Formulation Approaches for Buccal Delivery of Exemestane in Breast Cancer Therapy

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Abstract- **The most widespread clinical subtype of breast cancer is hormone receptor-positive tumor, which remains an important health issue in the world. Exemestane is a third-generation steroidal aromatase inhibitor commonly used to suppress estrogen levels in women who are post-menopausal. Its oral bioavailability is however variable and it is subject to high hepatic first-pass metabolism, and low water solubility limits its efficacy as a therapy. These downs compel the necessity of alternative delivery systems. Buccal drug delivery devices have been found to deliver a non-invasive method that does not depend on the initial tissue passages, diminishes gastrointestinal loss, and provides a more predictable systemic triumph of the drug. The formulation strategies used in distributing exemestane buccally that are the focus of the current research include mucoadhesive pills, films, patches, gels, and a nanotechnology-based system such as polymeric and lipid nanoparticles. We discuss the techniques that enhance the process of buccal absorption, such as increased solubility, increased absorption through the mucosal, degradation resistance, and controlled drug delivery. Evaluation metrics, safety concerns, issues related to formulation, and prospects, including quality-by-design and hybrid mucoadhesive-nanocarrier are also highlighted. Another possible strategy in long-term cancer therapy of breast cancers is buccal intake, which would help enhance treatment efficiency and treatment adherence.**

I. INTRODUCTION

Breast cancer is one of the most common malignancies in the world as it claimed the lives of nearly 570,000 individuals in 2015. Globally, over 1.5million women are found to have breast cancer every year, which is 25 per cent of all the cancer afflicted women.

Breast cancer is categorized into three primary types, based on the presence or absence of molecular markers of the human epidermal growth factor 2 "(ERBB2; HPV: formerly HER2)" and estrogen or progesterone receptor, namely: hormone receptor positive/ERBB2 negative (70 per cent of patients). "ERBB2 positive (15 per cent -20 per cent)", and triple-negative (tumors negative on all three common molecular markers; 15 per cent). Breast cancer has remained one of the largest causes of cancer related morbidity and mortality among women worldwide. Aromatase inhibitor plays an imperative role in the treatment of metastatic and adjuvant hormone receptor-positive breast cancer, which is a major form of the disease.

Third generation steroidal aromatase inhibitors, such as exemestane, a commonly used drug in postmenopausal women, are known to block the aromatase enzyme in order to permanently block the production of estrogen. Exemestane is also an adjuvant therapy that has undergone or is currently undergoing several clinical trials on postmenopausal women, which will be the indication discussed in the review. The relative risk of death or recurrence of breast cancer in case of exemestane usage after two to three years of tamoxifen usage is reduced by 24%.

1.1. ROLE OF AROMASTASE IN BREAST CANCER

Aromatase inhibitors (AIs) play a crucial role in management of hormone receptor-positive breast cancer particularly in postmenopausal women when peripheral conversion is the main way of making estrogen than when ovarian secretion is the main means. Endocrine therapy of breast cancer- both at an early stage and at an advanced phase- has become a widespread use of AIs due to their ability to prevent the growth and spreading of estrogen-dependent breast cancer cells by suppressing the production of estrogen.

1.2. MECHANISM OF ESTROGEN SUPPRESSION

Aromatase inhibitors act on the aromatase enzyme (CYP19A1) that converts androgens such as

androstenedione and testosterone into estrogens (estrone and estradiol) in the peripheral tissues. This pathway is the primary cause of circulating estrogen among postmenopausal women. AIs greatly reduce the levels of estrogen present in the body by inhibiting aromatase activity, which denies estrogenic stimulation to the hormone sensitive tumor cells.

1.3. PHARMACOLOGICAL PROFILE OF EXEMESTANE

1.3.1. CHEMICAL NATURE AND LIPOPHILICITY

Exemestane is a 3rd generation steroidal aromatase inhibitor based on androstenedione. The steroidal backbone of the aromatase enzyme allows it to bind with high affinity to the enzyme leading to irreversible inactivation of the enzyme by the mechanism-based suicide inactivation. Exemestane is lipophilic and therefore does not dissolve in water well, as would be the case with a water permeable membrane despite promoting the permeability of the membrane.

