FORMULATION AND EVALUATION OF SUSTAINED RELEASE ANASTROZOLE TABLET FOR TREATMENT OF BREAST CANCER

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ABSTRACT

Breast cancer is the major global health concern and second most common cancer in women. While breast cancer can also occur in men, but it is much less common. Early detection and treatment are important for improving the outcome of breast cancer. The past decade has gain significant advancements in both understanding breast cancer and developing preventative methods. The most common preventive method is the chemotherapy which including various types of medication. Anastrozole is a nonsteroidal drug and act as selective aromatase inhibitor, which plays a crucial role in endocrine therapy for certain hormone sensitive breast cancers. However, treatment with conventional tablets of anastrozole drug may have limitations such as frequent dosing, fatigue, muscle and joint pain, nausea, hot flashes and potential side effects. This study aimed to develop and evaluate a novel formulation of anastrozole tablets to minimize this serious adverse effect of conventional oral formulation.

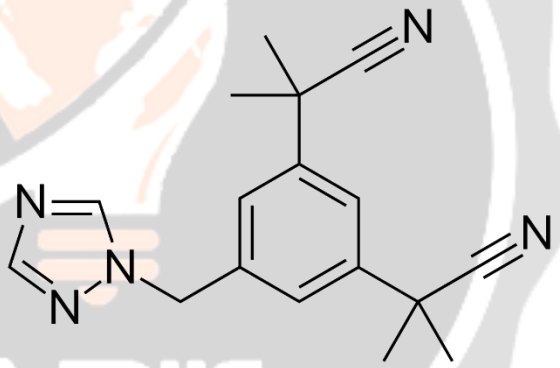
KEYWORDS: Breast cancer, Treatment, Conventional formulation, Anastrozole, Sustained release tablet.

1. INTRODUCTION-

Breast cancer is one of the second most common cancer and cause of cancer-related death in women world-widely, its approximately 570,000 deaths accounted in 2015. Every year Over 1.5 million women (25% of all women with cancer) are diagnosed with breast cancer throughout the world. [1] There are various risk factor associated with the breast cancer such as age, family history, genetics, dense breast tissue, menstrual history, hormone use, lifestyle factors. [2,3]

- **Age:** Increasing in women age also increases the risk of breast cancer.
- **Family history:** Having a close relative (mother, sister, daughter) with breast cancer increases risk of breast cancer.
- **Genetics:** Inherited changes in certain genes, such as BRCA1 and BRCA2, can significantly increase breast cancer risk.
- **Dense breast tissue:** Women with dense breast tissue have a higher risk of breast cancer than women with less dense tissue.
- **Menstrual history:** Starting your period before age 12 or going through menopause after age 55 can increase your risk.
- **Hormone use:** Taking hormones, such as estrogen and progesterone, for many years, such as in hormone replacement therapy (HRT), can increase your risk.

- **Lifestyle factors:** Obesity, lack of physical activity, and alcohol consumption can increase your risk of breast cancer.

Drug name	Anastrozole
Indication	Treatment of early-stage breast cancer. Selective aromatase inhibitors.
Mechanism of action	It is a nonsteroidal aromatase inhibitor which inhibit aromatase enzyme. Inactivation of aromatase result in the blocking of estrogen production.
Chemical name	2,2-[5-(1H-1,2,4-triazol-1 ymethyl)-1,3-phenylene]bis(2-methyl-propiono-nitrile))
Chemical Structure	
Route of administration	Oral administration is effective.
Pharmacokinetic and pharmacodynamic properties	Anastrozole Rapidly absorb orally, apparent clearance is 1.54 liters/h and a terminal half-life is 46.8 h. Metabolize by liver.

While there are many treatment options available for breast cancer such as endocrine therapies, radiotherapy, chemotherapy, surgery, and combination of these therapies are available for patients who having early-stage breast cancer. Some treatment can cause serious side effects and may not prevent the cancer from spreading. [4] In the last years a number of targeted drugs have been developed successfully and approved, including the selective aromatase inhibitors, which are widely prescribed by physician for the effective treatment of hormone-sensitive breast cancer in postmenopausal women. [5] Anastrozole is a medicine that helps to fight against breast cancer in women after menopause. It works by blocking the body from the production of estrogen, which can cause some breast cancers. It targets a specific enzyme (aromatase) that creates estrogen and stops it from working. By lowering estrogen levels, anastrozole may help to slow or stop the growth of these cancers. [6]

Drug profile [7,8,9]

Anastrozole is commercially available in the conventional oral tablet form with lots of side effects such as gastrointestinal disturbance, vaginal bleeding, skeletal complications, anemia. [10] To overcome this adverse drug reaction there is need to develop a novel formulation. In this study we developed a sustained release tablet for anastrozole delivery and in vitro evaluation test was performed to confirm and explore the effectiveness and quality of formulated sustained release tablet.

