1. INTRODUCTION

1.1 Breast Cancer

Cancer is generally named after the part of the body into which it originated; thus, breast cancer refers to the irregular growth and proliferation of cells that originate in the breast tissue (1). Breast cancer refers to cancers that arise from breast tissue, most commonly from the milk ducts (inner lining) or the lobules that provide the ducts with milk (2). The breast consists of two main tissue types i.e., glandular tissues and stromal (supporting) tissues. Glandular tissues contain the milk-producing glands (lobules) and the ducts (milk passages) while stromal tissues include fatty and fibrous breast connective tissues (3-5). It also consists of tissue-immune lymphatic system tissue that extracts cellular fluids and waste. Multiple types of tumours can grow in different breast areas. (Fig 1.1)

Breast cancer is the most diagnosed cancer among women and the second leading cause of cancer-related deaths among women affecting about 2.2 million women worldwide (6). Globally, the burden and incidence rates of breast cancer are enormously increasing than the other cancers (7). As estimated by World Health Organization (WHO), by 2050, it is expected that 27 million new breast cancer cases and 17.5 million breast cancer deaths will occur per annum (8). Breast cancer remains a major health issue and currently constitutes a top priority for biomedical research (9). The aggressive nature, early recurrence, rapid metastasis (to secondary sites such as the lung and brain), and poor breast tumour prognosis make the disease enigmatic and incurable (10).

Most cancers arise from benign (non-cancerous) changes in the breast (11). Fibrocystic change, for example, a non-cancerous condition where development of cysts (fluid packets accumulation), fibrosis (scar-like connective tissue formation), and thickening areas with lumpiness, breast pain or tenderness occurs in women (12, 13). Most breast cancers are in the cells which line up the ducts. Most originate in the lobules (lobular cancers) cells, whereas (14) the other tissues start with a small number (15). Most of these tumors are initially dependent upon activation of ERαand Erβ nuclear receptors promotes proliferation and survival of both normal and cancerous breast tissues through transcription of pro-survival genes and activation of cellular signalling (16, 17). Owing to the strong dependency of breast tumorigenesis on the estrogen-ER axis, estrogen suppression and ER antagonists have remained main stay of ER^+ breast cancer treatment for several years (7).

Traditional breast cancer treatments include radiation therapy- chemotherapy and endocrine therapy, which has improved the therapeutic effect, but the risks and side effects associated with these therapies inhibit the clinical usefulness (18). Most of the commonly used cytotoxic medications are chemotherapeutics that are delivered into systemic circulation (19). The administration of chemotherapeutics of low molecular weight into systemic circulation exhibits rapid clearance, low pharmacokinetic profile, and sub-optimal tissue distribution and only a small fraction reaches the tumour/tumour cell. Hydrophobic polymer loaded chemotherapeutic agents exhibits large volumes of delivery leading to increased accumulation at healthy tissue sites (20).

Endocrine therapies such as selective ER modulators (SERMs), selective estrogen down regulators (SERDs) and aromatase inhibitors are approved as an adjunct therapy for patients with ER^+ breast cancer (15). Aromatase Inhibitors deplete the levels of systemic estrogen by blocking the conversion of androgens to estrogen (21). SERMs compete with estrogen for binding to ER and have mixed agonist/antagonist capacities and are first line of treatment for pre-menopausal women. SERDs such as fulvestrant are said to work by suppressing ER activity by impairing intra-nuclear ER mobility.

1.2 Fulvestrant

Fulvestrant (FLV), a newer anticancer agent is utilized in management of progressive breast cancer. The action of drug includes binding, blocking and degradation of estrogen receptors, leading to cessation of estrogen signalling through receptors in body (22). It acts as complete antagonist unlike SERMs like tamoxifen, it doesn't show any agonist activity, which in turn leads to blockage of estrogen activity completely (23). The formulation is available in pre-filled intramuscular injection which is well tolerable. But due to being non-targeted, it presents various side effects, that are related to estrogen deficiencies such as weight gain, thromboembolic problems, neutropenia, leukaemia, anaemia. Some fewer common side-effects observed are vulvovaginal dryness, pelvic pain, and vaginitis (24). This negative aspects of fulvestrant is the major hindrance for its efficiency against breast cancer and therefore it demands the development of new formulation which is targeted and have control release efficiency (25).

