International Advance Journal of Engineering, Science and Management (IAJESM)
ISSN -2393-8048, January-June 2022, Submitted in June 2022, iajesm2014@gmail.com

Review of Literature on Study on The Pharmaceutical Formulations (Lipid Nanostructured Carriers) Development for Combinatorial Access Opposite to Breast Cancer

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Abstract

Solid–lipid nanoparticles and nanostructured lipid carriers are delivery systems for the delivery of drugs and other bioactives used in diagnosis, therapy, and treatment procedures. These nanocarriers may enhance the solubility and permeability of drugs, increase their bioavailability, and extend the residence time in the body, combining low toxicity with a targeted delivery. Nanostructured lipid carriers are the second generation of lipid nanoparticles differing from solid lipid nanoparticles in their composition matrix. The use of a liquid lipid together with a solid lipid in nanostructured lipid carrier allows it to load a higher amount of drug, enhance drug release properties, and increase its stability. Therefore, a direct comparison between solid lipid nanoparticles and nanostructured lipid carriers is needed. This review aims to describe solid lipid nanoparticles and nanostructured lipid carriers as drug delivery systems, comparing both, while systematically elucidating their production methodologies, physicochemical characterization, and in vitro and in vivo performance. In addition, the toxicity concerns of these systems are focused on.

Keywords: lipidnanoparticle; **NLC**; **nanocarrier**; **nanoparticlecharacterization**; **nanoparticle production**; **SLN**

INTRODUCTION:

Nanomedicine aims to provide accurate diagnoses and treatments for diseases more effectively, with minimal adverse effects. Nanomedicine has gained popularity because of its efficiency in delivering drugs and other bioactives to target tissues more accurately in a controlled manner by encapsulating or attaching them to nanostructures [**1**]. These drug delivery systems involve nanocarriers that are colloidal drug carrier systems having submicron particle sizes, typically below 1000 nm. Due to their high surface area to volume ratio, nanocarriers can modify the basic properties and bioactivity of drugs. They also allow drug protection (e.g., from humidity, pH changes, and enzymes); improved pharmacokinetics and biodistribution of the drugs; either by passive or active targeting, resulting in reduced toxicities and improved therapeutic benefits [**3**]; enhanced bioavailability; controlled drug releasing profiles; prolonged blood circulation times; enhanced intracellular penetration; and site- and organ-specific targeted delivery.

Different types of materials have been used to produce nanoparticles, mainly polymeric, lipid, and inorganic materials. Among these, lipid nanocarriers have considerable advantages due to their biocompatibility, biodegradability, low toxicity, scale-up capacity, and delivery of both hydrophilic and lipophilic drugs in a controlled or targeted manner [**6**]. These carriers may also permeate physiological barriers, such as the blood–brain barrier and the intestinal epithelium [**8**]. Further, to combine the advantages of different materials, hybrid nanoparticles may also be obtained to improve the features of lipid-based nanoparticles. For example, a new approach can be developed based on the physical modification of the lipid matrix with polymers, producing a lipid–polymeric matrix to entrap the drugs [**9**]. With the introduction of liposomal Doxorubicin, Doxil® entered into the United States market in 1995 for the treatment of AIDS-related Kaposi sarcoma and ovarian cancer, thereby increasing the interest in lipid-based drug delivery systems [**14**]. Further, scientists investigated new and advanced drug delivery technologies combining the advantages of liposomes, nanoemulsions, and solid lipid nanoparticles (SLN) [**18**]. SLNs are solid colloidal particles in the sub-micron range, ranging from 4 to 1000 nm, and contain in their formulation physiological, biodegradable, and biocompatible lipids and surfactants, which can incorporate both lipophilic and hydrophilic drugs inside the lipid matrix. The solid lipid is the dispersed phase, whereas the surfactant acts as an emulsifier. The first one is usually produced from triglycerides, glyceride mixtures, or even waxes, and it remains in the solid state at room and body temperature. On the other hand, to enhance formulation stability, the range of surfactant concentration is typically 0.5 to 5% (*w*/*v*). The choice of lipids and

surfactants greatly impacts the physicochemical properties (e.g., particle size and drug loading) of the nanoparticle formulation [**3**,**17**]. In comparison with liposomes, SLNs have better drug stability and prolonged release, and in comparison with polymeric nanoparticles, they are safer due to the absence of organic solvents in the production phase. More recently, nanostructured lipid carriers (NLCs) have been developed by adding a liquid lipid to the matrix, enhancing the advantages of SLNs [**15**]. For that reason, NLCs are usually denominated as second-generation lipid nanoparticles. In fact, NLCs have improved stability and drug loading capacity, preventing unwanted drug expulsion during shelf life. They are distinguishable from SLNs due to their solid matrix composition, where the lipidic phase contains both solid and liquid lipids at the body and room temperature.

