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THE DEVELOPMENT AND EVALUATION OF LYCOPENE CO-DELIVERED TAMOXIFEN LOADED DAMMAR GUM NANOPARTICLES TO FIGHT CANCER CELL LINE

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Abstract

Drug resistance is a frequent problem with chemotherapy-based cancer treatments. Secondary metabolites of plants with anticancer potential can be successfully enhanced at the nanoscale. Lycopene have a molecular formula $C_{40}H_{56}$. It is a tetraterpene and a carotene used in cosmetics as antiwrinkle agent, has the capacity to kill cancer cells by impeding cellular proliferation. Tamoxifen, a selective oestrogen receptor modulator, is employed to treat oestrogen receptor-positive breast cancer, reduce the risk of invasive breast cancer following surgery, or lessen the risk of breast cancer in high-risk women. To improve bioavailability and have a synergistic effect, Lycopene and TAM loaded dammar gum nanoparticles (LTDNPs) were made using oil in oil (O/O) emulsion solvent evaporation procedures. Zeta potential, a measure of a nanoparticles relative stability, was found to be -45.1 mV for LTDNPs. The percentage encapsulation efficiency values for Lycopene and TAM were found to be 70% and 76%, respectively. The LTDNPs have particles with a size between 28 and 32 nm, according to TEM. Compared to free Lycopene and TAM particles alone, the LTDNPs had far stronger anti-oxidant and anti-cancer capabilities and had sustained release. The *in vitro* experiments revealed that the combination of Lycopene, TAM, and dammar gum significantly inhibited the growth of MCF-7 cell lines

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compared to Lycopene, TAM, and dammar gum together, highlighting the combination's substantial anticancer potential.

Keywords Dammar gum, Lycopene, Tamoxifen, Anti-cancer, Nanoparticles

Introduction

The application of nanotechnology to the treatment of cancer opens up a completely new field of pharmaceutical study. Nanoscale drug molecules provide a novel, very effective bioactive-loaded nanoplatform to fight cancer cells. Chemotherapy is frequently used to treat a variety of cancers [1]. Contrarily, these conventional therapeutic approaches have a detrimental effect, particularly in terms of medication tolerance or resistance [2, 3]. Life-saving treatments made possible by nanotechnology are very popular these days. The bioactive compounds with improved antioxidant and anticancer capabilities at the nanometric size also show good absorption at low doses. The National Institute of Cancer in the USA has encouraged research into the potential anticancer properties of numerous plant secondary metabolites [4, 5]. Phytochemicals including Lycopene has been shown to have cytotoxic effects in the literature [6].

Recent studies have shown that the morphological properties of nanoparticles are essential for obtaining anticancer activity with few adverse effects [7]. Size, shape, and surface features of nanoparticles have an impact on their pharmacokinetic and pharmacodynamic properties.

The aglycone of saponins and free carboxylic acid are both types of Lycopene triterpenoid) [8]. It causes glucocorticoid receptor modification in human breast cancer cell lines (Michigan Cancer Foundation-7) and reduces Bcl2 (anti-apoptotic proteins) levels [9, 10]. Due to its low level of toxicity and natural origin, Lycopene is frequently used in pharmaceutical formulations that can be applied topically and taken orally [11, 12].

The optimal characteristics to take into account when choosing an agent for drug encapsulation are biodegradability and biocompatibility [13, 14]. Dammar gum is a new encapsulation ingredient used for medicinal action, and studies have shown that as gum concentration is increased, encapsulation effectiveness increases proportionally [15].

A type of hormonal therapy is a selective oestrogen receptor modulator (SERM), like tamoxifen. The drug binds to hormone receptors, which are particular proteins found on breast cancer cells.

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Once the medication has reached the cells, it blocks the cancer's access to the hormones it requires for growth and spread. [16,17]. Since the Food and Drug Administration (FDA) approved tamoxifen in 1998, it has grown to be one of the most frequently prescribed therapies for breast cancer. It is a nonpolar molecule with two primary mechanisms of action: (1) competing with 17-estradiol (E2) at the receptor site to stop E2 from causing breast cancer; and (2) binding DNA following metabolic activation and initiating carcinogenesis [18,19]. It has anticancer efficacy due to its structural affinity for the cell membrane and adjuvant hormonal therapy [20].