1.3.2. PHARMACOKINETIC AND METABOLISM

Exemestane is rapidly absorbed following orally; optimum plasma concentrations are typically achieved in a matter of a few hours. Nonetheless, it has low absolute bioavailability due to the hepatic high first-pass metabolism. The aldoketoreductases and cytochrome P450 enzymes, in particular CYP3A4, are the main enzymes involved in the metabolism of exemestine. These formed metabolites are excreted by the fecal and renal systems. Due to the high plasma protein binding and low elimination half-life of the drug, constant daily dose is necessary to maintain a sufficient level of estrogen suppression.

- Formulation related property
  a) Lipophilicity favors membrane permeation
  b) Poor water solubility presents formulation challenges
  c) Low daily dose requirement
  d) Potential candidate for alternative delivery routes such as buccal systems

1.3.3. LIMITATION OF CONVENTIONAL ORAL DRUG DELIVERY

- ✓ First pass metabolism

Oral medications sometimes undergo significant liver processing before entering the bloodstream, which lowers their bioavailability.

- ✓ Poor and variable bioavailability

Interpatient variability and uneven absorption are caused by a number of factors, including medication solubility, gastrointestinal motility, and enzyme degradation.

- ✓ Poor aqueous solubility of drug

Exemestane and other lipophilic medications dissolve poorly in gastrointestinal fluids, which leads to erratic and insufficient absorption.

- ✓ Gastrointestinal Degradation and Irritation

Patient comfort and adherence may be impacted by drug degradation or gastrointestinal side effects brought on by exposure to gastric acid and digestive enzymes.

1.4. Need for alternative drug delivery routes

- Rational for non-invasive delivery system

Standard oral and parenteral medication administration has limits, as seen by the growing dependence on long-term pharmacotherapy in chronic conditions such hormone receptor-positive breast cancer. Because of its increased patient acceptability, lower risk of infection, and simplicity of self-administration, non-invasive delivery methods are recommended. These devices provide more dosage flexibility while doing away with the pain and difficulties that come with injections. Non-invasive methods offer an efficient way to improve systemic exposure and therapeutic results for medications with low oral bioavailability or high first-pass metabolism.

1.5. BUCCAL DRUG DELIVERY SYSTEM

Buccal drug delivery refers to the administration of a drug by the inner lining of the cheek of the mouth to generate systemic or local action. Buccal tablets, films or patches or gels are dosage forms that release the drug that is then absorbed through paracellular and transcellular routes across the buccal epithelium. Mucoadhesive polymers allow the drug to remain in greater contact with the mucosa, enhancing its absorption efficiency since drugs can rapidly enter the systemic circulation via an extensive network of the vascularity under the epithelium.

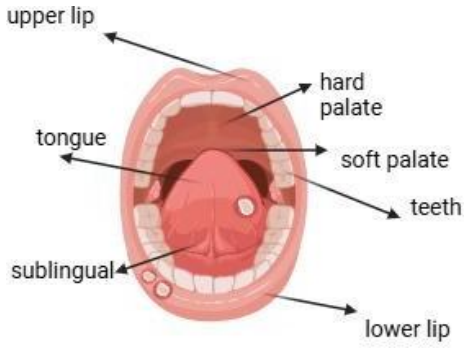

Fig 1: Oral cavity with Buccal mucosa

- Advantage
  - ✓ Improves bioavailability by avoiding hepatic first-pass metabolism
  - ✓ Prevents gastrointestinal tract deterioration and stomach acid irritation.
  - ✓ Increases the consistency and predictability of plasma medication levels
  - ✓ lessens the variation between patients in oral absorption
  - ✓ Perfect for long-term treatment, especially for chronic illnesses like breast cancer

1.5.1. SUITABILITY FOR SYSTEMIC DRUG DELIVERY

Buccal drug delivery systems fit well in the systemic administration of strong drugs that require the release to be under control and gradually. The ability to develop unidirectional and mucoadhesive formulations ensures consistency in systemic exposure, whereas the low levels of enzyme activity and moderate level of permeability through buccal mucosa facilitate long term drug absorption. Another promising route of systemic drug delivery is by buccal administration due to its excellent effectiveness in low dose requirement drugs, large first pass metabolism or low oral bioavailability drugs, e.g. exemestane.

