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MANGIFERIN LOADED NANOPARTICLES FOR CANCER THERAPY: AN APPROACH FOR IMPROVEMENT OF BIO-EFFICACY USING NANOTECHNOLOGY

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ABSTRACT: Cancer is the malignant form of uncontrolled growth of cells and tissues. The drugs currently used for treating cancer can only increase the lifespan of a patient but cannot cure the disease due to their high toxicity and poor targeting of specific sites. Drugs developed from natural compounds are believed to combat those problems due to their ability to stimulate various physiological pathways with multiple targets. However, the use of natural compounds is restricted because of their physicochemical characteristics. This research article focuses on the use of Mangiferin as anti-cancer agent and its safe and effective delivery using nanotechnology. Mangiferin-loaded poly (lactic-co-glycolic acid) nanoparticles were prepared by single emulsion-solvent evaporation technique and evaluated for yield, particle size, morphology analysis, zeta-potential, drug loading, encapsulation efficiency, *in-vitro* drug release study and MTT assay on A549 cell line. Mangiferin was successfully loaded onto polymeric nanoparticles using a simple single emulsion solvent evaporation technique using PLGA as a polymer and PVA as a stabilizer with spherical narrow size distribution. Mangiferin-loaded PLGA NPs proved to be more cytotoxic to A549 cell lines than the free mangiferin solution with reduced IC_{50}. Various studies in this article discussed the mangiferin-loaded polymeric nanoparticles and how the bio-efficacy has been improved for treating cancer.

INTRODUCTION: Poor food habits, stress, and chemical substances, like various critical factors, lead to serious diseases in the large human population when exposed to those critical factors [1]. Those serious diseases include cancer and cardiovascular diseases. It is the second source of death, and the number of deaths due to cardiovascular disease and cancer involve 25.4% and 23.2%, respectively.

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In developing countries, due to the limitation of preventive and curative measures, cancer has become the largest dreaded non-communicable disease [2, 3]. An estimated 14.1-18.1 million and 8.2-9.6 million new cancer cases and deaths occurred worldwide in 2012-2018 [4, 5]. The currently used drugs can only increase a patient's lifespan but cannot cure the disease due to their high toxicity and poor targeting to the specific sites.

Due to its poor specificity to the cancer cells damages healthy human cells by inhibiting DNA synthesis or interfering with various metabolism and cell division pathways of rapidly proliferative cells [6, 7]. The dosages of a chemotherapeutic agent cannot be increased because high dosages lead to various side effects like bone marrow suppression,

cardiomyopathy, nephrotoxicity, neurotoxicity, and multidrug resistance [8]. Recently there has been an emerging trend in developing drugs from natural compounds to combat the problems associated with currently used chemo-preventive agents. It is well known that natural products can stimulate various physiological pathways with multiple targets which may have a beneficial effect with reduced side effects for treating stubborn diseases like various cancer types [9, 10].

Mangiferin or Mgf ($C_{19}H_{18}O_{11}$) (C-2-β-D-glucopyranosyl-1,3,6,7 tetrahydroxy xanthone, also named C-glucosyl xanthone) **Fig. 1** is a naturally occurring polyphenolic compound largely found in leaves and stem bark of *Mangifera indica* (Family Anacardiaceae), which is a tropical fruit having high nutritional and medicinal value [11, 12]. Mgf has been shown to exert various beneficial bioactivities, including antiviral, anticancer, antidiabetic, antioxidative, antiaging, immunomodulatory, hepatoprotective, and analgesic effects [13]. In this research work, we are more concerned about two bioactivities, *i.e.*, antioxidant and anticancer properties. Mgf exhibits a high level of antioxidants properties in both *in-vivo* and *in-vitro* conditions by quenching free radicals and reactive oxygen species (ROS) due to the presence of a pharmacophore *i.e.,* catechol moiety and free hydroxyl groups[14]. Mgf will prove to be a promising chemotherapeutic agent in the future because various researchers have investigated its involvement in treating cancer. For example, it has been reported that Mgf shows significant tumor growth inhibition in various cancer-induced animal models [15, 16]. Mgf shows its chemo-preventive and therapeutics activities by inhibiting cancer initiation, promotion, and metastasis due to its ability to suppress multiple molecular targets such as pro-inflammatory transcription factors, cell cycle proteins, inflammatory enzymes, kinases, chemokines, growth factors, adhesion molecules, and cytokines [17, 18].

