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SYNTHESIS AND EVALUATION OF MESOPOROUS SILICA NANOPARTICLES (MSN) LOADED COX-II INHIBITOR – MELOXICAM FOR TARGETED COLORECTAL CANCER TREATMENT

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ABSTRACT: Polymer functionalised mesoporous silica nanoparticles hold great promise to enhance drug targeting and cell internalisation for cancer cells. Since the presence of abundant folate receptors on cancer cells, folic acid functionalised mesoporous silica nanoparticles (MSN) were used as folate marker and polyethyleneimine was used to improve cell internalisation. Meloxicam was loaded into the pores of nanoparticles through $-NH_2$ linker and polyethyleneimine-folic acid was grafted onto mesoporous silica nanoparticles. The functionalised MSN were characterised for particle size, surface charge, and elemental analysis. The release of meloxicam from the functionalised nanoparticles exhibited sustained release through membrane diffusion drug release method. Cell viability and cytotoxicity study was performed using HT-29 Human Colon cancer cell line as an *in-vitro* model. The results of scanning electron microscopy and energy dispersive spectroscopy demonstrated the presence of SiO_2 group and the particle size of functionalised nanoparticles to be between 200-800 nm. The zeta potential of the coated MSN exhibited positive surface charge, enhancing the targeting of negatively charged cancer cells and cell internalisation. Moreover, the cytotoxicity studies indicated the uptake of Meloxicam from the functionalised particles. The study provides evidence that polymeric coating eased the cell internalisation of MSN into the cancer cells. Results indicated that Meloxicam delivered with the help of mesoporous silica nanoparticles coated with polyethyleneimine and folic acid increased the *in vitro* cytotoxicity, enhancing antitumor activity.

INTRODUCTION: Colon cancer is one of the most prevalent cancer and is ranked as the second most common type of cancer¹. However, when colorectal cancer reaches to stage III, it causes uncontrolled growth and uncontrolled cell proliferation leading to metastasis².

The cancerous cells penetrate the walls of blood vessels, after which these circulating tumour cells need new blood cells for growth and spread across the body. This refers to as angiogenesis³.

Many anti-angiogenesis drugs were used, but these drugs were not found to be efficacious for long term treatment⁴⁻⁶. This might be because of development of resistance towards antiangiogenic agents by the metastatic cancer cells. Meloxicam as NSAIDs, is selective COX-II inhibitor. COX-II influences all aspects of cancer cells like, cell proliferation, survival, motility, invasiveness and apoptosis resistance⁷.

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Inhibition of COX-II activity by Meloxicam may execute its antitumor effects by blocking PEG-2 regulated cell signalling pathways⁸⁻¹¹. This, indicates that Meloxicam's anti-angiogenic activity interfere with the growth of metastatic tumours. Meloxicam might have therapeutic potential for metastasis of colorectal cancer¹²⁻¹⁴. The purpose of this study was to investigate the effect of Meloxicam, a selective COX-II inhibitor for antitumor activity delivered through mesoporous silica nanoparticles (MSN). Mesoporous silica nanoparticles were synthesised by sol-gel process¹⁵⁻¹⁸. The synthesised MSN were functionalised with -NH₂ linker with the help of 3-aminopropyl triethoxysilane (APTES). Meloxicam was loaded on MSN through -NH₂ linker, followed by polyethyleneimine (PEI) coating to facilitate cell internalisation and then functionalisation with folic acid to target folate receptors on cancer cells. The functionalised MSN were then characterised for drug loading efficiency, particles size, surface charge, release profile of drug and were subsequently tested for *in vitro* cytotoxicity.

MATERIALS AND MATHOD:

Materials: Meloxicam was obtained as a free gift sample from Apex Healthcare, Mumbai, India. Folic acid was obtained as a free gift sample from LOBA chemie Pvt. Ltd., Mumbai, India. Pluronic P-123, Tetraethyl orthosilicate (TEOS) and 3-aminopropyl triethoxysilane (APTES) was purchased from Sigma-Aldrich, India. Polyethyleneimine (PEI) was purchased from TCI chemicals Pvt Limited, India. All other reagents in the experiments were of analytical grade, HPLC grade solvents for HPLC analysis and used without additional purification.