Literature review related to the anticancer activity of RLX

RLX is a potent anti-cancer drug used in the prevention and treatment of breast cancer. Besides this, it is having its potential application in the treatment of osteoporosis, especially in postmenopausal women. It is belonging to second-generation selective estrogen receptor modulators with established antiestrogenic activity on breast tissue which makes it a potential candidate to be used in the prevention of invasive breast cancer (Olver, 2016).

The clinical finding that patients treated with RLX to improve bone density showed significant reductions in breast cancer (Delmas *et al*., 2015), provided clinical evidence of the laboratory principle and demonstrated the potential of RLX as a chemopreventive agent for breast cancer (Powles *et al*., 1999). Data from the study tamoxifen and RLX (STAR) study, which compared RLX directly with tamoxifen for chemoprevention of breast cancer, showed that RLX has chemopreventive properties similar to that of tamoxifen, but has a profile that is significantly better in safety (Jordan *et al*., 1999).

Based on the results of five recently conducted pivotal studies (Multiple Outcomes of Raloxifene Evaluation [MORE], Raloxifene Use for the Heart [RUTH], Study of Tamoxifen and Raloxifene [STAR], Continuing Outcomes Relevant to Evista [CORE], and Evista Versus Alendronate [EVA]) shows that RLX is the most attractive agent among SERMs. The MORE, CORE and RUTH studies showed that RLX not only reduced the incidence of fractures associated with osteoporosis but was also effective in preventing breast cancer. In addition, comparisons between RLX and tamoxifen as a chemopreventive agent for breast cancer (STAR pathway) have confirmed that RLX is an excellent choice for breast cancer prevention (Lee *et al*., 2008).

RLX is a BCS class II drug (biopharmaceutical classification system) and faces a solubility issue that becomes a major obstacle to its efficacy. Many research groups have explored RLX to satisfy different purposes we review the most important work have been done by the different research groups.

Taurin *et al*. evaluated the therapeutic effect of RLX in induced triple-negative breast cancer in mouse models. RLX was administered orally to mice at various daily doses. The result of the study showed that a dose of 0.85 mg/kg inhibited the growth of TNBC tumors. Treatment with RLX showed a 54% decrease in microvascular density and an increase by a 7-fold apoptosis. In addition, the expression of the receptor for the epidermal growth factor was reduced by 27 times by treatment with RLX. Data have shown that RLX works independently of the estrogen receptor and can be relevant for treatment and decrease the progression of TNBC (Taurin *et al*., 2013).

Xu *et al*. study the sensitization ability of RLX to multidrug-resistant breast cancers to paclitaxel, particularly, in estrogen receptor-negative (ER-) breast cancer. The results of the *in vitro* and *in vivo* studies demonstrated that RLX significantly sensitizes MDR- ER-negative breast cancers to paclitaxel. Coadministration of RLX with paclitaxel significantly improves cell apoptosis and inhibition of cell proliferation in MDR tumors paclitaxel (Xu *et al*., 2015).

RLX in combination therapy

RLX has been used in combination with other therapies in recent years to improve its effects. A research group reported making such an attempt by combining RLX and letrozole to counteract RLX 's bony adverse effects. They disclosed that the combination of letrozole and RLX had an additive effect on cytotoxicity when tested on MCF-7 cancer cell lines, but had no

significant effect on cytotoxicity when tested on HEK normal cell lines, indicating that RLX does not interfere with the co-administered drug and thus can be used for dual drug therapy (Vohora *et al*., 2017). In another study, RLX was found to show enhanced antiproliferative activity when evaluated along with trichostatin A (histone deacetylase inhibitor). In combination, both drugs showed the antiproliferative effect of each other by promoting cell death via apoptosis and cell cycle arrest (Tu *et al*., 2012).