1.3 Exemestane

Aromatase inhibitor drugs presently employed in clinic settings for breast cancer treatment (hormone dependent) are more effective with minimal side effects than tamoxifen (26). Exemestane (EXE) is approved by the USFDA for hormone dependent breast cancer treatment in postmenopausal females and marketed as Aromasin® tablet formulation at a dose of 25 mg, consumed once in a day after meal (27). It is orally active potent irreversible steroidal aromatase inactivator which behaves as a false substrate for the aromatase enzyme and is converted into an intermediate, which causes enzyme inactivation by binding to its active site, also called as suicide inhibition (28, 29). However, oral clinical applications of Exemestane is limited because of its low aqueous solubility (80 μg/mL), high lipophilicity, poor oral bioavailability (5%) and rapid first pass metabolism (30). Therefore, to improve the clinical effectiveness of Exemestane, higher solubility increased bioavailability and prolonged circulation of Exemestane are highly desired (31).

1.4 Quercetin

It is naturally occurring dietary flavonoid which has been found to have anticancer activity and application in the treatment of breast cancer. Quercetin shows a wide range of biological and pharmacological effects including antioxidative, anticancer, anti-inflammatory, antidiabetic, hepatoprotective and anti-obesity activities. Among polyphenols, quercetin has been shown as one of the most potent antioxidants. It can inhibit several enzymes that produce oxidative species such as xanthine oxidase, NADP and phosphate oxidase. It has been shown that quercetin inhibits cell proliferation as it may induce apoptosis and/or cell cycle arrest (either G2/M arrest or G1 arrest. In fact, the ability of this polyphenol to interfere with various target molecules identified as hallmarks of cancer, renders it as a multi-target key molecule in different types of tumours. Despite its health benefits, poor bioavailability of quercetin limited its therapeutic approach so far. The bioavailability of quercetin is low mainly because of its limited absorption (due to its poor water solubility, low stability, and short half-life) and rapid elimination (32).

1.5 Role of Nanocarriers in Cancer therapy

Nanotechnology appears an excellent approach for improving the efficacy of drugs by means of targeted delivery and has gained more attention due to their unique accumulation behaviour(33). Hence, to achieve targeted delivery, accumulation and decrease the side effects

of Fulvestrant and Exemestane, nanotechnology holds promising potential by employing targeted drug delivery approach. Past 2–3 decades have seen rigorous research on nanomedicine for cancer treatment. Over the last two decades, many nanoparticle delivery systems have been developed for cancer therapy, including organic and inorganic materials (34). Nanoscale drug delivery vehicles have shown the ability to encapsulate a variety of therapeutic agents such as small molecules (hydrophilic and/or hydrophobic), peptides, protein-based drugs, and nucleic acids (35). Encapsulated molecules can be released from nanocarriers in a controlled manner over time to maintain the drug concentration within its therapeutic window or the release can be triggered by some stimulus unique to the delivery site (36). Advances in cancer proteomics and bioinformatics have allowed the development of targeted therapies, which were referred to as a "magic bullet". Nanocarriers may be surface functionalized to increase the blood circulation half-life and influence the biodistribution as well as to facilitate the attachment of biomolecules to achieve active tumor targeting (37). Surface ligands include antibodies, aptamers, peptides, or small molecules which recognize tumor specific or tumor-associated antigens in the tumor microenvironment (38). In general, ligands such as peptides, sugars, and small molecules are more attractive than antibodies due to higher stability, higher purity, ease of production through synthetic routes, and non-immunogenicity (39). The active targeting mechanism takes advantage of highly specific interactions between the targeting ligand and certain tissues or cell surface antigens to increase cellular uptake and increase tumor retention. The net result of these properties is to lower the systemic toxicity of the therapeutic agent while increasing the concentration of the agent around interest, resulting in a higher therapeutic index for the therapeutic agent (40-43). These nanocarriers include polymeric nanoparticles, dendrimers, nano shells, liposomes, inorganic/metallic nanoparticles, hybrid nanoparticles, micelles, and magnetic and bacterial nanoparticles.

Nanotechnology provides an innovative and promising alternative to conventional small molecule chemotherapeutics, circumventing multi drug resistance by encapsulating, attaching, and conjugating drugs or therapeutic biological products to nanocarriers. Nanocarriers can include small molecules such as lipids or polymer nanoparticles that target the therapeutic payload to tumors or tumor cells (44-46). Simultaneously, multifunctional drug-loaded nanocarriers can also enhance particle penetration of physiological barriers and protect the labile drugs or therapeutic biological products.

