World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

DEVELOPMENT AND EVALUATION OF BIODEGRADABLE SUSTAINED RELEASE TABLET FORMULATION OF ANASTROZOLE INTENDED TO TREAT BREAST CANCER

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Article Received on 03/02/2025 **Article Revised on 24/03/2025** **Article Accepted on 14/03/2025**

ABSTRACT

Breast cancer is a leading cause of cancer-related mortality among women, with over 1.5 million new cases diagnosed annually. Risk factors include age, genetics, dense breast tissue, hormonal influences, and lifestyle choices. Anastrozole, an aromatase inhibitor, is widely used for treating hormone receptor-positive breast cancer in postmenopausal women. It works by selectively inhibiting the aromatase enzyme, reducing estrogen production, and slowing tumor growth. This study focuses on the formulation and evaluation of sustained-release Anastrozole tablets using the wet granulation method. Various excipients, including fillers, disintegrants, lubricants, and glidants, were used to optimize tablet characteristics. Granules were evaluated for flow properties such as angle of repose, bulk density, and compressibility index, ensuring uniform tablet production. The formulated tablets were assessed for physical parameters, including hardness, friability, weight variation, disintegration, and dissolution rate. The results demonstrated that all formulations met standard pharmaceutical requirements, with good flowability, uniform hardness, low friability, and effective dissolution profiles. In-vitro dissolution studies showed sustained drug release over 12 hours, with formulations achieving up to 99.15% cumulative drug release. These findings confirm that the developed sustained-release Anastrozole tablets offer controlled drug release, potentially improving therapeutic efficacy and patient compliance. In conclusion, the formulated tablets provide a promising approach for breast cancer treatment, ensuring prolonged drug action and stable plasma concentration levels. Further in-vivo studies are recommended to validate the clinical efficacy of the sustained-release formulation.

KEYWORDS: Sustained release tablet, Anastrozole, Breast cancer, Treatment.

INTRODUCTION

The condition known as breast cancer occurs when aberrant breast cells proliferate uncontrollably and develop into tumors. The tumors can grow throughout the body and become lethal if they are not treated. Breast cancer cells start inside the breasts milk form (in situ) is possible and poses little harm to life. It is possible for cancer cells to invade neighboring breast tissue. This results in tumors that thicken or produce lumps. Invasive tumors have the ability to metastasis has the potential to be lethal.[1,15]

In 2015, there were about 570,000 recorded fatalities. Worldwide, more than 1.5 million women receive a breast cancer diagnosis each year, accounting for 25% of all cancer-stricken women. Age, family history, genetics, dense breast tissue, menstrual history, hormone use, and lifestyle variables are some of the risk factors linked to breast cancer.[2]

- **Age:** The risk of breast cancer also rises with a women's age. The chance of developing breast cancer is increased if have a close relative (mother, sister, or daughter) who has the disease.
- **Genetics:** The risk of breast cancer is higher for women with thick breast tissue than for those with less dense tissue.
- **Menstrual history:** Experiencing menopause after the age of 55 or beginning period before the age of 12 may raise risk.
- **Hormone use:** Hormone replacement therapy (HRT) and other long-term usage of hormones, such as progesterone and estrogen, can raise risk.

- **Lifestyle factors:** Drinking alcohol, being obese, and not exercising can all raise risk of developing breast cancer.[3,16]

DRUG PROFILE

Drug name: Anastrozole

Chemical name: 2,2-[5-(1H-1,2,4-triazol-1 methyl)-1,3-phenylene] bis (2-methyl-propiono- nitrile))

Anastrozole contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{17}H_{19}N_5$ calculated on the anhydrous basis.

Category: Anticancer

Description: A white to off white, crystalline powder.

Chemical formula: $C_{17}H_{19}N_5$

Chemical structure:

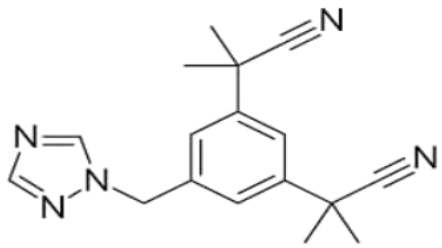

Fig. 1: Structure of Anastrozole.