Preparation of Mesoporous Silica Nanoparticles:

Mesoporous silica nanoparticles (MSN) were prepared by using Sol-Gel method. To the mixture of surfactant Pluronic P-123 and 0.2M HCl solution, tetraethyl - orthosilicate was added dropwise and kept on stirrer at 300 rpm for 20 hours. After stirring, the solution was kept in oven for aging at 80 °C. The particles formed were separated through vacuum filtration and washed with ethanol and water in the ratio of 1:1, 3:2, 1:0, 1:0, 1:0 to remove the surfactant template. Traces of surfactant were further removed by refluxing the particles for 7 hours with ethanol and HCl.

The particles were -NH₂ functionalized by 3-aminopropyl triethoxysilane (APTES). Synthesised MSN were dispersed in toluene and ATPES was added to this mixture. The mixture was stirred for 24 hours. After stirring, the particles were centrifuged at 10,000 rpm for 20 mins. The particles were then washed with methanol and water.

Preparation of Meloxicam Loaded Mesoporous Silica Nanoparticles:

Meloxicam was loaded onto synthesised -NH₂ functionalised MSN by dissolving Meloxicam in dimethyl formamide and MSN. The dispersion was stirred at 300 rpm for 24 hours at room temperature. After stirring, the particles were separated and the supernatant was collected. The particles were washed with methanol to remove the excess of drug from the surface of particles.

Drug loaded particles were coated with polyethyleneimine. 50mg of drug loaded particles were dispersed in 5ml methanol and to 2.5mg/ml of ethanolic solution of polyethyleneimine. This mixture was stirred at 300 rpm for 30 minutes at room temperature.

Folic acid was functionalised onto polyethyleneimine coated nanoparticles. To 10ml dimethyl sulfoxide (DMSO), 25mg of folic acid was dissolved. To this solution MSN's were dispersed and stirred at 300 rpm for 24 hrs. After 24 hrs, the folic acid functionalised particles were subjected to centrifugation at 10,000 rpm for 20 mins at room temperature. After separation of the particles, the supernatant was collected. The particles were washed with ethanol and dried at 70°C.

Characterisation of Functionalised Nanoparticles:

FT-IR analysis was carried out to confirm the functionalisation on MSN. Zeta potential instrument (Malvern Nano Zetasizer ZEN3690) was used to study particle size and surface charge of the functionalised nanoparticles. A SEM (Icon analytical laboratories) was used to study the overall shape and size of the nanoparticles. EDS on SEM was used to study the elemental composition of silica nanoparticles.

Determination of Meloxicam Loading Efficiency of Nanoparticles:

The loading efficiency of drug

was back calculated using Shimadzu, UV spectrophotometry, model-Lambda 25. The supernatant collected after drug loading and folic acid functionalisation was collected and scanned for the amount of unloaded drug and folic acid.

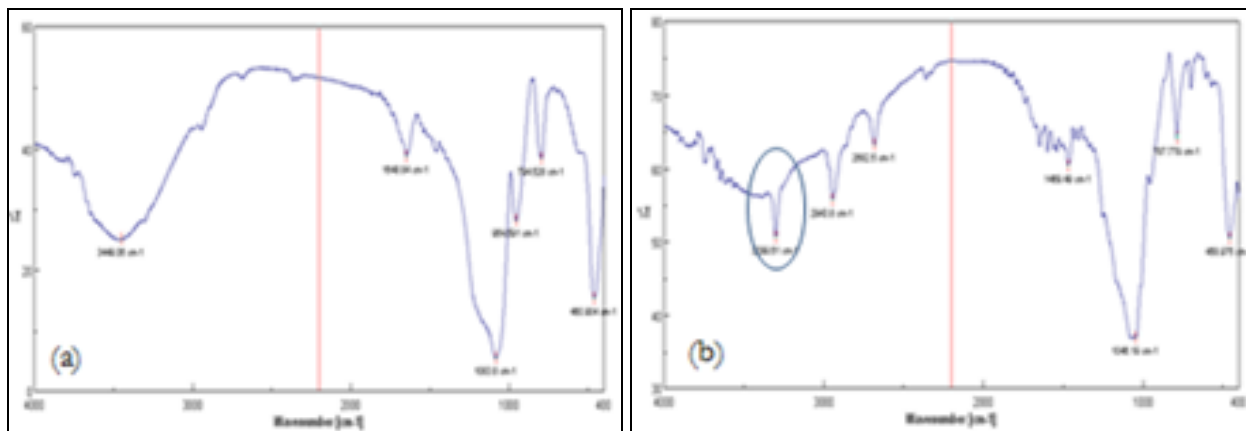
Determination of Meloxicam Content in Nanoparticles: Assay was performed to determine the drug content of functionalised MSN with validated HPLC method using Perkin Elmer, manual HPLC, model- Series 200- HPLC with Total chrome Navigator, Series 200-UV/Vis LC detector, Series 200- LC pump. The particles were dispersed in N, N-dimethyl formamide and sonicated for 15 minutes. After sonication, the particles were separated and 1 ml of supernatant was diluted with HPLC mobile phase. The mobile phase used was 0.02M potassium dihydrogen phosphate buffer pH 3.5 and acetonitrile (40:60). The column used was C18 (4.6 x 150mm) 5 μ m. The solution was injected in HPLC at a flow rate of 0.5ml/min and detected at 360nm and the drug content was calculated.

