

DEVELOPMENT AND OPTIMIZATION OF FLIBANSERIN 100 MG FILM-COATED TABLETS USING WET GRANULATION TECHNIQUE

Anıl Kıyılar^{*1}, Cuneyt Toprak², Gokay Gun³, Erdinç Babuç⁴

¹Product Development Responsible Specialist, Research and Development Center, World Medicine İlaç San. ve Ticaret A.Ş., Istanbul, Türkiye.

²Scientific Department Manager, Research and Development Center, World Medicine İlaç San. ve Ticaret A.Ş., Istanbul, Türkiye.

³Product Development and Technology Transfer Manager, Research and Development Center, World Medicine İlaç San. ve Ticaret A.Ş., Istanbul, Türkiye.

⁴R&D Director, Research and Development Center, World Medicine İlaç San. ve Ticaret A.Ş., Istanbul, Türkiye.

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***Corresponding Author: Anıl Kıyılar**

Product Development Responsible Specialist, Research and Development Center, World Medicine İlaç San. ve Ticaret A.Ş., Istanbul, Türkiye.

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ABSTRACT

Flibanserin is a centrally acting serotonin receptor modulator indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. Due to its poor aqueous solubility and limited bioavailability, formulation development poses significant challenges. The present study aimed to develop and optimize a 100 mg film-coated tablet formulation of Flibanserin using the wet granulation method to ensure uniformity, stability, and compliance with pharmacopeial quality standards.

KEYWORDS: Flibanserin, wet granulation, film-coated tablet, formulation development, dissolution, content uniformity, BCS Class II.

1. INTRODUCTION

Flibanserin is a dual-action psychotropic drug. It is primarily a serotonin 5-HT_{1A} receptor agonist and serotonin 5-HT_{2A} receptor antagonist.^[1] Many neurotransmitters are involved in the sexual response in women. Flibanserin modulates some of these neurotransmitters, which may contribute to the drug's mechanism of action and efficacy^[1]

The drug is indicated for the treatment of premenopausal women with acquired generalized hypoactive sexual desire disorder (HSDD), characterized by low sexual desire that causes significant distress or interpersonal difficulty and is NOT due to.

1. A comorbid medical or psychiatric condition,
2. Relationship problems, or
3. The effects of a drug or other substance.^[2]

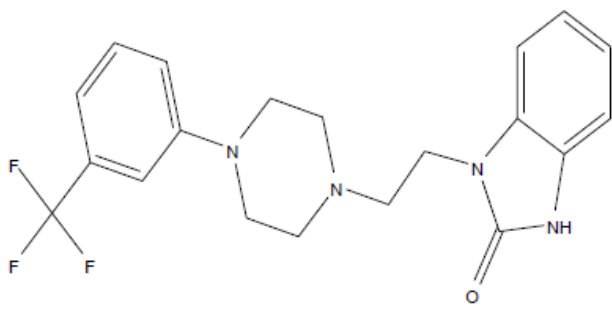
During pharmaceutical product development, the poor aqueous solubility and limited oral bioavailability of Flibanserin present significant challenges in dosage form design and manufacturing.^[3,5] As a Biopharmaceutical Classification System (BCS) Class II compound, Flibanserin requires careful formulation strategies to ensure uniform content distribution, adequate flowability of the powder blend, and desirable physical and chemical characteristics of the final product. Selection of an appropriate manufacturing method is therefore critical to ensure product quality and process robustness.^[3,5]

Wet granulation is a commonly employed manufacturing technique for active pharmaceutical ingredients (APIs) that are characterized by poor flow properties, low dosage strengths, or sensitivity in content uniformity.^[6,10] In this method, a granulating fluid is added in a controlled manner to the dry powder mixture to form wet masses, which are then dried to yield free-flowing and compressible granules. This process minimizes problems encountered during tableting and improves critical quality attributes (CQAs) of the final dosage form.