RLX has also been evaluated with fluoxetine (a selective serotonin reuptake inhibitor that has anticancer properties) for effect on dimethyl benzanthracene (DMBA) induced breast cancer in Wistar rats. The combination demonstrated significant reductions in tumor volume, tumor necrosis factor-alpha, tissue malondialdehyde, interleukin 6, and transforming growth factor beta1 levels, indicating that it is a more effective treatment modality without impairing the intrinsic properties of the individual components. The combination of RLX and fluoxetine may be effective in alleviating symptoms associated with breast cancer in an experimental model (Kabel *et al*., 2016).

Notably, the combination of RLX and epigallocatechin gallate increased the cytotoxicity of MDA-MB-231 cells. The strong effect was determined to be due to the drugs' individual and synergistic inhibition of EGFR and protein kinase B phosphorylation (Stuart *et al*., 2008).

A combination of RLX and resveratrol was found to reduce the viability of MCF7 and MDA-MB-231 cells by a significant amount, and their combination yielded an even greater reduction. The research found that when RLX and resveratrol were used in combination, both cell lines exhibited an increase in apoptosis. Moreover, the protein Bcl2 decreased in expression, and the proteins Bax and p53 increased. Based on the synergistic effects of RLX and resveratrol on the Bcl-2/Bax ratio and expression of the p53, caspase-3, and caspase-8 genes, it appears that both drugs may be more beneficial to breast cancer cells than they are to their own (Mirzapur *et al*., 2018).

RLX and curcumin derivative (2,6-bis(pyridin-4-ylmethylene)-cyclohexanone) (RL91) have been shown to inhibit the growth of ER-negative breast cancer cells *in vitro* and *in vivo*. The cytotoxicity of the combination therapy was investigated in four breast cancer cell lines (MDA-MB-231, Hs578t, MDA-MB-468, and SkBr3). When compared to non-combination therapies, the combination therapy consistently induced significantly greater cytotoxicity and apoptosis in all cell lines tested (Taurin *et al*., 2016).

Literature review related to RLX delivery systems

Kanade *et al.* developed mixed micelles loaded RLX to enhance the bioavailability and improve the anticancer activity of RLX on MCF-7 breast cancer cell lines. The *in vitro* cytotoxicity study of prepared micelles shows greater anticancer activity on the MCF-7 breast cancer cell line as compared with pure RLX. Moreover, the *in vivo* oral bioavailability of female Wistar rats show 1.5-fold more improvement (Kanade *et al*., 2017).

Shah *et al.* constructed nanostructured lipid carriers NLCs to improve the oral bioavailability of RLX. The NLCs were prepared from glyceryl monostearate and capmul MCM C8 using the solvent diffusion method. *In vitro* release study demonstrated burst release for an initial 8 h followed by a sustained release for the remaining time up to 36 h. The *in vivo* pharmacokinetic profiles of the optimized NLCs formulation showed 3.75-fold enhancements in bioavailability as compared with free drug suspension (Shah *et al*., 2016).

Almutairi *et al.* developed RLX-loaded chitosan nanoparticles functionalized with hyaluronic acid (RLX-HACS NPs). The cytotoxic and proapoptotic effects of the prepared were investigated in against A549, HepG2, and Huh-7 cell lines. The entrapment efficiency for RLX-HA-CS NPs, RLX-HA NPs, and RLX-CS NPs were (92%), (87.5%), and (68%), respectively. Moreover, higher cytotoxicity was induced by RLX-HACS NPs against A549 cells as compared to other cell lines. The higher cytotoxicity against the A549 cell line was attributed to the reduction of glucose uptake glucose that result in reduced bioenergy of cancer cells and activation of apoptosis via nitric oxide level elevation (Almutairi *et al*., 2019).

Beckenkamp *et al.* prepared polymeric nanocapsule loaded RLX by interfacial deposition method using Eudragit® RS100 and Eudragit® S100 polymers. The prepared nanocapsules exhibited a high entrapment efficiency, medium nanometric size, and low polydispersity.

Controlled release of RLX from anionic nanocapsules, which can be explained by a stronger interaction with these nanocapsules and by the higher amount of the drug contained. Inaddition, MCF-7 cell viability and cell count studies showed that Eudragit® RS100 nanocapsules loaded with RLX promoted the best antiproliferative activity after 24 hours of treatment, whereas the significant antiproliferative activity was reported for RLX-loaded Eudragit® S100 nanocapsules after 72 hours (Beckenkamp *et al*., 2014).