Creating a Lycopene co-delivered TAM polymeric nanoplatform to boost bioavailability, foster synergism, and reduce adverse effects was the aim of the current work. The encapsulation of TAM and Lycopene allows for the longer release of the polymeric nanoparticles and enhanced therapeutic efficacy at low dosage.

Materials and Methods

Materials

Gum dammar was bought from MP Biomedicals, LLC, a French firm. We purchased tamoxifen and Lycopene (>90%) from Sigma Aldrich in India. The cell line MCF-7-Human breast cancer cells was donated by the National Centre for Cell Science (NCCS), located in Pune. All of the chemicals used in this study were of the analytical kind.

Lycopene & TAM loaded Dammar gum nanoparticles preparation (LTDNPs)

The LTDNPs were produced by solvent evaporation in an oil-in-oil emulsion [21]. 150 mg of dammar gum, 80 mg of Lycopene, and 25 mg of TAM were dissolved in 200 ml of propanol. The aforementioned solution was mixed with 30 mg of magnesium stearate and stirred magnetically at 1200 rpm for 40 minutes. 80 cc of liquid paraffin oil was gradually added to the mixture after the mixture had been continuously stirred for 8 hours at 1200 rpm at 40 C and centrifuged for 40 minutes at 10000 rpm at 4 C. The pellet was separated, placed in a cryoprotectant (5% w/v D-Mannitol), and then dried using a freeze-drying technique.

Characterization of synthesized LTDNPs

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The Zetasizer Nano ZS-90 was used to assess the average size and size distribution (polydispersity index) of the optimized nanoformulation of LTDNPs. After a 40-minute centrifugation at 10000 rpm (4 °C), the supernatant containing the unbound medication was collected and analysed by HPLC. The encapsulation efficiency was (Total Drug-Unbound Drug/Total Drug), where the formula for percent entrapment efficiency is 100.

The size and shape of the optimized batch of LTDNPs were studied under a transmission electron microscope. In the range of 4500-500 cm^{-1}, the Fourier transform infrared spectrophotometer was used to evaluate the FTIR analysis of Lycopene, TAM, dammar gum, and LTDNPs.

In vitro release profile of LTDNPs

The dialysis sac technique was used to study the release profile. Water (10 ml), ethanol (25%) phosphate buffer (0.1 M) saline pH 7.4 were added to a dialysis sac containing 10 mg of Lycopene co-delivered TAM loaded dammar gum nanoparticles. The mixture was then continuously stirred at 100 rpm at a constant temperature of 37 °C [21]. One ml samples were taken, collected, and evaluated using HPLC Lycopene (219.9 nm, 5.58 min.) and TAM (256 nm, 7.01 min.) at regular intervals of 1, 2, 3, 6, 12, and 24 hours.

Antioxidant activity

The antioxidant ability of Lycopene, TAM, Dammar Gum, and LTDNPs was evaluated using the DPPH test [22]. The 3.9 mg/100 ml of methanol was uniformly mixed with the free radical DPPH. Pure Lycopene, TAM, Dammar Gum, and LTDNPs were incubated with DPPH for 30 minutes in the dark to examine the inhibition of DPPH in duplicate runs. A UV spectrophotometer was used to quantify the absorption peak at 517 nm. Blank dammar NPs were used as the negative control, while pure Lycopene and TAM were used as the positive controls. The percentage of DPPH inhibition by pure Lycopene, TAM, and LTDNPs was calculated using the following formula:

$$\text{Percent antioxidant activity} = \frac{\text{Absorbance of control} - \text{Absorbance of sample}}{\text{Absorbance of control}} \times 100$$

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In-vitro assay for cytotoxic activity (MTT assay)

Incubated at a temperature of 370 °C and in an atmosphere with 5% CO_2, cell lines (both healthy and malignant) were cultured in media supplemented with inactivated FBS solution (10%), antibiotic streptomycin concentration of 80 l/ml, and antibiotic penicillin concentration of 80 l/ml [21, 23]. Subcultures were carried out employing 0.25% trypsin solutions in sterile laminar air flow after reaching 75% confluence. In 96-well plates with 104 cells per 100 l in each well, cell seeding was examined. The growth characteristic pattern of each cell line was evaluated to gauge its density. After 8 hours of incubation, the wells were subjected to three days (in triplicate) of treatment with various doses of LTDNPs (0.1-500 g/ml) and Lycopene.