However, despite its potent antioxidant and anticancer activities, the therapeutic application of Mgf is limited due to its poor hydrophilicity and lipophilicity. Due to low aqueous solubility and low intestinal permeability Mgf comes under class-IV of biopharmaceutics classification system. Besides, Mgf has shown to have extensive P-gp efflux, high first-pass metabolism and considerable metabolism stimulated by an enzyme present in gut enterocytes *i.e.*, cytochrome P450 and it also shows to have a short half-life due to the occurrence of rapid clearance from the body by glucuronidation of the hydroxyl groups which is present in the xanthone moiety [19, 20]. To overcome these problems and achieve maximum therapeutic effects of Mgf, novel nano-based drug delivery techniques need to be applied to enhance the release duration and improve the compound's bioavailability [21].

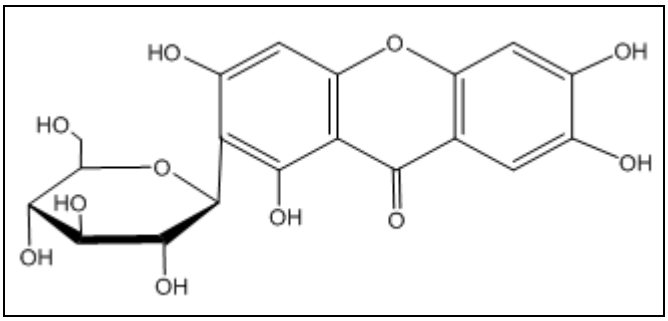

FIG. 1: CHEMICAL STRUCTURE OF MANGIFERIN (MGF)

Among these polymeric nanoparticles of Poly-D, L-lactide-co-glycolide (PLGA) has been extensively investigated due to its high biodegradability, low toxicity and high biocompatibility. The final degradation product is safe because it is degraded *in-vivo* by hydrolysis of the ester linkage to glycolic acid and lactic acid, which are then easily metabolized by the lungs and kidney and eliminated as water and carbon dioxide [22, 23]. This study aimed to fabricate PLGA nanoparticles containing Mgf and was tested for cytotoxicity in A549 lung cancer cell line. Various studies were conducted to characterize Nanoparticles such as particle size, surface charge, morphological analysis, encapsulation efficiency (EE), and drug loading (DL). In-vitro drug release and cytotoxicity studies were also conducted. The found-out results were discussed in the following sections.

Materials and Methods: All chemicals were research grade unless otherwise stated. Mangiferin was gifted by CSIR-NEIST, Jorhat, Assam. Poly-D, L-lactide-co-glycolide (PLGA) with a copolymer ratio of D, L-lactide co-glycolide of 50:50, molecular weight 30,000-60,000 was purchased from Sigma-Aldrich and PVA was

obtained from Loba Chemie Pvt Ltd (Mumbai, India). HPLC-grade acetone and methanol were purchased from Merck. Milli-Q water produced in-house (18.2 MΩ·cm at 25°C Millipore company). All chemicals used in cell culture were procured from standard vendors. A549 Cell line was obtained from NCCS, Pune, India. DMSO, MTT, DMEM, FBS, Trypsin-EDTA solution, Penicillin-streptomycin solution, and gentamycin solution were purchased from Himedia. A phosphate buffer saline tablet (pH 7.4 for cell culture) was brought from Merck.