In vitro Release Experiment: The *in vitro* release profile of Meloxicam from silica nanoparticles was studied with help of phosphate buffer saline of pH 6.8. The study was performed by adding the dispersion of 10mg of product in 1ml of phosphate buffer saline of pH 6.8, in dialysis membrane having 50mm pore diameter. The membrane was added in the measuring cylinder with 30ml of PBS maintained at room temperature with gentle stirring at 150 RPM for 24 hrs. At different time intervals 5ml of aliquots were withdrawn and replaced with equal volume of buffer solution. Collected samples were analysed for Meloxicam released.

Cell Culture and Cytotoxicity of Functionalised Nanoparticles: HT-29 colorectal cancer cells were grown in RPMI 1640 medium containing 10% fetal bovine serum and 2mM L-glutamine. Cytotoxicity was assessed on HT-29 cells using SRB assay which was conducted at Tata Memorial Centre's Advance Centre for Treatment Research and Education in Cancer. Cells were inoculated into 96 well microtiter plates in 100 μ L at plating densities depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates were incubated at 37 °C, 5% CO₂, 95% air and 100% relative humidity for 24 hr prior to addition of experimental drug. The study was carried out for five samples Sample 1 (code: MEL), Sample 2 (Code: MSME), Sample 3 (Code: MSFAPE), Sample 4 (Code: MSMEFA), Sample 5 (Code: MSMFP). Meloxicam at different concentrations (10, 20, 40 and 80 μ g/ml) was added in triplicate in each well separately and cells were incubated at 37 °C for 48 hrs.

RESULTS: The formulation of mesoporous silica nanoparticles loaded with Meloxicam was developed using sol-gel method. Drug loading and surface functionalisation was confirmed by FT-IR analysis.

In the IR interpretations the peaks at 3299.61cm in **Fig. 1(b)** represents the NH stretch which indicates that NH functionalisation was successful. Drug was loaded onto MSN with the help of NH- linker. In **Fig. 1(c)** the peak intensity reduces indicating successful drug loading onto MSN. After the drug loading folic acid functionalization was done. In **Fig. 1(d)** the peak around 3250cm completely disappears.



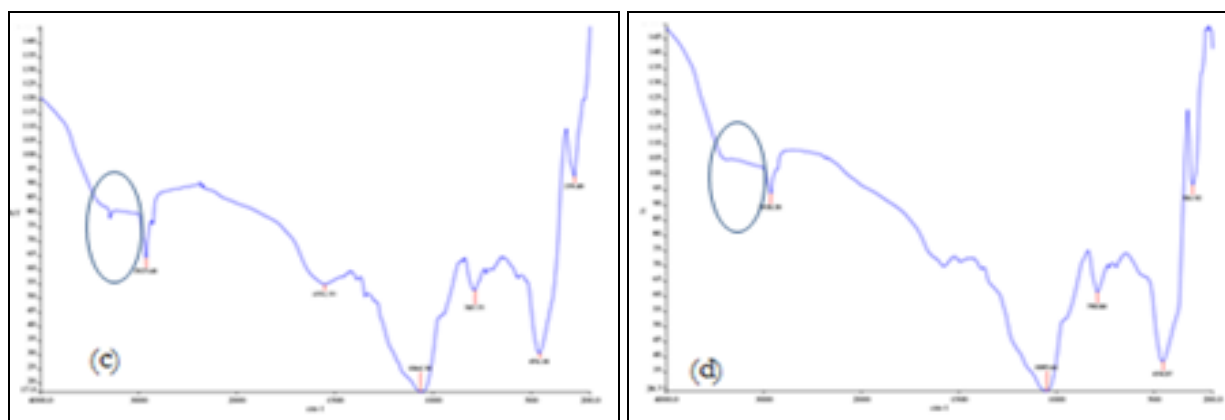


FIG. 1: FT-IR SPECTRA OF (A) PLAIN MSN (B) APTES FUNCTIONALISED MSN (C) DRUG LOADED MSN (D) FOLIC ACID FUNCTIONALISED MSN

Assay of the functionalised MSN was performed on HPLC. The % Drug content was calculated

using the peak area obtained from the sample. The drug content was found to be 93%.