2. MATERIALS AND METHOD-

Material-

1. Active Pharmaceutical Ingredient (API):

Anastrozole [ANS] (99 % purity) was purchased from JK chemicals, Valsad, India. It cost around 1600 rupees per kg. This is the core ingredient, the actual medication that delivers the therapeutic effect. [11]

2. Release-controlling polymers:

Hydrophilic polymers: Hydroxypropyl methylcellulose (HPMC) or Hydroxypropyl cellulose (HPC) or Sodium carboxymethylcellulose (CMC) or **Hydrophobic polymers:** Ethyl cellulose were purchase from chemical store of Shivajirao Pawar College of Pharmacy. They form a matrix or coating that regulates the rate at which the drug dissolves and releases from the tablet. [12]

3. Excipient:

All excipient were purchased from the chemical store of Shivajirao Pawar College of Pharmacy.

- Fillers: Lactose, Microcrystalline cellulose, Dicalcium phosphate. These make up the bulk of the tablet and provide structure.
- Disintegrants: Sodium starch glycolate, Croscarmellose sodium. These help the tablet break apart after ingestion, allowing for faster drug release.
- Lubricants: Magnesium stearate, Stearic acid. These prevent sticking during tableting and ensure smooth passage down the throat.
- Glidants: Colloidal silicon dioxide, Talc (pharmaceutical grade). These improve powder flow during manufacturing.
- Solvents: Water, Ethanol.
- Sweeteners or flavorings: Mannitol, Sucrose. Used to improve palatability. [13,14]

Method for preparation of sustained release tablet-

Sustained release tablet, each tablet containing 1 mg Anastrozole were prepared by conventional wet granulation method. [15] The composition of various formulations of the sustained release tablets with their taken quantity is shown in Table 1. In each formulation the quantity of active pharmaceutical ingredient is 1 mg and the total weight of tablet is 100 mg. Total 10 tablet was prepared with each formula. Formulation was done by following steps of method. [16]

- **Sieving:** All ingredients are passed through a 60-mesh sieve to ensure a uniform particle size.
- **Blending and Mixing:** Except for the glidant and lubricant (which will be added later), all the ingredients are blended and mixed thoroughly.
- **Wet Granulation:** A water or methanol solution is used to bind the powder particles together and form wet masses. This is done manually.
- **Sieving and Drying:** The wet masses are passed through a 12-mesh sieve to create granules of a specific size. These granules are then air-dried for 10 minutes, followed by final drying in a tray dryer at 45-50°C for 2 hours.
- **Sizing and Lubrication:** The dried granules are passed through a 16-mesh sieve to achieve the desired final size. Then, magnesium stearate, a lubricant, is added to improve flow during tableting.
- **Tablet Compression:** The lubricated granules are compressed into tablets using a tablet compression machine with a constant compression force. Before compression, the machine's die and punches are also lubricated with magnesium stearate to prevent sticking.

- **Storage:** The finished tablets are stored in airtight containers for further testing or use.

Table 1. Composition of sustained release tablet formulation- [17,18]

Ingredients	Formula 1 (mg)	Formula 2 (mg)	Formula 3 (mg)
Anastrozole	1	1.5	1.2
Release-controlling polymers	3.2	3.5	4
Fillers	90	89	88
Disintegrants	1.5	1.2	1.8
Lubricants	0.12	0.15	0.10
Glidants	0.15	0.12	0.15
Solvents	q.s	q.s	q.s
Sweeteners or flavorings	q.s	q.s	q.s

Evaluation test for granules- Granule evaluation is a crucial step in the tableting process, ensuring the granules possess the characteristics necessary for forming good quality tablets. Here are some common tests performed on granules: [19,20,21]