1.6 Polymer Lipid Hybrid Nanocarriers (PLHNCs)

Among all the nanocarriers, liposomes and polymeric nanoparticles have been most widely researched as novel strategy for delivery of variety of therapeutics including genetic materials due to their biocompatibility and in-vivo drug targeting (47, 48). Polymeric nanoparticles possess key attributes i.e., long- term stability and tunability but generally lacking in inherent biocompatibility and potential toxicity of long-term accumulation of synthetic molecules in the body (49). On contrary, liposome is biocompatible, non-denaturing interface of liposomal capsules but unfortunately, the lack of long-term stability (50). Polymer lipid hybrid nanocarriers (PLHNCs) has advantages of both liposomes and polymeric nanoparticles (51). Some extraordinary advantage provided by PLHNCs are listed here. The solid core made up of polymer acts as a cytoskeleton that provides mechanical stability, controlled released morphology, narrow size distribution, and higher availability of specific surface area. The outer lipid coat that encapsulates the polymeric core is biocompatible in nature and mimics the characteristic of cellular membranes. The lipid shell can interact with a huge variety of drugs and indigenous molecules and surface can be modified for efficient targeting (52-54).

Briefly, to create a potentially superior delivery system, the biomimetic properties of lipids and the architectural benefit of the polymer structure are combined. PLHNCs are solid, submicron-sized particles composed of minimum two components: the polymer and the lipid. In the developed hybrid system, various bioactive molecules such as drugs, genes, proteins, and targeting ligands may be entangled, adsorbed, or covalently bound. Polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL), dextran, or albumin are likely choices for biodegradable polymers because of their biocompatibility, biodegradability, non-toxicity, and prior use in licensed products. Zwitterionic, cationic, anionic, and neutral phospholipids such as lecithin, 1,2-dipalmitoyl-sn-glycero-3- (DPPC), 1,2-dipalmitoyl-3-trimethylammonium-propane (DPTAP), 1,2- dipalmitoyl-3-trimethylammonium-propane (DOTAP), or 1,2-dipalmitoyl-sn glycero-3-phosphoethanolamine (DOPE) are commonly used lipids (55, 56).

1.7 Mesoporous Silica Nanoparticles (MSNs)

Inorganic nanomaterials have special structures and physicochemical properties. Various metal-based nanoparticles have shown great prospect as antibacterial agents, in medicine, imaging and drug delivery. In addition to these applications, metal nanoparticles are considered to interfere with different other biological processes such as autophagy induction and angiogenesis (57, 58).

Among inorganic nanomaterials, mesoporous silica nanoparticles are centre of focus because of their unique properties. Since the first report using MCM-41 type mesoporous silica nanoparticles (MSNs) as drug delivery system in 2001, the few years have witnessed an exponential increase in research on biomedical applications of MSNs. It has been one of the hottest areas in nanobiotechnology and nanomedicine for designing biocompatible MSNs and multifunctional counterparts in disease diagnosis and therapy. Mesoporous silica nanoparticles (MSNs) have some unique advantages including high surface area and large pore volume, tuneable particle size (10-1000 nm) and pore diameter (2-30 nm), uniform mesoporosity, flexible morphology, facile surface functionalization and excellent biocompatibility and biodegradation. Textural properties of MSNs provide the possibility to load high amount of drugs within MSNs. On the other hand, there are abundant silanol groups on the surfaces of mesoporous channels and the outer surfaces of MSNs, which facilitate their surface functionalization. As nanocarriers, mesoporous silica nanoparticles with unique mesoporous structure have been explored as effective drug delivery systems for a variety of therapeutic agents to fight against various kinds of diseases including bone/tendon tissue engineering, diabetes, inflammation, and cancer (59-61).

The biggest challenge in application of MSN for cancer treatment is to obtain "zero premature drug release". Variety of biocompatible and biodegradable polymers such as polyethylene glycol (PEG), poly (acrylic acid), natural polymers like gelatin36 etc can be used for surface capping of mesoporous silica based nanosystems. These polymer end cappers possessing significant diffusion barrier properties can act as a gatekeeper to provide the intracellular drug release from mesoporous silica nanoparticles (62, 63). Moreover, some of these polymeric materials are capable of responding to some stimulus due to their intrinsic ability to alter their physical or chemical properties and by using such polymers, nanoparticulate drug delivery systems can be engineered in such a way as to selectively change their properties/functions (for example, facilitate drug release or cellular uptake) in response to specific internal or external stimuli/triggering mechanisms, i.e. behave as smart stimuli-sensitive preparations (64-66). Such nano-preparations are designed to behave dynamically in response to various internal cues in the microenvironment of the pathological area or to certain external stimuli. Internal stimuli that are characteristic for the pathological areas, such as tumors, infarcts, sites of infection, etc., include local changes (compared to normal physiological values) in pH, temperature (local hyperthermia that accompanies inflammation), redox conditions (such as high intracellular glutathione levels), and the expression of certain molecules, including those

with enzymatic activity. External stimuli or stimuli that could be artificially applied from outside of the body include heat, magnetic fields, light, and ultrasound, and can be employed to facilitate “on-demand” changes of certain functions of nanomedicine. Among the different endogenous and exogenous stimuli, redox potential has recently appeared as the most unique, fascinating, promising and clinically applicable trigger for ‘‘active’’ intracellular drug and gene release. As compared to various stimuli such as light and magnetic field that are applied externally and require sophisticated devices, redox is a ubiquitous internal stimulus existing naturally in tumor tissues as well as in cancer cells (67).