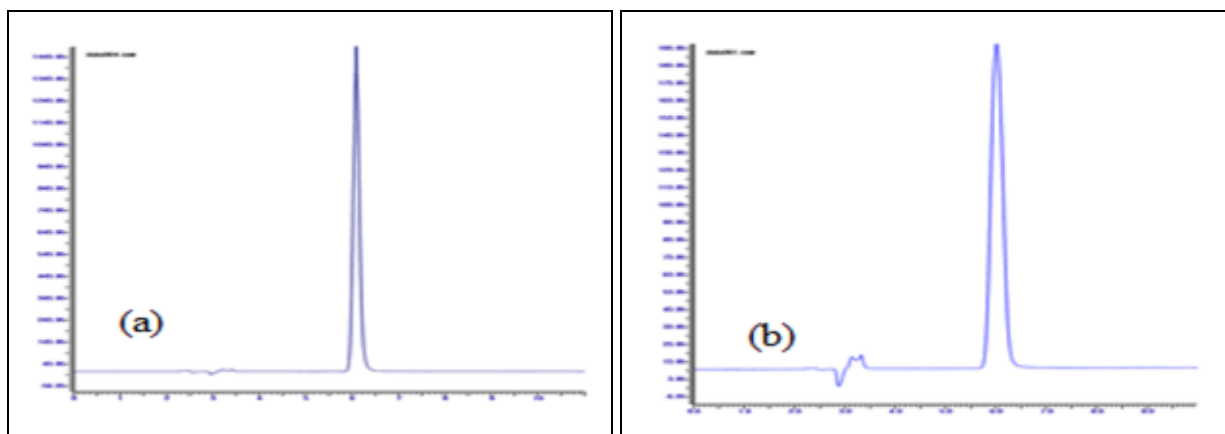


FIG. 2: (A) CHROMATOGRAM OF MELOXICAM STANDARD SOLUTION (B) ASSAY CHROMATOGRAM OF MELOXICAM FUNCTIONALISED MSN

TABLE 1: PHYSICAL PROPERTIES, ZETA POTENTIAL AND LOADING EFFICIENCY OF FUNCTIONALISED MSN

Batch No.	Weight Ratio	Zeta size (nm) \pm SD	Polydispersity	Zeta potential \pm SD	% Drug Loading efficiency	% Folic acid functionalised
Batch III (trial batch)	1:5:5	-	-	-	73%	94%
Batch III Code: MSME	1:0:0	-	-	-	85%	-
Batch IV Code: MSFAPE	0:4:1	-	-	-	-	93.4%
Batch IV Code: MSMEFA	8:0:1	130 \pm 9.4	1	-0.916 \pm 4.10	86.09%	95.8%
Batch IV Code: MSMFP	14:1:1	169.8 \pm 16.4	0.826	28.7 \pm 4.00	86.1%	95.1%

Surface charge of the particle with and without the presence of PEI was determined. The presence of PEI on functionalised MSN (Batch MSMFP) effectively made the zeta potential positive. Whereas, the zeta size in the presence of PEI was observed to be higher than the uncoated particles. Silica nanoparticles represent average particle size ranging from 200 - 400 nm.

Energy dispersive spectroscopy is an elemental analysis performed on SEM. It was studied to determine the formation of SiO₂ particles. The formation of SiO₂ particles F (factor for redox reaction) should be one. The peaks of oxygen and silica are based upon their energy utilised by the number of atoms in the orbit of the molecule. (Fig. 3).