Table 1: Comparative Overview of Buccal Dosage Form

Dosage form	Polymer type	Advantage	Limitation	Typical drug studies
Buccal Films	HPMC, PVA, Chitosan	Comfort, flexibility	Saliva washout	Various small drugs
Buccal Tablets	Carbopol, NaCMC	High adhesion	Harder to fabricate	Hormones & small drugs
Gels/Sprays	Carbopol, Poloxamer	Easy application	Short residence time	Local delivery

Interpretation: Some of the buccal dosage forms are compared in the table based on their polymers, advantages and disadvantages. To achieve systemic delivery, films and tablets are more effective in achieving mucoadhesion, gels and sprays are viable, but have a limited residence time. Nanoparticle system provides improved bioavailability and penetration, but formulation is complicated because they are complex.

1.5.2. ADVANCE IN BUCCAL DRUG DELIVERY

- Mucoadhesive system

Mucoadhesive buccal systems extend residence time and improve drug absorption by using polymers that stick to the mucosal surface. By interacting with mucin glycoproteins, polymers including chitosan, HPMC, and carbopol create a semi-permanent sticky coating that reduces medication loss during salivary washing. For medications like exemestane, these methods are very helpful for regulated release, guaranteeing maintained plasma levels and enhanced therapeutic efficiency.

1.6. BREAST CANCER

Breast cancer is a malignant disease that develops in the cells of the breast most commonly in women. It usually begins in the ducts “(which carry milk to the nipple)” or in the lobules (glands that produce milk). Breast Cancer Genetics: Diagnostics and Treatment The disease occurs when abnormal breast cells grow uncontrollably and form a tumor which may be detected as a lump or through screening techniques like mammography. Several factors contribute to breast cancer. Including genetic mutations “(such as BRCA1 and BRCA2)”,hormonal influences lifestyle choices and age. Common symptoms include a lump in the breast, changes in breast shape or size skin dimpling, nipple discharge, or pain.

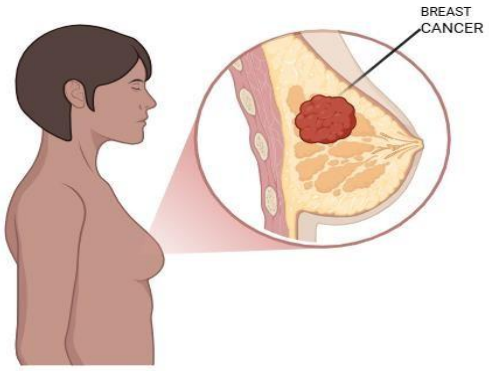

Fig2: Structure of Breast cancer.

1.6.1. Exemestane Treatment in Breast Cancer

"Exemestane is a third-generation, steroidal aromatase inhibitor widely used in the treatment of estrogen receptor-positive (ER+)" breast cancer, especially in postmenopausal women. It works by irreversibly binding to the aromatase enzyme. By inhibiting this process Exemestane significantly reduces circulating estrogen levels there by limiting the growth of estrogen- dependent breast cancer cell.

1.7. NANOTECHNOLOGY BASED FORMULATION

Nanotechnological formulations have demonstrated potential in enhancing the absorption and bioavailability of low dose poorly soluble drugs by the buccal route such as exemestane. Nanoparticles are ultrafine carriers that normally measure 1-500 nm in length to provide the medicine with enhanced physicochemical and pharmacokinetic properties.

1.7.1. Types of nanoparticles for Buccal delivery

1. Polymeric nanoparticles: Such nanoparticles comprising of biodegradable polymers such as PLGA, chitosan, and Eudragit provide controlled drug release, protect the drug against enzyme degradation, and provide mucoadhesion. Besides, chitosan nanoparticles are better penetrators because they disrupt the tight junctions in the mucosal epithelium temporarily.
2. Solid lipid nanoparticle (SLNs): The SLNs consist of solid lipids and enhance the solubility of lipophilic drugs, protect them against destruction, and provide sustained release. Their lipid composition promotes transcellular or adhesion to the buccal epithelium by promoting contact with the buccal epithelium.
3. Nanostructured lipid carriers (NLCs): These hybrid methods provide regulated and extended release of lipophilic compounds by combining liquid and solid lipids to improve medication loading and stability.
4. Polymer –lipid hybrid nanoparticles: The benefits of lipid and polymeric systems are combined in hybrid nanoparticles, which provide effective mucosal penetration, enhanced stability, high drug loading, and controlled release.