Mechanism: Anastrozole works against estrogen by selectively and competitively inhibiting the aromatase enzyme, which is mostly located in the liver, fatty tissues, and adrenal glands. Since many breast tumors are hormone receptor-positive, hormone like estrogen and progesterone either promote or sustain growth. Estrogen in postmenopausal women is mostly produced by the aromatase enzyme, which converts adrenally produced androgens into estrogens. By competitively blocking the biosynthesis of estrogen at these enzymes, anastrozole effectively lowers circulating estrogen levels and, in turn, inhibits the growth of tumors that are hormone receptor-positive.[4]

Indication

Anastrozole is prescribed as a first-line treatment for hormone receptor-positive (or hormone receptor-unknown) locally progresses or metastatic breast cancer in postmenopausal women, as well as an adjuvant medication for hormone receptor-positive early breast cancer in these women. Additionally, postmenopausal women who continue to have disease progression after taking tamoxifen may use it to treat metastatic breast cancer.[5]

Route of administration: Oral administration.

MATERIALS AND METHODS

Materials

1. **Active Pharmaceutical Ingredient (API):** Anastrozole [ANS] (99 % purity) was purchased from Bioneeds India PVT Ltd. This is the core ingredient, the actual medication that delivers the therapeutic effect.
2. **Excipients:** All excipient were gifted from the chemical store of Narasaraopeta institute of Pharmaceutical Sciences.

- **Polymer:** Hydroxypropyl methylcellulose (HPMC) which is a Hydrophilic polymer from the chemical store of Narasaraopeta institute of Pharmaceutical Sciences. They form a matrix or coating that regulates the rate at which the drug dissolves and releases from the tablet.
- **Binder:** Poly vinyl pyrrolidine. Improves the cohesion of powder mixtures, which helps make tablets and reduces the risk of breakage.
- **Filler:** Microcrystalline cellulose. These make up the bulk of the tablet and provide structure.
- **Glidant:** Talc. These improve powder flow during manufacturing.
- **Super disintegrant:** Sodium starch glycolate. These help the tablet break apart after ingestion, allowing for faster drug release.
- **Sweetener:** Sucrose. Used to improve palatability.
- **Lubricant:** Magnesium stearate. These prevent sticking during tableting and ensure smooth passage down the throat.[6]

Method

We aim to prepare sustained-release tablets using the wet granulation method. This method ensures improved flowability, density, compressibility, and homogeneity of active pharmaceutical ingredients. Our focus will be on the preparation, evaluation, and characterization of the granules and final tablet formulation.

Ingredients: Each tablet contains 1 mg of anastrozole, with a total weight of 100 mg. The formulation details, including the specific quantities of excipients, are provided in Table 1.

Stepwise Methodology for Tablet Preparation

Sieving: All ingredients, including anastrozole, excipients, and binders, are passed through a 60-mesh sieve to ensure uniform particle size distribution for proper blending.

Blending and Mixing: Dry ingredients (excluding glidants and lubricants) are mixed thoroughly to achieve homogeneity.

Wet Granulation: A binder solution (water or methanol) is manually added to form a wet mass, ensuring proper adhesion of the particles.

Sieving and Drying: The wet mass is passed through a 12-mesh sieve to form granules. These are air-dried for 10 minutes, followed by tray drying at 45-50°C for 2 hours.

Sizing and Lubrication: The dried granules are sifted through a 16-mesh sieve. Magnesium stearate is added as a lubricant to improve flow properties and prevent sticking.

Tablet Compression: The lubricated granules are compressed into tablets using a tablet compression machine under controlled force.[8]

Table 1: Composition of sustained release tablet formulation.

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Anastrozole	1	1	1	1	1	1	1	1	1
2	Microcrystalline cellulose	82	79	80	82	83	79	80	81	82
3	Sodium starch glycolate	2	5	5	2	2	4	4	1	2
4	Magnesium stearate	3	2	1	3	2	3	1	3	2
5	Talc	2	3	3	1	2	5	3	3	3
6	Sucrose	1	1	3	2	1	3	2	3	1.5
7	Hydroxy propyl methyl cellulose	4	3	2	4	5	3	2	3	4.5
8	Polyvinyl pyrrolidone	3	4	3	3	2	3	4	4	3
9	Water	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s

EVALUATION TEST FOR GRANULES

Evaluating granules is an essential part of the research process, ensuring they have the necessary properties for tablet production.[9] The following tests help determine key characteristics such as flowability, density, and compressibility:

Angle of Repose: This test assesses the flowability of granules by measuring the angle formed when granules are poured onto a surface. A steeper angle indicates poor flowability, while a lower angle suggests better flow

$$\textbf{Angle of Repose } (\theta) = \tan^{-1} (h/r)$$

Bulk Density: Bulk density is the ratio of the mass of granules to the volume they occupy, including void spaces between particles.