Prakash *et al.* prepared RLX-loaded gellan gum nanoparticles by emulsion cross-linking processes and the nanoparticles produced exhibited a tight particle size distribution with an average size of 472 nm, a zeta potential of -40.6 mV, and with an uptake efficiency of 98 ± 3%. *In vitro* release studies have shown an initial burst release within 30 minutes, followed by a continuous release over 24 hours. *In vitro* cytotoxicity studies on the MCF7 cell line demonstrated that RLX-loaded gellan gum nanoparticles exhibited higher cytotoxicity than free RLX (Prakash *et al*., 2014).

Kushwaha *et al.* prepared solid lipid nanoparticles loaded with RLX to improve oral bioavailability. Compritol 888 ATO as a lipid carrier and pluronic F68 as a surfactant was used to prepare SLNs using the solvent emulsification/evaporation method. The entrapment efficiency and the particle sizes of the optimized formulation were in the range (55 to 66%.) and (250 to 1406 nm), respectively. Moreover, the *in vivo* oral bioavailability of RLX-SLNs on Wistar rats was 5 folds more compared with pure RLX (Kushwaha *et al*., 2013).

Hiep *et al.* prepared solid dispersion nanoparticles SD to improve the oral bioavailability of RLX. The RLX dissolution rate of the formulation was optimized at pH 1.2, 4, and 6.8, and the distilled water was more enriched than pure RLX. The oral bioavailability of RLX in rats was therefore improved. In addition, the pharmacokinetic profiles of the optimized formulation showed increases in RLX AUC0 - ∞ and Cmax by 3.3-fold and 2.3-fold, respectively (Hiep *et al*., 2013).

Jawahar *et al*. prepared RLX-loaded carbon nanotubes functionalized with folic acid (CNTs) using a modified Staudenmaier process. The *in vitro* cytotoxicity and intercellular internalization of the functionalized CNTs on MCF-7 cell lines were enhanced as compared with free RLX (Jawahar, 2019).

Nekkanti *et al.* prepared RLX-loaded solid lipid nanoparticles (SLN) from Tripalmitin, Trimyristin, and Tristearin using the hot homogenization method. The optimized nanoparticles show zeta potential and mean size in the range of (17 to –22 mV) and (154 to 175 nm), respectively. The entrapment efficiency of the drug was 98 %. Moreover, the *in vitro* drug release rate was higher compared to the free drug (Nekkanti *et al*., 2012).

Jain *et al.* Prepared self-nano-emulsifying cationic nanomicellar drug delivery systems loaded with RLX to enhance the oral bioavailability of RLX. *In vitro* cell line studies on Caco-2 and MCF-7 cells, in situ perfusion, and *in vivo* pharmacokinetic studies have shown that CS-SNEDDS significantly improves the biopharmaceutical properties of the drug compared to the drug alone (Jain *et al*., 2018).

Yadav *et al.* prepared RLX-loaded chitosan nanoparticle CH-NPs functionalized RGD peptide by ionic gelation method. The prepared nanoparticles show higher stability and zeta potential along with enhanced cellular internalization at acidic pH compared to physiological pH. Furthermore, RGD conjugation enhanced *in vitro* cellular internalization of CH-NPs in αvβ3 integrin-expressing breast cancer cells and induced higher cellular apoptosis in breast cancer cells. Moreover, RLX-loaded-RGD-CH-NPs significantly inhibited breast cancer cell metastasis and angiogenesis. *In vivo* studies showed that Cy5.5 conjugated RGD-CHNPs can distinctly visualize tumors and RLX loaded -RGD-CHNPs significantly inhibits breast tumor growth without causing any toxic effect to normal tissue as confirmed by hematology and blood biochemical studies (Yadav *et al*., 2020).

Aldawsari *et al.* prepared RLX-loaded self-nanoemulsion from Tween 80, peppermint oil, and PEG 200 to enhance the solubility and bioavailability. The *in vitro* drug release from SNEDDS was enhanced 3-fold as compared with pure drug. The *in vitro* cytotoxicity of RLX- SNEDDS in the MCF-7 cell line was greater as compared with pure RLX (Aldawsari *et al*., 2020).

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