Preparation of Mgf-NPs: Single emulsion (oil-water) solvent evaporation method is used to prepare nanoparticles. Briefly, PLGA was dissolved in an organic phase containing acetone, and Mgf was dissolved in methanol separately. Mgf and PLGA solution was mixed with three different concentrations of PVA aqueous solution such as 0.3%, 0.5% and 0.7% (which was heated and stirred previously to dissolve PVA completely). This mixture was sonicated using a probe sonicator for 10 min to produce the oil-in-water emulsion. The organic phase was evaporated by using a magnetic stirrer at room temperature. The NPs were recovered by ultracentrifugation at 12,000 rpm for 10 min (at 4 ºC) and washed three times with deionized water to remove free drugs. The washing solutions were eliminated by centrifugation using high-speed centrifuge. The produced suspension was lyophilized using freeze dryers to obtain fine NPs powder and kept under a vacuum desiccator. The composition for three prepared formulations is given in **Table 1,** and the percentage yield of Mgf-PLGA NPs were calculated gravimetrically [24-26].

TABLE 1: MGF-PLGA-NPS FORMULATION COMPOSITIONS

Formulation code	Drug (mg)	PLGA (mg)	PVA (%)
F1	3	35	0.3
F2	3	35	0.5
F3	3	35	0.7

Characterization of Nanoparticles:

Particle Size Distribution and Zeta Potential Analysis: Briefly, NPs (2-3 mg) were dispersed in 2 ml of milli Q water, then vortexed and sonicated for a few minutes for fine dispersions. The samples were diluted to a suitable concentration to prevent multi-scattering phenomena, and placed 2 ml of the sample was in a disposable glass cuvette. The dispersed NPs were analyzed for particle size and polydispersity index (PDI) by dynamic laser scattering (DLS) spectroscopy using Zetasizer at 250C. To determine the surface charge of the NPs zeta potential study was carried out by obtaining electrophoretic mobility of the diluted samples using the same instrument [27].

Morphological Analysis: Dried NPs were placed on a double-sided carbon tape, previously placed on a scanning electron microscope (SEM) stub, and loose NPs were removed using compressed air. Finally, the NPs were gold coated and analyzed by field emission scanning electron microscope (FESEM) [28, 29].

Mgf Encapsulation Efficiency (EE) and Drug Loading (DL): DL and EE were examined by extraction of Mgf from freeze-dried NPs using UV-VIS spectroscopy. Briefly, 10 mg of NPs were added to 10 ml of 1:1 mixture of acetone and methanol. The dispersion was subjected to a water bath shaker at room temperature. Then, the dispersion was centrifuged at 10,000 rpm for 15 mins to collect the clear supernatant which was filtered prior to taking the absorbance at λmax 369 nm. Quantification of Mgf was calculated according to the standard curve (10, 20, 30, 40, 50, 60 and 70 µg/ml) [30, 31]. The equation of the standard curve is as follows: A = 0.0137x+0.0131 (r = 0.9992). In this study, % EE and % DL was calculated using given formula

$$\% \text{ EE} = (\text{Amount of drug in the NPs}) / (\text{Drug added in the formulation}) \times 100$$

$$\% \text{ DL} = (\text{Mass of Mgf in the NPs}) / (\text{Mass of NPs}) \times 100$$

***In-vitro* Drug Release:** *A modified dissolution method examined the in-vitro release of Mgf from NPs*. In brief, the release study was carried out using pH 7.4 phosphate buffer saline (PBS) as PBS can mimic the physiological condition where the drug-loaded NPs are expected to be exposed during circulation in the body. Briefly, 20 mg of Mgf-PLGA NPs was suspended in a beaker containing 15 ml of PBS (pH 7.4) and incubated at 37 ± 0.5 ºc in a water bath shaker at 100 rpm. At predetermined intervals (i.e., 0, 2, 4, 6, 8, 24, 48, 72, 120, 144, 168, 216, 264, 312, 336 and 360 Hrs.)