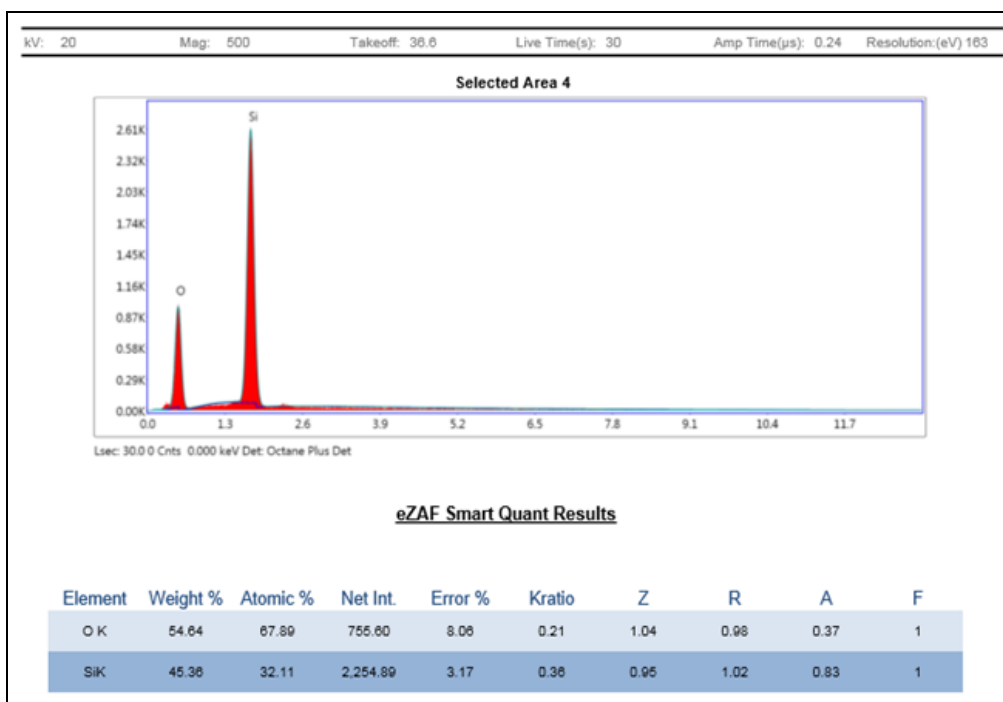


FIG. 3: ENERGY DISPERSIVE SPECTROSCOPY OF FUNCTIONALISED PARTICLES

The particle size was further measured by scanning electron microscopy, the particle size was ranging from 200 - 800 nm. (Fig. 4).