Bulk Density= Weight of sample in gram/ volume occupied by the sample

Tapped Density: This test determines the density after tapping the granules multiple times to assess powder settling. The tapped density was calculated using the following formula

Tapped density= weight of sample in gram/ tapped density

Compressibility Index: This index provides insight into how well granules compact. A high value indicates poor flowability, while a low value suggests better flow.

$$\textbf{Compressibility Index} = 100\times (pt\times pb)/pb$$

Hausner Ratio: This ratio compares bulk and tapped densities, with lower values indicating better flowability.[10]

$$\textbf{Hausner Ratio} = P_t/Pb$$

3. EVALURATION TEST FOR TABLETS

a. Size and shape: The shape and dimensions of compressed tablets are determined by the type of tooling used during the compression process. When a constant compression force is applied, tablet thickness may vary due to changes in die fill, particle size distribution, and powder packing. However, when die fill remains constant, thickness variations occur due to fluctuations in compression force. Consistency in tablet thickness within and across batches depends on the uniformity of the granulated powder blend's particle size.[11]

b. Hardness test: Tablet hardness determines its resistance to breaking, capping, or abrasion during storage, transportation, and handling. It is measured using devices like the Monsanto or Stokes hardness tester. These instruments apply force to the tablet diametrically until it breaks, helping evaluate the mechanical strength of the tablets.

c. Friability: Friability testing assesses a tablet's ability to withstand friction and mechanical stress, which can cause chipping, capping, or breaking. This test is closely related to hardness and is performed using a Roche friabilator, which subjects tablets to repeated impact and rotation to measure weight loss after testing.[12]

d. Weight variation test (U.S.P): Also known as the uniformity of weight test, this method is not applicable to layered or enteric-coated tablets. The weight of 20 individual tablets is recorded, and the mean weight is calculated. The percentage deviation is determined using the formula:

$$\textbf{Percentage deviation} = X\text{-}X^1/X \times 10$$

e. *In-vitro* dissolution test: This test evaluates the rate and extent of active pharmaceutical ingredient (API) release from the tablet into a solution under controlled conditions. It provides a detailed analysis of drug solubility and release, ensuring the medication reaches therapeutic levels in the bloodstream. It is considered more comprehensive than the disintegration test.[13]

f. *In-vitro* disintegration test: The disintegration test determines how long it takes for a tablet or capsule to break down into smaller particles when placed in a liquid medium under specified conditions. This test is crucial for assessing whether solid dosage forms, such as tablets and capsules, will disintegrate within the required time to ensure proper drug release and absorption.[14]

RESULTS

Table 2: Evaluation of anastrozole granules.

Formulation	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^2)	Compressibility index (%)	Hausner ratio	Thickness (mm)
F1	30±0.41	0.674±0.0012	0.932±0.0024	29.18±0.64	1.314±0.006	3.40±0.08
F2	38±0.63	0.680±0.0005	0.970±0.0025	27.21±0.155	1.475±0.005	3.46±0.02
F3	27±0.35	0.691±0.0015	0.830±0.005	27.21±0.745	1.307±0.007	3.52±0.03
F4	31±0.52	0.711±0.0022	0.830±0.006	24.65±0.386	1.489±0.004	3.56±0.07
F5	39±0.13	0.601±0.0014	0.567±0.0024	28.22±0.79	1.350±0.011	3.33±0.04
F6	37±0.43	0.387±0.0045	0.544±0.0064	26.00±0.13	1.409±0.003	3.29±0.09
F7	40±0.42	0.344±0.0081	0.528±0.132	24.00±0.03	1.396±0.008	3.40±0.01
F8	38±0.38	0.520±0.0072	0.569±0.168	24.00±0.25	1.396±0.010	3.47±0.025
F9	27±0.26	0.421±0.0059	0.518±0.146	27.78±0.86	1.299±0.012	3.65±0.75

Table 3: Evaluation of anastrozole tablets.

Formulation	Shape	Hardness (kg/cm^2)	Friability	Weight variation
F1	Round	3.6±0.34	0.61±0.5	100.86±0.11
F2	Round	3.5± 0.20	0.25±0.8	100.97±0.60
F3	Round	4.0± 0.19	0.31±0.6	94.6±0.52
F4	Round	3.5± 0.13	0.49±0.5	97.1±0.48
F5	Round	4.0±0.12	0.48±0.6	95.3±0.587
F6	Round	4.1± 0.10	0.52±0.4	89.2±0.352
F7	Round	4.2±0.11	0.48±0.6	90.2±0.269
F8	Round	3.7±0.9	0.37±0.5	88.45±0.735
F9	Round	3.9±0.13	0.42±0.4	92.4±0.28

Table 4: In-vitro dissolution studies (cumulative % drug release).