An aliquot of 4.5 ml samples was withdrawn and replaced with the same amount of fresh buffer solution to maintain the perfect sink condition. Then the withdrawn aliquot was transferred to a centrifuge tube and centrifuged at 15,000 rpm for 10 mins. The supernatant was collected, and 0.5 ml of methanol was added and analyzed at 369 nm using a UV-VIS spectrophotometer. The amount of drug release was calculated from the calibration curve of Mgf in PBS-methanol by converting drug concentration in solution to the percentage of drug release [32, 33].

***In-vitro* Cytotoxicity Study:** The *in-vitro* cytotoxic activities of Mgf-PLGA NPs were compared with the free drug solutions of Mgf on A549 cancer cell line by MTT (3- (4,5-dimethylthiazol – 2 - yl) - 2, 5 -diphenyltetrazolium bromide, a tetrazole) assay. The comparison was also made concerning cytotoxic activity of single drug and the combination of drug with polymers in the form of NPs. The IC_{50} values were determined. In brief, the cultured cells were trypsinized and diluted in DMEM to give a total cell count of 1×10^4 cells/ml, which was determined by a haemocytometer. The cell suspension was then transferred to 96 well plates to ensure 10,000 cells/well and allowed to attach overnight. The medium was changed to 100 µl medium containing free Mgf and Mgf-PLGA NPs of different concentrations (2, 4, 8, 15, 30, 50, 70, 80 µg/ml). The free Mgf and Mgf-PLGA NPs were dissolved and diluted with complete media (the concentration of DMSO was different in the final serial diluted media but was less than 0.1 %). Each formulation dilution was assessed in triplicate. Three wells containing only cells suspended in a complete medium were used as controls for cell viability. After incubation for 24, 48, and 72 hrs, the suspension was removed, and the wells were washed with PBS. 20 µl of MTT (5 mg/ml) and 100 µl of medium were added and incubated for around 3–4 Hrs. Then the media containing MTT was removed, leaving the precipitate. DMSO (100 µl) was added to the wells, and the plate was covered with aluminum foil to incubate on a shaker for 30 minutes to obtain the purple formazan. The plate was observed in a microplate reader at 570 nm using DMSO as blank [34]. The % cell viability was calculated using the given formula;

% Cell Viability = (Absorbance of sample-Absorbance of blank) / (Absorbance of control-Absorbance of blank)) × 100

RESULTS AND DISCUSSION:

Preparation of Mangiferin Loaded PLGA Nanoparticles: Mgf is a hydrophobic polyphenol with anticancer activity towards different cancer cells [35]. The therapeutic efficacy of Mgf can be improved by increasing its bioavailability through protection from degradation and metabolism. The free compound was encapsulated in polymeric nanoparticles to improve the systemic bioavailability of free Mgf. To obtain a high yield of nanoparticles, PLGA has been widely used as a carrier for drug delivery applications of hydrophobic drugs such as polyphenols due to its biodegradability, biocompatibility, and high stability. It has also gained approval by the USA Food and Drug Administration [36]. One of the most commonly used functional excipients in PLGA nanoparticle formulation is polyvinyl alcohol (PVA), partially hydrolyzed polyvinyl acetate due to its ability to reduce interfacial tension, which results in increasing emulsion stability and due to its high affinity to the PLGA particles, it acts as an efficient steric stabilizer that provides stability of the resulting nanosuspension [37].