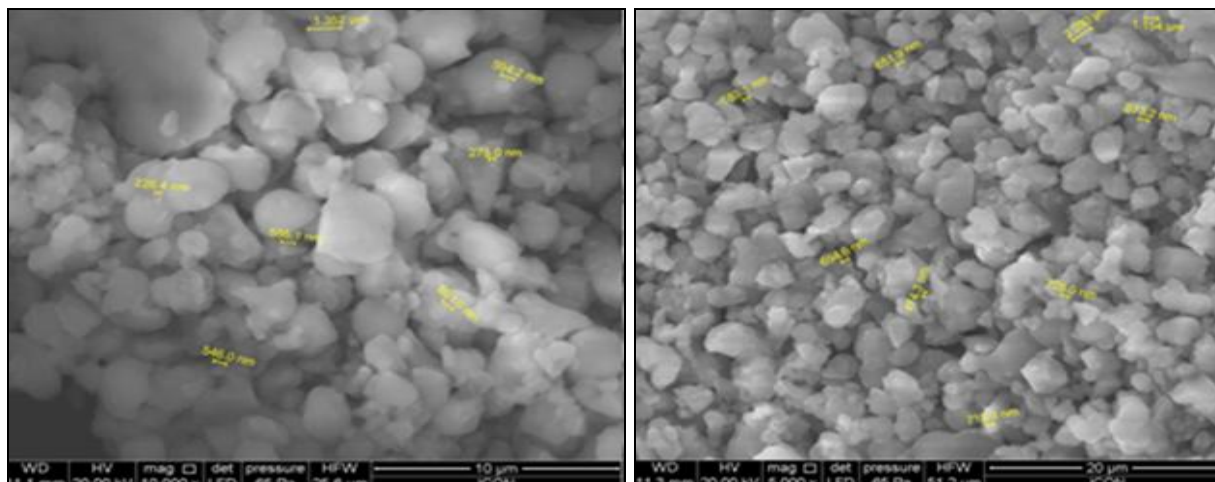


FIG. 4: SEM IMAGES OF FUNCTIONALISED MSN PARTICLES

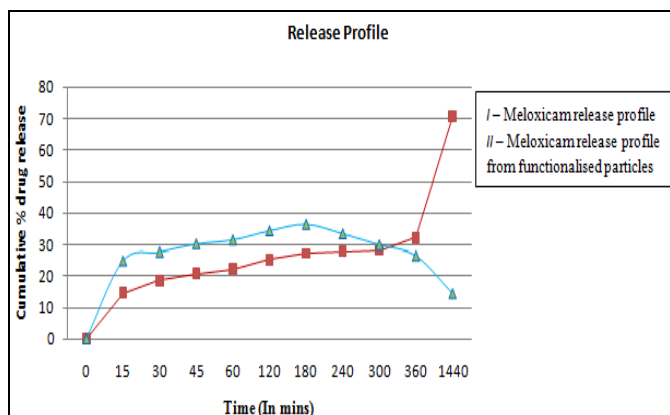


FIG. 5: RELEASE PROFILE OF MELOXICAM AND MELOXICAM LOADED SILICA NANOPARTICLES

As is evident from (Fig. 5) there was significant difference in Meloxicam release profile of Meloxicam alone and release profile of Meloxicam from batch code MSMFP. Meloxicam released from the formulation was approximately 36.2% within 3 hours, which reduced by 14% after 24 hours.

The *in vitro* cell viability and toxicity study was also performed to analyse cytotoxicity of Meloxicam from the formulation. An SRB assay was carried out on HT-29 cells to determine the Cell toxicity and viability of the final product.

The study was conducted at Advance Centre for Treatment Research and Education in cancer (ACTREC). The GI₅₀ value of formulation was <10 indicating activity. The cell proliferation inhibitory effect of formulation was significantly higher than Meloxicam alone.

inhibitor responsible to inhibit cell proliferation of cancer cells.

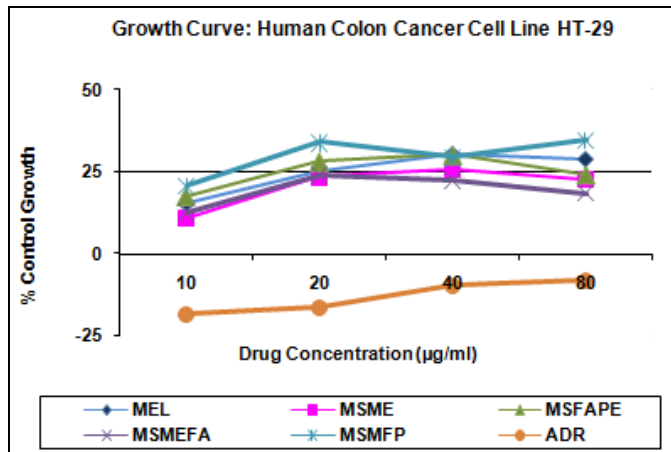


FIG. 6: GROWTH CURVE OF HUMAN COLON CANCER CELL LINE HT-29

The results obtained from the *in vitro* cytotoxicity by cell proliferation inhibitory effect. These obtained results confirm the fact that there is an exceptional effect of Meloxicam as a COX-II