1.8 Aim of the work

The present work was aimed to develop targeted delivery systems namely Polymer Lipid Hybrid Nanocarriers and Mesoporous Silica Nanoparticles with surface modifications to target the formulation to breast cancer cells.

1.9 Objectives

For PLHNCs

1. Selection of suitable polymers for synthesis of PLHNCs.
2. Development of PLHNCs.
3. Optimization of prepared formulation using Response surface methodology.
4. Evaluation of the prepared PLHNCs for their physicochemical properties.
5. Selection of suitable ligand for surface modification.
6. Attachment of ligand and evaluation of the product for cell cycle and cytotoxicity studies.

For MSNs

1. Selection of excipients and method of synthesis of MSN using OFAT analysis.
2. Synthesis of MSN with required characteristics such as surface area pore size and pore volume.
3. Optimization of prepared MSN using Response Surface Methodology.
4. Functionalization of prepared MSN surface.
5. Loading of FLV and EXE into functionalized MSN.

Overall objectives:

1. Preparation and optimization of nanocarriers for FLV and EXE.
2. Attachment of suitable ligand for active targeting of drugs to cancer cells.

3. Evaluation of prepared nano-carriers for their safety and efficacy profile by in-vitro and in-vivo studies.
4. Cell uptake and cell cytotoxicity studies using suitable cell lines.
5. Pharmacokinetic profile studies of developed nanocarriers.
6. In vivo anticancer study for developed nanocarriers
7. Stability study of developed nanocarriers

1.10 Rationale:

The rationale of the present work was to develop novel drug delivery systems for anti-neoplastic drugs for targeted delivery and improvement of both cellular uptake and efficacy of drug for the treatment of breast cancer. The existing formulation of **Fulvestrant** is depot formulation, which has some significant problems such as its inability to reach steady state plasma concentration, its route of administration, its termination of therapy and its metabolism. Similarly, for **Exemestane** its low solubility and bioavailability is matter of concern. Targeted, biodegradable polymer-based nanoparticles in the treatment of cancer can show selective accumulation of drug at tumor site and increase the drug concentration due to their nano dimension and thus lead to a reduction in the incidence of side effects of the anti-cancer agents. The addition of quercetin in MSNs can provide synergistic effect by pro-oxidation and pro-apoptosis of tumor cells. The addition of **targeting moieties** such as Folic acid can improve the specificity of the nanoparticles towards target, resulting in increase in intratumoral concentration of drug and decreasing its side effects.

1.11 Hypothesis:

It was hypothesized that prepared nanoparticulate formulation in association with attached ligands will achieve targeting of the nanocarriers to tumor cells which will facilitate enhanced cellular uptake and hence greater drug localization in cancer cells.

1.12 Envisaged outcomes

The formulations of drug loaded folate conjugated polymer lipid hybrid nanocarriers and mesoporous silica nanoparticles prepared for fulvestrant and exemestane.

- ✓ The formulated nanocarriers will have size less than that of 150 nm, which is the primary requirement for nanocarriers to perfuse through tumor vessels and perfuse into tumor cells.

- ✓ The efficacy of nanocarriers will be compared to the drug suspension for its efficacy in terms of in vitro release, cell cytotoxicity, in vivo pharmacokinetics, and anticancer activity.
- ✓ The attachment of folic acid will target the drug reducing the release of in blood and reduce the wastage of drugs.
- ✓ The addition of quercetin to MSNs will increase the oxidative stress in cancer cell and bring about apoptosis in the tumor cells.

1.13 Plan of Work

Months						
0- 3	**3 – 6**	**6 -12**	**12 -18**	**18 – 24**	**24 -30**	**30 – 36**
Literature Review						
	Preliminary Screening					
	Analytical Studies of API and Polymers					
		Formulation Development				
			Optimization of Formulation			
			Characterization of Formulation			
				In-vitro Cell Line Study		
					In-vivo animal study	
						Paper Publication and Thesis Writing

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