TABLE 2: EFFECTS OF DIFFERENT PVA CONCENTRATIONS ON DIFFERENT PARAMETERS OF PREPARED NPs

Parameters	F1	F2	F3
Yield (%)	77.28	71.31	68.34
EE (%)	87.65	43.28	21.82
DL (%)	8.95	4.42	2.22
MPS (nm) ± SD	137.7 ± 7.33	301.3 ± 6.70	274.7 ± 18.88
PDI ± SD	0.165 ± 0.002	0.189 ± 0.004	0.205 ± 0.002
ZP (mV)± SD	-13.50 ± 3.05	-11.25 ± 5.26	-6.12 ± 1.08

The single-emulsion solvent-evaporation method was successfully utilized for preparing three different Mgf-PLGA NPs formulations with different ratios of PVA (i.e., 0.3 %, 0.5 % and 0.7

%) and characterized according to the different parameters, such as measurements of mean particle size (MPS), polydispersity index (PDI), zeta potential (ZP), encapsulation efficiency (EE %) and drug loading (DL %) in order to find the most optimal Mgf-PLGA NPs composition as given in **Table 2.**

Characterization and Optimization of Prepared NPs: In this study, all formulated NPs achieved a % yield value between 68.34-77.28 %. The results showed that the percentage yield was largely dependent on the reaction process variables, i.e., an increase in PVA concentration reduced yield of the formulation. Mgf entrapment in different formulations were determined spectrophoto-metrically and the highest drug EE and DL obtained in optimized formulation F1 (i.e., NPs with 0.3 % PVA concentration) with 87.65 % EE, and 8.95 % loading value. And lowest was obtained in formulation with 0.7 % PVA concentration i.e., 21.82% with drug loading of 2.22%. A clear correlation can be observed between the particle yield and encapsulation efficiency at each of the formulations, which means the higher the yield, the higher the drug entrapment.

Particle size is an important parameter in nanoparticle-based drug delivery systems because it affects the pharmaceutical properties of the drug. The homogeneity of the size of the formulation is said to be an indicator of stability [38]. It is also known that particle size <10 nm is rapidly eliminated from the body by renal clearance. The particle size >300 nm is easily recognized by the reticuloendothelial system and removed from the blood circulation. Therefore, it has been said that nanoparticles ranging from 10-200 nm could extravasate from the disorganized tumor vasculature to the tumor microenvironment due to tumor angiogenesis. Therefore, manufacturing nanoparticles less than 200 nm in size and with a negative surface charge are desirable to prevent protein adsorption and promote accumulation in tumors [39].

DLS was used to measure the hydrodynamic size, prepared formulations PDI, and zeta potential. PDI was determined to examine the narrowness of the particle size distribution. The higher value of PDI, i.e., PDI >0.5 indicates the distribution of NPs with variable size range. This results in the formation of aggregates and could result in low stability of particle suspension and low homogeneity. Zeta potential indicated the surface charge on the particles and was measured to determine the stability of nanoparticles in the suspension. As the zeta potential increases, repulsion between particles will be greater, leading to more stable colloidal dispersion. If all particles in the suspension have a large negative or positive zeta potential, then they will tend to repel each other, and there will be no tendency for the particles to come together [40]. Literature has reported that NPs with zeta potential values greater than +25 mV or less than -25 mV typically have high degrees of stability, whereas dispersions with a low zeta potential value will eventually aggregate due to van der Waal inter-particle attractions [41].

In this Mgf-PLGA nanoparticle formulation process, the PVA solution act as a stabilizer. The effect of process variables, such as different PVA concentrations, is given in **Table 2**. The formulation was optimized at 0.3 % PVA concentration (F1) resulting in the smallest range of particle size 137.7 ± 7.33nm, PDI 0.165 ± 0.002, **Fig. 1** zeta potential -13.50 ± 3.05 **Fig. 2** which indicates the narrow particle size distribution with good stability.