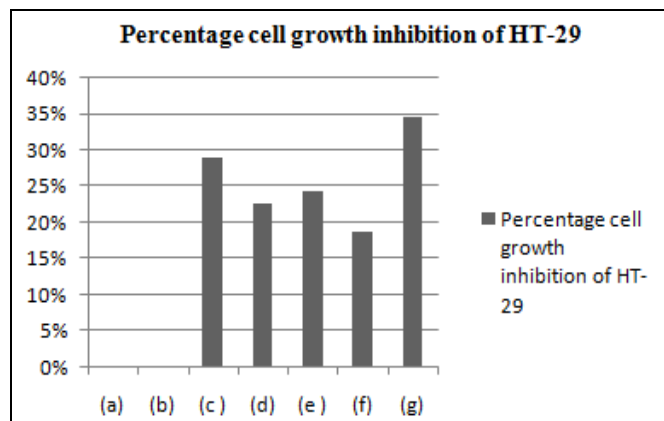
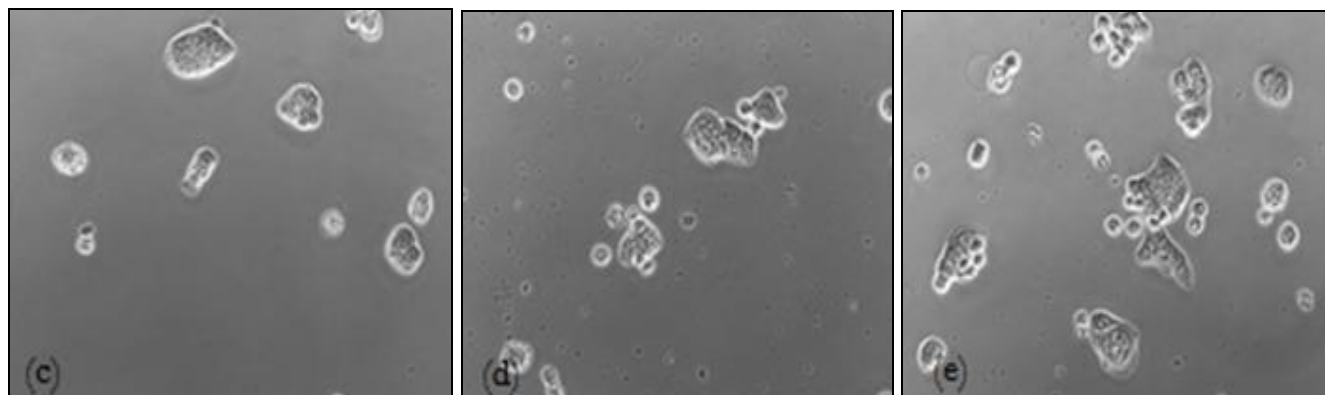
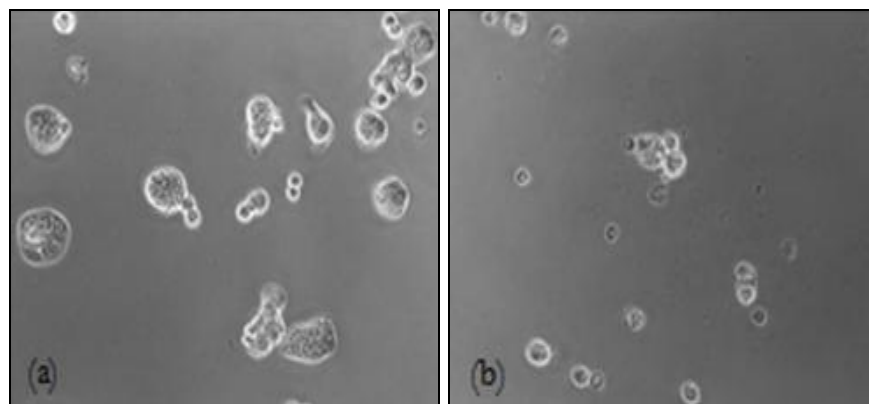


FIG. 7: PERCENTAGE CELL GROWTH INHIBITION OF HT-29 EXHIBITED BY FUNCTIONALISED MSN (A) HT-29 CONTROL (B) HT-29 POSITIVE CONTROL (C) HT-29 MELOXICAM (D) HT-29 MSN LOADED MELOXICAM (E) HT-29 POLYTETHYLIMINE-FOLIC ACID GRAFTED MSN (F) HT-29 MELOXICAM AND FOLI ACID FUNCTIONALISED MSN (G) HT-29 MELOXICAM AND POLYTEHYLENEIMINE-FOLIC ACID GRAFTED MSN

The morphological changes in HT-29 cells incubated with the samples were also studied using Bright field microscopy.



