface was placed on

filter paper. Time required to develop red color on the upper surface of the tablet is recorded as wetting time.

Invitro Disintegration Time

The disintegration time was measured using a modified disintegration method. For this Petri plate was filled with 10ml of water. The tablet was carefully put in the centre of the Petri plate and time for the tablet to completely disintegrate into fine particles was noted.

Invitro Dissolution Study

Dissolution Test for Fluoxetine [16]

The dose of Fluoxetine is 20 mg. It is taken in 900 ml of 0.1M HCl as dissolution medium with 50 rpm for 45 minutes. Withdraw a suitable volume of medium and filter. Determine it by Liquid Chromatography in diethyl amine phosphate suspension. To 250ml of acetic nitrile add 1 ml diethyl amine, mix and adjust the p^H to 3.5 with ortho phosphoric acid.

Test Solution – To 5ml of the filtrate obtained as given above add 2ml of diethyl amine phosphate suspension and mix well.

Reference- Dissolve 0.022gm of Fluoxetine HCl in sufficient amount of 0.1M HCl to produce 100ml and mix. Dilute 10ml of the solution to produce 100ml with 0.1M HCl. To 5ml of resulting solution add 2ml of diethyl amine phosphate suspension and mix well.

Mobile Phase: A mixture of 0.4 volumes of diethyl amine, 40 volumes of acetic nitrile and 60 volumes of water. Adjust to pH 3.5 with ortho phosphoric acid. Flow rate- 2ml/minute, Spectra set at 226nm, Injected volume: 50 µl

Dissolution Test for Tocopherol Succinate[17] **(Vitamin E Succinate)**

Dissolution test of tocopherol succinate was performed by paddle method with 100 rpm .In each basket one tablet was taken in 900ml solution of sodium lauryl sulphate in disodium hydrogen phosphate citric acid buffer solution. pH of buffer medium was 6.8. Samples were collected and diluted with methanol and measure the absorbance at 284 nm in UV Spectra.

RESULTS AND DISCUSSION

All the prepared tablets were evaluated for various physical properties. The bulk density for the granules of various formulations ranged between 0.92±0.10 and 2.15±0.13gm L^{-1} as determined by the Tap method.

This value of bulk density indicates the Good Packing character. The Compressibility Index for all formulation was found to be below 15% which indicates desirable flow properties.

Flow properties analyzed by determining the angle of repose. All granules exist the range between 22.4±0.1 to 25.04±0.3.This value indicates good flow property. Average weight of tablets was 350mg±0.2 .It shows tablets were compact and easy to swallow. Hardness 3.5kg/cm and thickness 4mm±0.21and percentage friability 0.7±0.02% shows optimized tablets were not break and retain the shape during packing and transport also. The fluoxetine drug content uniformity in bilayer matrix tablets was 99.8±0.12%.Wetting time and disintegration time values are given in Table 3, it shows quick release.

Dissolution profile of Fluoxetine shows that fluoxetine reaches the peak plasma within 20 minutes. Quick disintegration and dissolution was reached due to burst effect of croscarmellose. Burst effect of the tablets was proved by the presence of Superdisintegrants. The release of fluoxetine from fast release layer was analyzed by plotting the cumulative percentage of drug release Vs time was given in fig.1.It shows 98.9% of Fluoxetine released within 20 minutes

Like that Vitamin E layer also releases 99.2% antioxidant immediately within 25mins due to the addition of Polysorbate 80 and croscarmellose. The release pattern was given in figure II. All the disintegration and dissolution studies revealed that fast release Bilayer optimized formulation has the potency to wipe away depression immediately and it will fulfill the

requirements of Depression Patients problems such as free radical production and sexual dysfunction.

CONCLUSION

To overcome depression and dose dependant side effect like free radicals production, this optimized bilayer tablets were formulated .This fast release bilayer tablets have the potency to wipe away depression immediately with quick onset of action. For long term users it is a better therapy to rectify the sexual dysfunction .This fast release bilayer have the capacity to increase bioavailability and patient compliance. It was formulated with multi purpose and it will fulfill depression patient's requirements in future. Further Bio equivalence studies are necessary to establish this Optimized Formulation.

Table 1: Composition of Fluoxetine Fast Release Layer

COMPOSITION	FAST RELEASE LAYER (mg)
Fluoxetine	20 mg
Croscarmellose	2 mg
Microcrystalline cellulose	26 mg
Starch	50 mg
Talc	1 mg
Magnesium Stearate	1 mg
TOTAL	100 mg