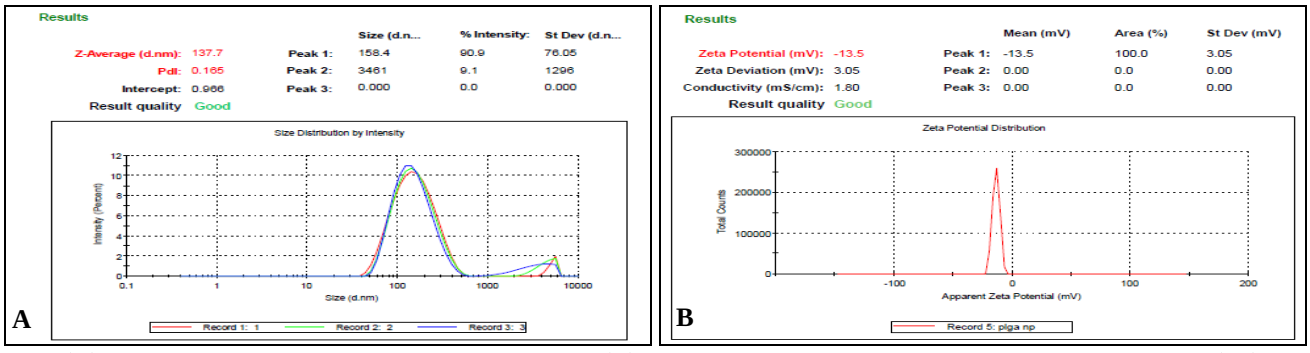

FIG. 2: (A) PARTICLE SIZE DISTRIBUTION AND (B) ZETA POTENTIAL GRAPH OF OPTIMIZED (F1) MGF-PLGA NPs

The surface morphology of the optimized formulation was analyzed using FESEM, and the obtained result showed homogeneous size distribution. It was found to be spherical and oval without any agglomeration **Fig. 3.**

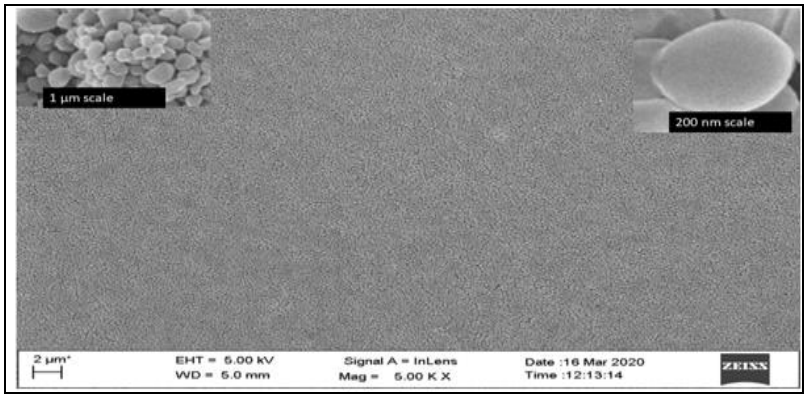

FIG. 3: SEM ANALYSIS: SURFACE MORPHOLOGY OF OPTIMIZED (F1) MGF- PLGA NPs

A stock solution of standard Mgf was prepared. Various dilutions of the stock solution were made in PBS (pH 7.4) to get the concentration in the range of 10-70 µg/ ml and the absorbance of the various dilutions was taken at 369 nm using a UV visible spectrophotometer to plot a linear calibration curve of standard Mgf **Fig. 4** to calculate drug release profile from the polymer matrix.