After the cells had been grown, the medium was replaced with 3 l of MTT solution (5 mg/ml), and the mixture was then incubated for 3 h. The percentage of metabolically active cells was compared to untreated controls based on the mitochondrial conversion of 3-(4, 5-dimethylthiazol-2-yl) 2, 5 diphenyltetrazolium bromide (MTT) to Formazan crystals. After dissolving the formazan crystals in DMSO, the mixture's absorbance at 570 nm was measured. In the MTT assay, pure OA and TAM were employed as the gold standard to evaluate the anticancer effectiveness of OTDNPs against the human breast cancer cell line MCF-7. The percentages of cytotoxicity (2) and inhibition of cell growth (1) were calculated using the next procedure.

%viability = $(A_{Tr} - A_{Bl}) / (A_{Ct} - A_{Bl}) \times 100$ ……. (1)

Where A_{Tr} = Absorbance for treated cells (drug); A_{Bl} = Absorbance for blank

A_{Ct} = Absorbance for control (untreated)

%cytotoxicity = 100 – Percent cell survival (%) ……. (2)

Results and Discussion

Particle size and Zeta Potential

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The LTDNPs' zeta potential and particle size were examined. The created nanoformulation was discovered to have a zeta potential value of -45.1 mV and a rather steady size for LTDNPs of 198.6 nm (Figs. 1 and 2).

Encapsulation efficiency

The % encapsulation efficiency number is influenced by the method utilized, the chemical composition of the encapsulating materials, and the dielectric constant of the medium used to create nanoparticles [21, 24]. The percentage of bound drug was calculated using the HPLC analysis of supernatant containing unbound drug, and the findings were 70% for Lycopene and 76% for TAM (Fig. 5). Lycopene and TAM are non-polar hydrophobic compounds. They dissolve relatively easily in propanol-based gum solution. Dammar gum has a great affinity for Lycopene and TAM because it is hydrophobic. The medication was better encapsulated in dammar gum as a result of the similar natural affinity.

Morphological characterization of* LTDNPs *by TEM

The LTDNPs were uniformly spherical, segregated, and ranged in size from 35 to 64 nm, as shown by Transmission Electron Microscopy (Figure 3). According to experimental studies, the size of the nanoparticles examined by TEM and PSA differed. This is due to the fact that PSA operates under the assumption that the ions of nanoparticles are fluidized around them, but TEM operates under the assumption that a particle's size will decrease in a solitary, dry atmosphere. The release rate of medications is influenced by the size of nanoscale particles [25, 26]. Depending on their size and shape, NPs are transported to various human organs at varied concentrations. Nanoparticles' relative stability, biocompatibility with the environment of the body, and ability to pass through cell membranes are all influenced by their shape and size [26]. Smaller nanoparticles are maintained in the systemic circulation for a longer period of time compared to larger nanoparticles [27].

FTIR Analysis of Drug Samples

FTIR spectroscopy is used to examine the interaction [27] and evaluate the nanoencapsulation of bioactive substances [28]. The FTIR spectra of the pure medicines Lycopene, TAM, dammar gum, and LTDNPs are shown in Figure 4. The absorption peak bands in the FTIR spectrum of Lycopene were 3000.0 cm-1 and 2401 cm-1 for the terminal -CH3 groups and 3412 cm-1 for the