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	12.81	15.13	10.5	11.91	15.22	12.89	14.64	10.48	10.13
1	22.36	24.69	26.03	22.32	20.39	21.68	21.96	15.96	18.46
2	31.10	33.43	29.52	31.95	28.07	25.21	29.16	23.89	20.11
3	43.91	37.97	36.94	48.19	35.42	38.21	39.14	31.12	27.58
4	52.62	46.83	43.96	55.05	42.91	45.11	46.98	36.96	35.64
5	64.02	51.76	55.84	62.92	56.95	50.21	54.46	45.03	45.12
6	69.19	57.10	60.75	76.46	62.72	56.25	63.54	56.86	53.14
7	78.60	66.30	67.31	82.08	73.41	60.45	69.54	63.21	60.28
8	86.91	67.29	75.66	87.40	78.68	69.12	77.76	70.58	69.74
9	89.05	73.87	79.59	92.01	80.09	76.98	85.56	78.46	76.59
10	96.18	86.04	83.20	98.00	86.71	82.16	92.45	82.35	85.64
11		90.42	88.91		95.75	88.15	94.57	87.14	95.54
12		95.84	90.34			94.68	98.96	90.12	

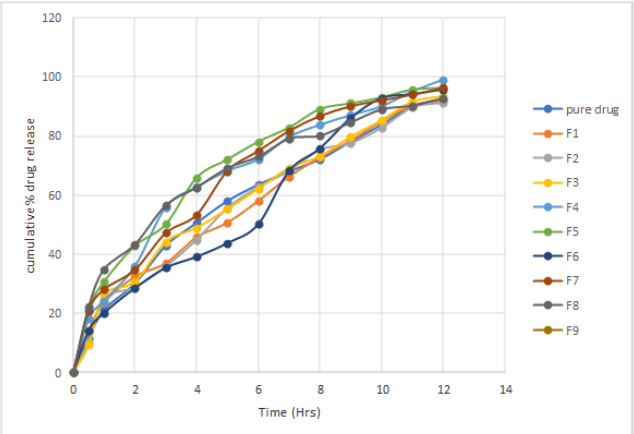

Fig. 2: Cumulative % drug release.

DISCUSION

The primary objective of this study was to develop and evaluate sustained-release Anastrozole tablets using the wet granulation method. Several formulations (F1-F9) were prepared and assessed for their physical and dissolution characteristics to optimize the drug release profile.

Granule Properties: The granules exhibited good flow properties, as indicated by the angle of repose, bulk density, tapped density, and compressibility index values. These parameters ensured uniform tablet compression and reduced processing issues like weight variation and segregation.

Tablet Evaluation: All formulations passed the standard pharmaceutical tests for hardness, friability, and weight variation, indicating good mechanical strength and durability during handling and transportation. The hardness values ranged from 5.5 to 8.6 kg/cm², while friability was below the acceptable limit of 1%, confirming tablet integrity.

In-Vitro Dissolution Study: Dissolution testing demonstrated that the sustained-release tablets effectively controlled the drug release over 12 hours, with formulations achieving up to 99.15% cumulative drug release. The controlled release mechanism can enhance patient compliance by reducing dosing frequency, ensuring steady plasma drug levels, and minimizing fluctuations that may lead to adverse effects.

Among the formulations, F5 and F6 showed the most consistent and prolonged drug release, making them the most promising candidates for further development. The inclusion of HPMC (Hydroxypropyl Methylcellulose) as a polymeric matrix played a crucial role in modulating drug release, highlighting its effectiveness in sustained-release formulations.

CONCLUSION

The study successfully formulated and evaluated sustained-release Anastrozole tablets that met standard pharmaceutical quality requirements. The optimized formulations demonstrated excellent physical properties, controlled drug release, and improved dissolution profiles, making them suitable for prolonged therapeutic action.

The sustained-release approach for Anastrozole has the potential to improve treatment adherence, patient compliance, and overall therapeutic efficacy in postmenopausal women with hormone receptor-positive breast cancer. However, further in-vivo studies are recommended to validate the clinical effectiveness and pharmacokinetic profile of the developed formulation before progressing to commercial production.

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