1.7.2. MECHANISM OF ACTION

- Nanoparticles enhance buccal absorption through multiple mechanisms:
  - Improved solubility: Lipophilic medications appear more soluble in the mucosal environment when they are encapsulated.
  - Enhanced permeation: Transcellular and paracellular transport across the buccal epithelium is facilitated by nanoparticles.
  - Protection from Degradation: The nanoparticle matrix shields the drug from enzymatic activity and salivary washout.
  - Controlled Release: Stable plasma levels and extended exposure are guaranteed by sustained drug release from nanoparticles.

1.8. EVALUATION OF BUCCAL FORMULATION

- In vitro studies:
  - Drug release kinetics: Assessment of the quantity and percentage of exemestane discharged out of buccal preparations in buffer or simulated saliva solutions. assists in recognizing attributes of controlled or constant discharge.
  - Swelling and Mucoadhesive Strength: Polymer hydration, swelling behavior, and adhesion force to mucin or pseudomucosa are evaluated. essential to guaranteeing a longer stay on the buccal surface.
- Ex vivo studies
  - Retention and Adhesion Time: An indicator of mucoadhesion efficiency is the duration of time the dosage form stays adhered to the buccal mucosa in simulated saliva.

- Stability studies:
  - Physical and chemical stability: observing the stability of the formulation overall, drug degradation, polymer integrity, particle size, and aggregation under varied circumstances.
  - Shelf line assessment: Long-term and accelerated stability studies to guarantee steady performance and security throughout time.
- Safety and toxicity:
  - Cytotoxicity Studies: To make sure the medication and excipients are safe, formulation biocompatibility is assessed using epithelial or mucosal cell lines.
  - Histopathological Evaluation: Buccal tissue is examined after being exposed to the formulation to look for any indications of inflammation, irritation, or structural damage.

1.9. CHALLENGES AND LIMITATION OF BUCCAL DRUG DELIVERY SYSTEM

- ✓ Limited Absorptive Surface: The amount of medication administered systemically may be limited by the buccal mucosa's comparatively tiny region for drug absorption.
- ✓ Salivary washout: Bioavailability may be decreased if the medicine or dosage form is continuously secreted from the mucosal surface before it has had time to fully absorb.
- ✓ Formulation Complexity: Developing buccal systems based on mucoadhesive or nanoparticle technology that are stable, repeatable, and patient-friendly is a technical challenge.
- ✓ Polymer and Nanoparticle Interactions: Mucoadhesive polymers and nanoparticle compatibility needs to be carefully controlled to avoid aggregation, decreased adherence, or uneven release.
- ✓ Permeation Limitations: Permeation enhancers may be necessary for lipophilic medications to effectively pass through the buccal epithelium without harming tissue.

1.10. FUTURE PROSPECTS AND INNOVATION IN BUCCAL DRUG DELIVERY

1. Quality by design (Qbd) approaches: Through the identification of key quality attributes (CQAs) including drug loading, release profile, mucoadhesive strength, and particle size, the application of QbD principles enables the systematic improvement of buccal formulations. This guarantees scalable, reliable, and repeatable formulations for clinical use.
2. Smart and stimuli-responsive system: Stimuli-responsive polymers, which release the medication in response to changes in pH, temperature, or enzyme activity, may be included into future buccal systems..
3. Personalized and precision therapy: Personal metabolism, level of hormones, disease evolution: It is a positive side that the evolution of the pharmacogenomics and patient-directed treatment enables the personalization of the buccal preparations. It is also needed especially during the long term management of breast cancer using such medicines as exemestane.
4. Combination strategies: Mucoadhesion + Nanotechnology: The two benefits of using a combination of mucoadhesive polymers and nanoparticle-based carriers include longer residence time and greater absorption of medication. It is hoped that these hybrid systems would enhance patient compliance, reduce the dosage frequency, and enhance bioavailability.
5. Advanced dosage form: New technologies that provide the fine control of drug release kinetics and directionality are multilayered buccal films, unidirectional patches, and gels loaded with nanoparticles. These equipments reduce drug wastage into the oral cavity and maximize absorption to the body.

II. CONCLUSION

Multilayered films, unidirectional patches, and nanoparticle-filled gels are considered advanced systems of buccal drug delivery that represent a significant step forward in the technology of transmucosal drug delivery. These systems are used to optimize systemic absorption of drugs by accurately controlling drug release kinetics and targeted delivery to minimize loss of drugs to the mouth cavity. Turned together, these advances offer a feasible remedy to heightening bioavailability, therapeutic efficiency and patient adherence, particularly in longer course medications such as exemestane-based breast cancer treatment.

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