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-OH group. The distinctive absorption band for =C-H stretching at 2876 cm-1 and for C=C ring stretching at 1600 cm-1 were visible in the FTIR spectra of TAM in Figure 4B. Wave number values at 1501 cm-1 and 3401 cm-1 indicated -NH2 structure. The peak at 3412 cm-1 for the -OH stretch and the peak at 2900 cm-1 for the aliphatic -CH stretch, respectively, are shown in Figure 4 C's FTIR analysis of dammar gum. Figure 4D shows the FTIR spectra of LTDNPs, which show variations between wave numbers 3409 cm1, 1400 cm1, 2458 cm1, and 2901 cm1. The IR stretching vibration zones for functional groups like OH, C=C Stretch, CH_3 Stretch, and C-H Stretch are located here. Dammar gum's OH and the drug's C-H combine to generate dipole-dipole interactions, hydrogen bonds, and weak Van der Waals forces, among other weak physical bonds. The drugs' and excipients' FTIR spectra showed unique peaks. The change in the bands and decrease in peak intensity indicated that TAM, Lycopene, and dammar gum were physically interacting.

In-vitro drug release

The continuous release of bioactive compounds from nanoparticles cages protects them from rapid metabolism and oxidation [29]. Figure 5 displays the in vitro drug release characteristics of Lycopene, TAM, and LTDNPs. The drug was highly effectively and efficiently entrapped in dammar gum, which resulted in LTDNPs showing sustained drug release. The in-vitro results on drug release showed that 90% of pure Lycopene and 95% of pure TAM were only released in 5 hours. 16% Lycopene and 17.81% TAM were released by the LTDNPs one hour after administration. LTDNPs released 75% of Lycopene and 84% of TAM after 24 hours. Because Lycopene and TAM are hydrophobic (nonpolar), LTDNPs' total drug release showed sustained release characteristics of Lycopene and TAM throughout time. In order to guarantee a continual release of the Lycopene and TAM particles, dammar gum also creates a dense matrix with a thick, sturdy wall around them.

Anti-oxidant activity

To quantitatively evaluate the antioxidant activity/potency of compounds that have been encapsulated, the DPPH analysis approach is used [31]. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) stable free radical absorbs light to show excitation and emits a deep violet colour when it does. It has unpaired electrons that have distributed randomly throughout the molecule. At 517

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nm, it exhibits absorption [32]. When a DPPH solution is uniformly mixed with a molecule that has the potential to donate (oxidizing nature) a hydrogen atom, the violet colour disappears. It is well known that Lycopene and TAM have antioxidant properties. When the antioxidant molecules Lycopene and TAM were dissolved in DPPH, a stable non-radical version of DPPH was created, turning the violet colour to pale yellow. Consequently, the absorption band contracted. Inhibiting DPPH can happen when labile hydrogen atoms in the Lycopene and TAM are released. The LTDNPs wide surface area and small nanometric dimension shielded Lycopene and TAM from oxidation during dark incubation, leading to a higher percentage of DPPH inhibition than Lycopene and TAM alone.

Anti-cancer activity

The improved cytotoxic efficacy and powerful anticancer characteristics of the nanoparticles depicted in Figures 6 were greatly enhanced by their higher surface area [33]. Nanoparticles in the 100 nm range are more able to infiltrate cancer cells quickly or effectively due to the retention effect and increased vascular penetration [34]. As a result, NPs' efficiency against cancer cell lines depends on their size [35,36]. Nanoscale particles can more efficiently reach the cancer cells. In the current study, LTDNPs' anti-cancer action was revealed to be more effective than pure active drug alone. In an in vitro experiment, Lycopene and TAM coupled with dammar gum more successfully inhibited the development of MCF-7 than the free drugs did. Data also shows the IC50 values (g/ml) of synthesized nanoparticles. When compared to the traditional drugs TAM and Lycopene alone, the optical microscope examination on the cancer cell line MCF-7 showed that LTDNPs had a potent anticancer impact with an IC50 of 3.94 g/ml. The potent anticancer impact of LTDNPs was primarily attributed to the synergistic interaction between TAM and Lycopene in these drugs.