The aim of this study is to develop a 100 mg Flibanserin film-coated tablet formulation using the wet granulation technique at the laboratory scale and to evaluate the relevant formulation and process parameters. The study examines the choice of excipients, processing steps, and quality control results of the final product. In addition, the impact of critical process parameters (CPPs) on product quality is discussed. The findings are intended to provide a scientific basis for potential scale-up in industrial production settings.^[11]

Table 1: Physicochemical properties of Flibanserin.

Molecular formula	C ₂₀ H ₂₁ F ₃ N ₄ O
Molecular weight	390.40 g/mol
Chemical name	1-(2-{4-[3-(Trifluoromethyl) phenyl] piperazin-1-yl} ethyl)-1, 3-dihydro-2Hbenzimidazol-2-one
CAS Number	167933-07-5
Appearance	White to off-white color powder
Solubility	Soluble in chloroform and methanol, insoluble in water
Stereochemistry	No isomers are there in Flibanserin. No chiral center in the Flibanserin.
Hygroscopicity	Slightly hygroscopic
Melting range by DSC	162.56°C
pKa (Strongest Acidic)	12.91
pKa (Strongst Basic)	7.03
Log P: Partition coefficient	3.39
BCS Classification	Class II (low solubility, high permeability)
pH	6.10±0.02
Molar absorptivity	0.02014 mg/ml
Ultraviolet maxima	256.1 nm

Structural formula	
Therapeutic Category	Hypoactive sexual desire disorder

2. MATERIALS AND METHODS

2.1 Materials

In this study, the active pharmaceutical ingredient (API) and excipients used for the formulation of Flibanserin 100 mg film-coated tablets were of pharmaceutical grade. All raw materials were evaluated in accordance with the relevant monographs of the European Pharmacopoeia (Ph. Eur.) and/or the United States Pharmacopeia (USP).^[8,9,12,13] The excipients and their respective functions within the formulation are listed below.^[4, 7]

Components	Function
Flibanserin	Active substance
Lactose Monohydrate	Filler
Hypromellose	Binder
Croscarmellose Sodium	Disintegrant
Microcrystalline Cellulose	Diluent
Magnesium Stearate	Lubricant
Pure Water	Solvent
Film Coating Polymer (PVA based)	Film-Coating Agent

2.2. Manufacturing Process

2.2.1 Pre-mixing

The active ingredient (Flibanserin), lactose monohydrate, hypromellose and croscarmellose sodium were accurately weighed and blended in a high-shear mixer for 10 minutes until a homogeneous powder mixture was obtained.

2.2.2 Wet Granulation

Pure water was added gradually and uniformly to the powder blend while mixing in a high-shear granulator. The granulation process was continued until a cohesive and plastic wet mass was formed.

2.2.3 Wet Sifting

The wet granules obtained as a result of wet granulation are sieved through a sieve in line with the targeted parameters.

2.2.4 Drying

The wet granules obtained are dried in a fluid bed dryer with a maximum of 1.50% as a result of drying loss.

2.2.5 Dry Sifting

The dried granules were further sieved through a 16 mesh to achieve a uniform particle size distribution.

2.2.6 Sifting and Mixing

Microcrystalline cellulose is sifted through a 630 micron vibrating sieve and added to the dry granules and mixed for 15 minutes until a homogeneous mixture is obtained.

2.2.7 Lubrication

Magnesium stearate is sifted through a 630 micron vibrating sieve and added to the dry granules and mixed for 3 minutes until a homogeneous mixture is obtained.

2.2.8 Tablet Compression

The lubricated blend was compressed into tablets containing 100 mg of Flibanserin using a single-punch tablet press. Compression force and tooling dimensions were kept constant during the process. Physical parameters such as tablet appearance, weight variation, and integrity were monitored.

2.2.9 Film Coating

The compressed tablets were coated in a perforated pan coater using an PVA-based film-coating solution. The coating process was performed under controlled parameters including inlet air temperature, spray rate, and pan rotation speed. Upon completion, the coated tablets were allowed to stabilize at ambient conditions for 24 hours.