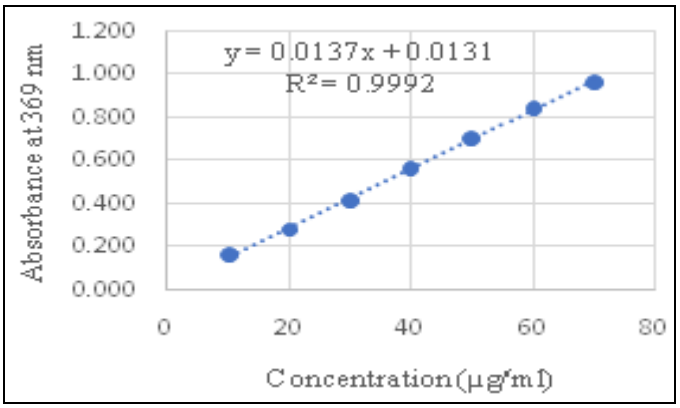

FIG. 4: GRAPHICAL REPRESENTATION OF MGF CALIBRATION CURVE

***In-vitro* Drug Release:** The *in-vitro* release of Mgf from PLGA was carried out in PBS at pH 7.4 (the temperature at 37 ± 0.5ºC) for 15 days. From the observed data we can say that the release occurs in two stages, first initial burst release followed by continuous release up to 15 days. For better understanding of drug release profile, a graph was plotted using percent drug release in Y-axis and time in X-axis **Fig. 5**. Stage I is the initial burst release stage which is observed within first 24 hrs. which is followed by a stage II, where slow and continuous release has been observed up to 15 days. The initial burst release occurred during first 4 hrs. with cumulative Mgf % release of 28.48 ± 0.83 %, which may be due to the poor Mgf entrapment in the polymer matrix. After 15 days, slower and continuous release of Mgf occurred with cumulative % release of 70.53 ± 1.06 %. The reason may be due to the diffusion of the drug localized in the PLGA core of the nanoparticles. These data indicated that Mgf might be useful as a controlled release system for anticancer treatment because an anticancer treatment demands a longer duration of action of the drug. The initial release gives maximum relief immediately, and the following control release is desirable to avoid repeated administration.

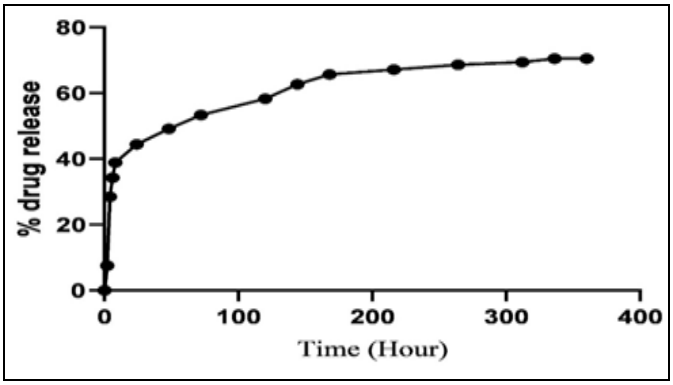

FIG. 5: *IN-VITRO* % DRUG RELEASE GRAPHICS OF OPTIMIZED FORMULATION I.E., F1

The antiproliferative activity of the Mgf-PLGA NPs and free Mgf were determined by MTT assay using A549 lung cancer cell line. The different concentration of both free drug and Mgf-PLGA NPs showed a dose-dependent percentage inhibition after 48 hrs of incubation, indicating a

decrease in cell viability and growth. The result of the cell viability studies of both free drug and drug loaded nanoparticles against A549 cell lines were represented graphically while that of control A549 cell group, free drug treated A549 cell group and Mgf -PLGA NPs treated cell groups are shown in **Fig. 6**. The sublethal doses of drugs/ IC_{50} was calculated and found to be 67.15 µg/ml, 27.06 µg/ml for free Mgf and Mgf -PLGA NPs respectively. This result showed a significant reduction of the IC_{50} value with Mgf -PLGA NPs than the free drug, indicating that Mgf -PLGA NPs were more effective in arresting cell growth than free Mgf.