Angle of Repose- This test measures the angle formed by a pile of granules when poured freely. A steeper angle indicates poor flow, while a shallower angle indicates good flow. The angle of repose (θ) was calculated as follows:

- Angle of Repose (θ) = $\tan^{-1}$ (2h / d)

Bulk Density and Tapped Density- Both bulk density and tapped density are important for understanding the behavior of powders and granules in tableting processes. Here are the formulas for each:

- Bulk Density (ρb): M / V
- Tapped Density (ρt): M / Vf

Compressibility Index and Hausner Ratio- The Compressibility Index and Hausner Ratio are both calculated using the values of bulk density (ρb) and tapped density (ρt) obtained from the formulas you saw earlier. Here's how they are related:

- Compressibility Index (CI): 100 * (ρt - ρb) / ρb
- Hausner Ratio (H): ρt / ρb

Evaluation test for tablet- [22,23]

Size and Shape- A size and shape evaluation test are a routine quality control procedure performed on tablets during manufacturing. For thickness, a tolerance of ±5% deviation from the standard value is generally considered acceptable. This ensures consistent tablet weight and drug delivery. Shape is evaluated visually to confirm it matches the intended design, such as round.

Hardness Test- This testing plays a vital role in maintaining the quality and consistency of pharmaceutical tablets. This test done by using Monsanto hardness tester. Tablet Crushing Strength/Hardness: all tablet passed a test to measure their resistance to breaking under pressure. Acceptable Range: The crushing strength for all tablet fall within an acceptable range of 5kg/cm² to 10kg/cm².

Friability- It is an important quality control procedure in the pharmaceutical industry that evaluates a tablet's resistance to chipping, cracking, or breaking under physical stress during handling, transportation, and storage. Friability test was done by using rochefriabilator. The friability is expressed as a percentage of the weight lost compared to the initial weight of the sample. Each tablet formulation typically has a predefined acceptable friability limit (usually less than 1%).

Weight Variation Test (U.S.P.)- This test ensures that the weight of individual tablets within a batch is consistent. This consistency is important for maintaining accurate medication dosing.

Disintegration test- It helps to know about the solubility of active pharmaceutical ingredient in gastric fluid of digestive system. This disintegration rate is essential for ensuring proper drug release and absorption in the body. This test is done by using tablet disintegration machine.

Dissolution test- This test is essential for the measurement of rate and extent of drug release form the tables (under standardized condition of temperature and solvent composition) is estimated by basket dissolution test apparatus.

4. RESULTS AND DISCUSSION-

The anastrozole granules was prepared and formulation of sustained release anastrozole tablet were done also evaluated for various parameter and average of results of three formulas are shown in following table 2 evaluation of anastrozole granules and table 3. evaluation of anastrozole tablet.

Table 2. Evaluation of anastrozole granules.

Test	Observational values	Standard values
Angle of repose (^{0})	31	25±5
Bulk density (g/cm^3)	0.6	0.5±3
Tapped density (g/cm^3)	0.85	1±5
Hausner ratio	1.74	1.10±5
Carr's Index (%)	17	10±5

Table 3. Evaluation of anastrozole tablet.

Test	Observational values	Standard values
Size and Shape	Round	-
Hardness Test (kg)	4	6±3
Friability (%)	1.23	Not more than1
Weight Variation (%)	3	Not more than5
Disintegration test min	5	10±5
Dissolution test(min)	64	80 %

All the prepared formulations passed or having nearby observational values as compared to standard values. The values of angle of repose, bulk density, tapped density, hausner ratio and carrs index shows that anastrozole granules have good flowability. Table 3. Shows that the all anastrozole tablet have good hardness, low friability, also disintegrate and statistically dissolve in standard medium.

5. CONCLUSION-

Anastrozole is belong to third-generation medication and selective competitive inhibitor of aromatase, the enzyme responsible for converting androgens to estrogen in postmenopausal women. Oral medication therapy with anastrozole leads to number of side effects as well as maximum drug concentration, worse bioavailability, uncontrolled delivery of a drug. To overcome these limitations, we formulate a sustained release anastrozole tablet and also evaluate for various parameter to ensure the safety and quality standard of the formulated standard. According to evaluation results formulated anastrozole tablet comply with standard values of all evaluation parameter.

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