Conclusions

Nanotechnology-based medicines are now able to successfully address and treat a variety of ailments thanks to significant advancements in the drug formulation sector. One use of nano-drug delivery is the systems for delivering nanoparticles with bigger payloads, such as dual drug delivery to give synergistic effects of secondary metabolites with pharmaceuticals at therapeutic

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size. Despite the large number of anticancer medication compounds that have been identified, the main drawbacks of these therapeutic molecules are their low bioavailability, short half-lives in the body, and potential for tolerance and resistance. Designing new nanoformulations consisting of more efficient excipients is essential in order to increase solubility in water, bioavailability to blood from the intestine, therapeutic potential to kill cancer cell lines, and decrease dosage. Due to its synergistic antioxidant and anticancer capabilities, the current work's novel nanoformulation, which includes Lycopene acid co-delivered TAM loaded dammar gum nanoparticles, has emerged as a viable chemical to successfully combat cancer.

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Figure 1. PSA image of LTDNPs

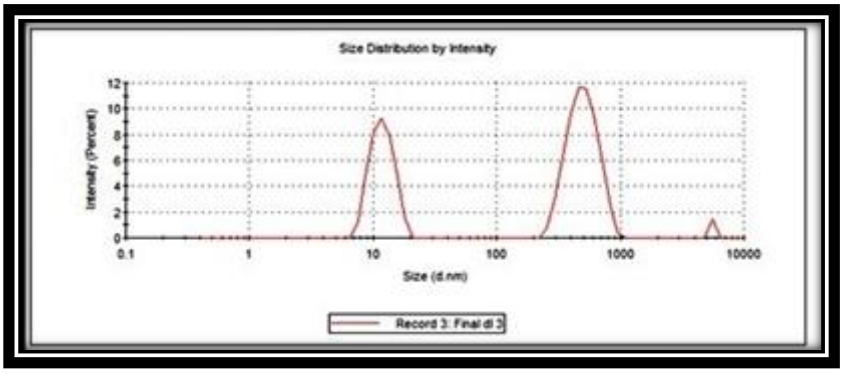

Figure 2. Zeta potential of LTDNPs

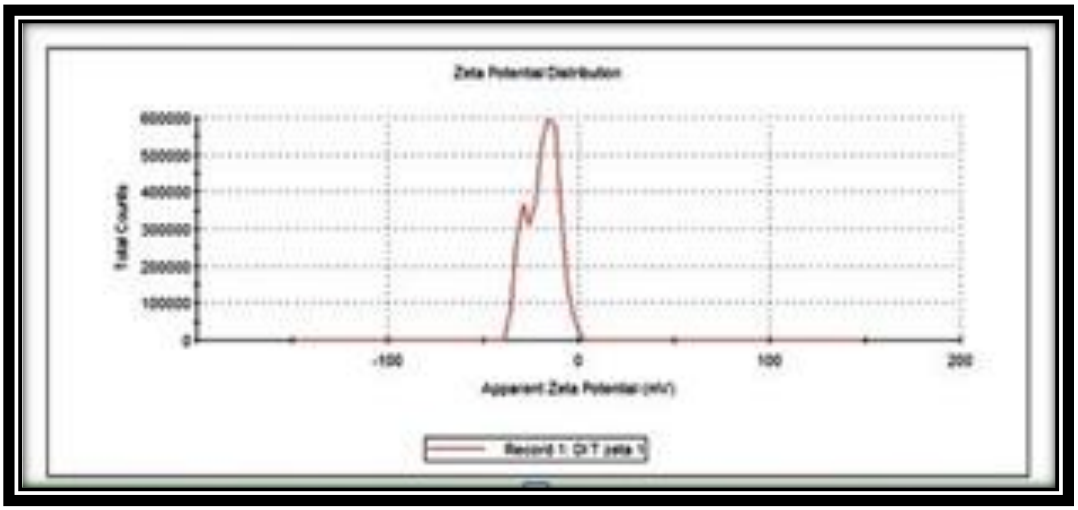

Figure 3: TEM image of LTDNPs

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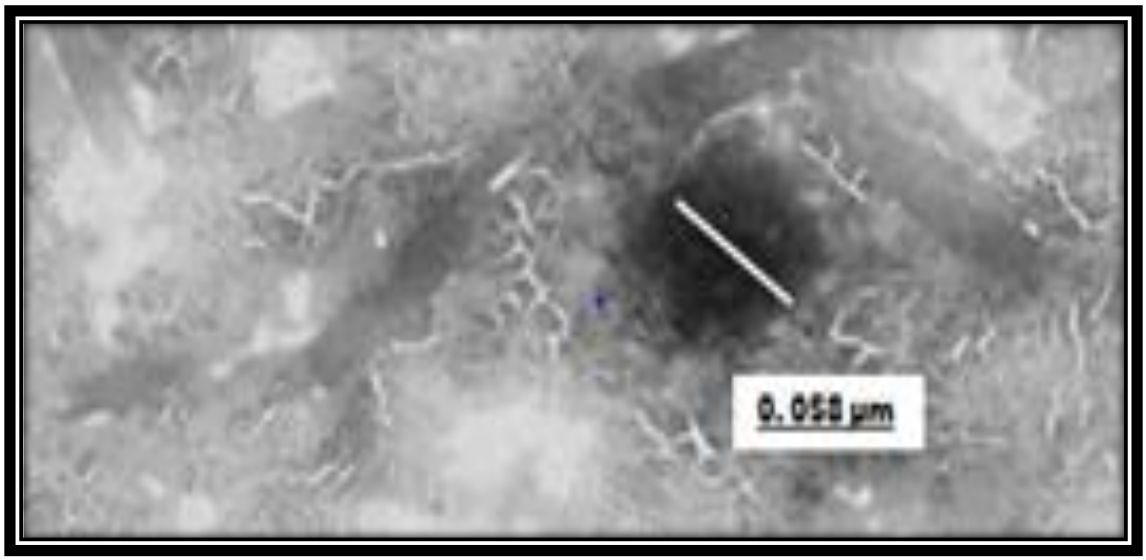

Figure 4. The FTIR spectra of pure drug (A) Lycopene, (B) TAM, (C) Dammar gum, (D) LTDNPs

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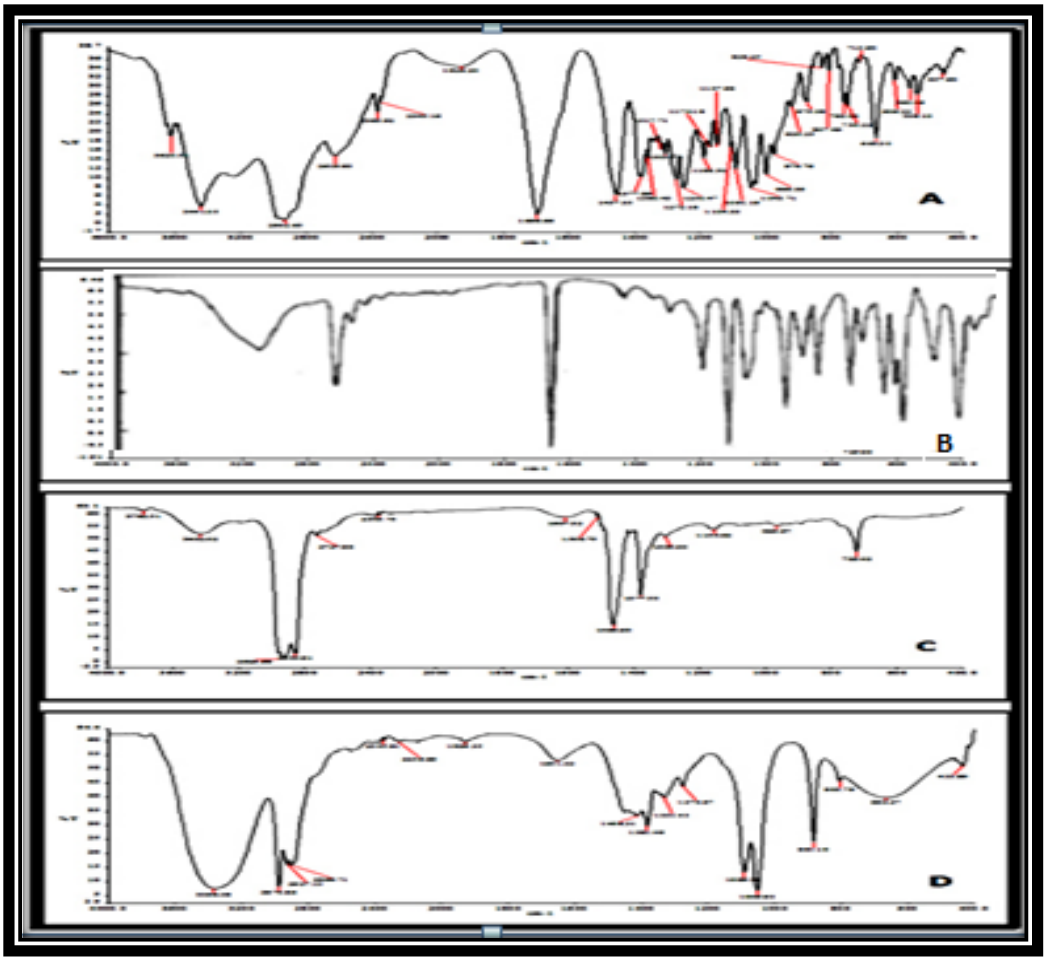