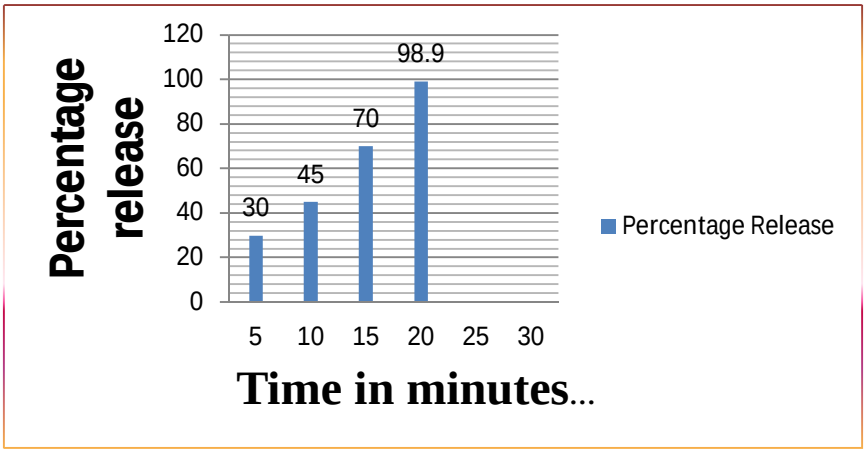
Table 2: Composition of Vitamin E Fast Release Layer

COMPOSITION	FAST RELEASE LAYER (mg)
Vitamin E(tablet granules)	200 IU (182mg)
Microcrystalline cellulose	56 mg
Polysorbate 80 powder	5 mg
Croscarmellose	5 mg
Talc	1 mg
Magnesium Stearate	1 mg
TOTAL	250mg

(α-Tocopherol Succinate = 0.91mg)[18]

Table 3: Physico-Chemical Parameters for Optimized Formulation

Average Weight	Hardness	Thickness	Friability %	Drug Content	Wetting time (sec)	Disintegration Time (sec)
350±0.2mg	3.5kg/cm²	4 mm±0.2	0.7±0.02%	99.8±0.12%	27±0.2 sec	40±0.3sec



Invitro Dissolution of Fluoxetine

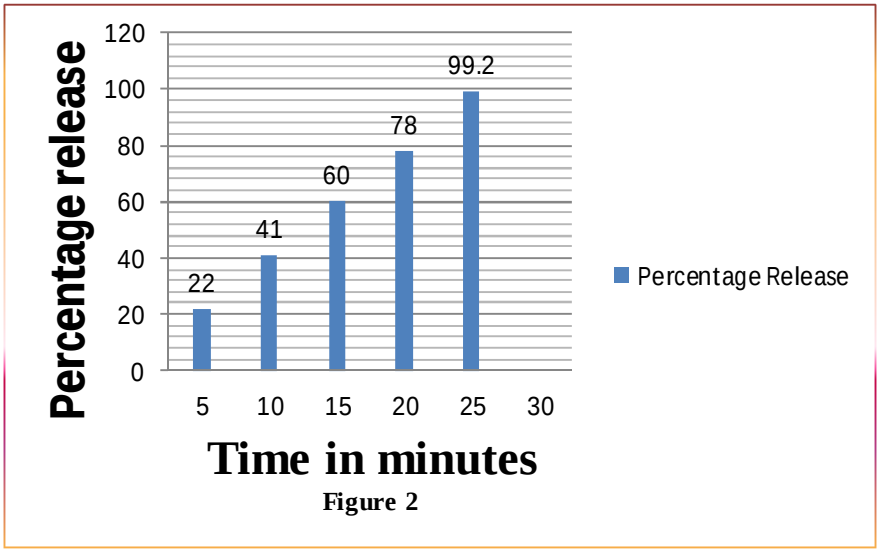


Figure 2

Invitro Dissolution of Vitamin E

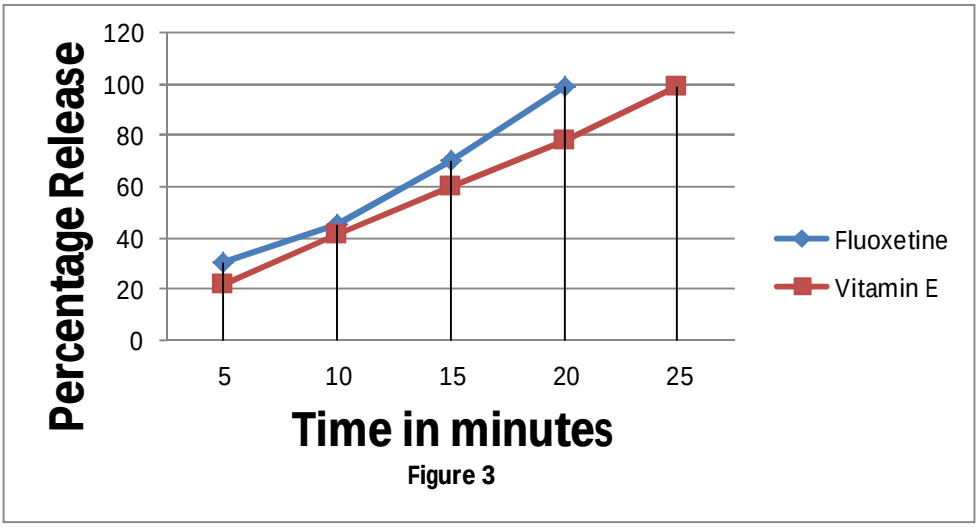


Figure 3

Invitro Dissolution of Bilayer

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