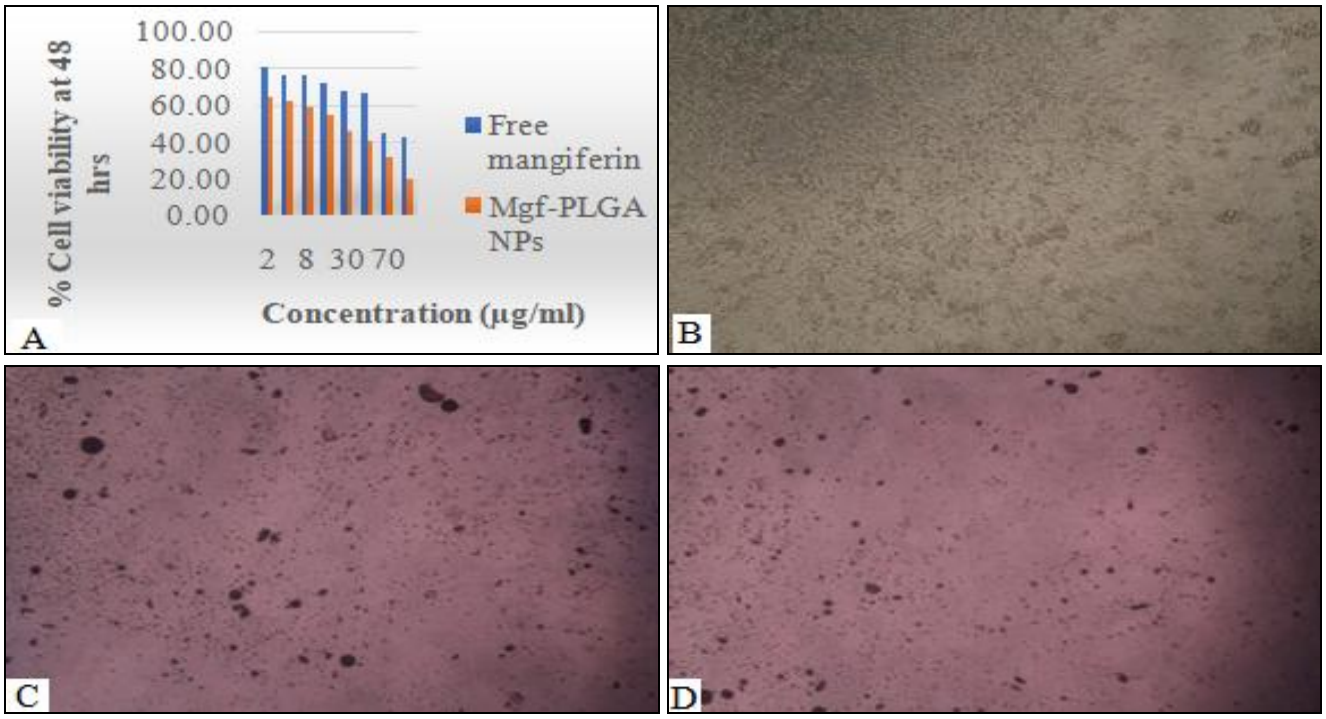

FIG. 6: (A) GRAPHICAL REPRESENTATION OF % CELL VIABILITY AFTER 48 HRS INCUBATION WITH BOTH FREE MGF AND MGF -PLGA NPS (B) A549 CONTROL GROUP (C) A549 TREATED WITH FREE MGF (D) A549 TREATED WITH MGF-PLGA NPs

CONCLUSION: Nanoparticles of Mgf were developed by a single emulsion-solvent evaporation technique characterized and optimized based on the particle size, PDI, zeta potential, yield, drug entrapment and drug loading. Among the three different formulations, formulation with 0.3% PVA concentration was optimized with an average particle size of 137.7 nm, PDI of 0.165, zeta potential of -13.50 mV, yield of 77.28 %, high entrapment value of 87.65 %, and loading value of 8.95%.

SEM image confirms the optimized formulation's surface morphology, which was spherical in shape with smooth surface. *In-vitro* release study and release kinetics shows the Mgf release from the polymer matrix in a controlled manner. Furthermore, *in-vitro* cytotoxicity assay shows that the prepared nanoparticles' anticancer activity was much better compared to pure Mgf. The overall result suggests that PLGA polymer-based nanoparticles could be a potential option for Mgf delivery for cancer therapy.

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