3. RESULTS

Film-coated tablets containing 100 mg of Flibanserin were successfully produced using the wet granulation method at laboratory scale. The results of the physical and chemical quality control tests conducted on the final product are summarized below

3.1 Physical Properties

Table 2: Physicochemical properties of Flibanserin 100 mg Coated Tablets.

Test Parameter	Acceptance Criteria (USP/Ph. Eur.)	Observed Value
Average weight Weight Uniformity	±5% deviation (for 347 mg/fct) A maximum of 2 of the individual weights may deviate more than 5.0% of the average weight and none may deviate more than 10.0%.	347 ± 10 mg Complies
Hardness	Min 70 N	Complies
Friability	NMT 1.0%	0.1 %
Disintegration Time	NMT 30 minutes	≤ 30 minutes

3.2 Chemical Properties

Table 3: Chemical properties of Flibanserin 100 mg Coated Tablets

Test Parameter	Acceptance Criteria (USP/Ph. Eur.)	Observed Value
Assay (API Content)	95 – 105 % of label claim	99.7 %
Dosage Units Homogeneity	Acceptance value (AV) must meet the requirements. L1: Max 15.0, L2: max 25.0	Complies
Water Content	Max 6.0 %	<6.0 %
Dissolution	At least 80.0% of the label value after 45 minutes (Q=75.0%)	100.5 %
Microbiological Quality TAMC TYMC Escherichia coli	NMT 10 ³ CFU/g NMT 10 ² CFU/g Shouldn't/g	<10 CFU/g <10 CFU/g Absent/g

All quality attributes were within pharmacopeial specifications, and consistent results were obtained across all batches. [8,9,12,13]

4. DISCUSSION

This study demonstrated the successful development of a 100 mg Flibanserin film-coated tablet formulation using the wet granulation technique. The results of the quality control tests indicate that the formulation met predefined specifications and that the manufacturing process was robust and reproducible.

4.1. Effectiveness of the Wet Granulation Process

Wet granulation was found to be an effective technique for improving the flowability and compressibility of powder blends containing Flibanserin, a poorly water-soluble and low-dose API. The resulting granules exhibited good flow characteristics, facilitating smooth tableting without processing difficulties. The low relative standard deviation (RSD) in the content uniformity results indicates that the hypromellose was homogeneously distributed throughout the formulation.

4.2. Evaluation of Tablet Properties

Tablet hardness, friability, and disintegration time were all within acceptable limits, confirming that both the formulation and process parameters were appropriate. The inclusion of croscarmellose sodium as a superdisintegrant played a critical role in achieving a rapid disintegration profile, which is essential for consistent dissolution and therapeutic efficacy.

4.3. Dissolution Performance and Biopharmaceutical Considerations

Given that Flibanserin is classified as a Biopharmaceutical Classification System (BCS) Class II compound, dissolution rate becomes a key factor in determining oral bioavailability. The observed dissolution rate (>90% at 45 minutes) indicates that the formulation successfully enhanced the solubility and dissolution of Flibanserin. This improvement is likely attributable to increased surface area and improved wettability achieved through wet granulation.

4.4. Implications for Scale-Up

The positive outcomes achieved at laboratory scale suggest that the formulation and manufacturing process are amenable to scale-up. Critical process parameters (CPPs) such as granulation time, solution volume, and drying conditions must be carefully controlled to ensure consistent product quality at commercial scale.

5. CONCLUSION

In this study, a 100 mg film-coated tablet formulation of Flibanserin was successfully developed and optimized using the wet granulation technique. The granulation process, performed under controlled conditions, yielded granules with suitable physical properties, enabling the production of tablets that met pharmacopeial specifications for both physical and chemical quality attributes.^[8,9] Key parameters such as content uniformity, tablet hardness, friability, and disintegration time were all within acceptable limits, confirming the robustness of both the formulation and manufacturing process.^[8,9,10,11,12,13] Furthermore, dissolution testing demonstrated a rapid and efficient release profile, indicating the potential for improved bioavailability of Flibanserin. Overall, the findings suggest that the developed formulation is suitable for potential scale-up to industrial production and can be standardized according to quality assurance requirements.

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