Figure 5. In-vitro release study

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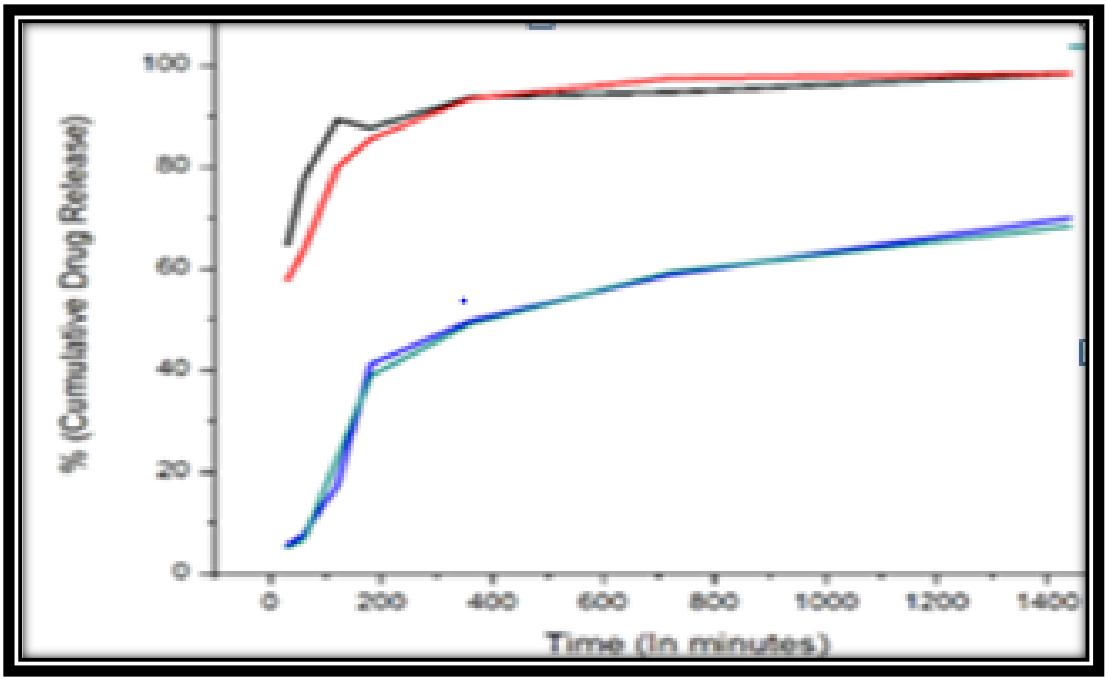

Figure 6. Optical microscope images of Cytotoxic effect of Lycopene (B1), TAM (F1) and LTDNPs (N1), MCF-7 cell lines after 24 h.