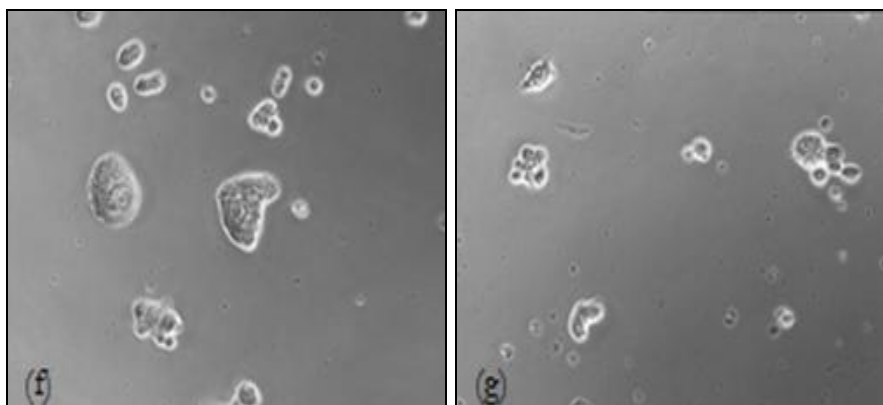


FIG. 8: BRIGHT FIELD IMAGES OF HT-29 HUMAN COLON CELLS WITH OR WITHOUT TREATMENT OF MELOXICAM AND MELOXICAM LOADED SILICA NANOPARTICLES (A) HT-29 CONTROL (B) HT-29 POSITIVE CONTROL (C) HT-29 MELOXICAM (D) HT-29 MSN LOADED MELOXICAM (E) HT-29 POLYTETHYLIMINE-FOLIC ACID GRAFTED MSN (F) HT-29 MELOXICAM AND FOLIC ACID FUNCTIONALISED MSN (G) HT-29 MELOXICAM AND POLYTEHYLENEIMINE-FOLIC ACID GRAFTED MSN

The controlled HT-29 human colon cancer cells (**Fig. 8 (a)**) showed no morphological changes. In HT-29 positive control with Adriamycin (**Fig. 8b**) most of the cells were shrunken and dead. HT-29 cells were treated with drug loaded silica nanoparticles and exhibited shrunken morphologies. The final product MSMFP containing drug, polyethyleneimine coating and functionalized folic acid (**Fig. 8g**) showed maximum cell growth inhibition where cell morphologies showed round and shrunken cells more than MSMEFA containing drug and functionalised Folic acid (**Fig. 8f**). Meloxicam alone (**Fig. 8c**) also showed some activity but less than as compared to final product MSMFP. Whereas, MSN and drug alone (**Fig. 8d**) and MSN coated with polyethyleneimine and functionalised Folic acid (**Fig. 8e**) showed less cell death than other groups. Our data showed that Meloxicam treatment decreased HT-29 cell proliferation in concentration dependent manner. In comparison to the control, 80µg/ml of meloxicam in 48 hrs inhibited cell viability by 34.7%.

DISCUSSION: Meloxicam is one of the NSAIDs which is commonly used for treatment of arthritis and osteoarthritis. But the promising properties of Meloxicam as, COX-II inhibitor, mainly associated with cancer cells, promoting cytotoxicity enable this compound to be a potential antitumor agent¹⁹. Mesoporous silica nanoparticles have emerged as promising drug delivery systems which improves the efficacy of targeted therapeutic agents to the site of actions^{20, 21}. They have been extensively used for drug loading of various bioactive

molecules and also hydrophilic and hydrophobic drugs^{22 - 24}. The objective of the study was to investigate whether Meloxicam loaded mesoporous silica nanoparticles can prove to be effective for antitumor activity compared to Meloxicam alone which have proved some antitumor activity.

MSN were synthesised using Pluronic P-123 as a template for structure directing agent and tetraethylorthosilicate. Through FT-IR analysis the formation of silica nanoparticles was confirmed. Furthermore, the EDS analysis also confirmed the formation of SiO₂ particles. Functionalisation was also confirmed using FT-IR analysis. The intensity of -NH₂ group was targeted to analyse the functionalisation. As Meloxicam is loaded the intensity of the NH₂ peak decreases whereas, after folic acid functionalisation the peak completely resolves indicating functionalisation.

Nanoparticle size plays a key role in the interaction and activation of drug molecules in cells. Recent research has shown that nanoparticles less than 100 nm in size could result in severe cytotoxicity due to nonspecific cellular interactions. Also previous reports suggested that particles with an average particle size of approximately 150 - 300 nm should be favourable due to ease of internalisation considering the EPR (Enhanced Permeability and Retention) effect²⁵. Characterisation of functionalised particles indicated the size range between 200 -800 nm. Moreover, the functionalised particles had an approximately positive surface charge due to the presence of polyethyleneimine^{26 - 28}.

The zeta potential value of the final product was found to be +28.7 mV whereas batch MSMEFA which was not coated with polyethyleneimine exhibited a negative shift in surface charge to -0.919 mV. The positive zeta potential of MSMFP facilitated cellular internalisation through negatively charged cell membrane during biological investigations. Hence, from the cell toxicity study it is very evident that the particle size of the MSN was appropriate to ease internalisation. The polymeric coating of polyethyleneimine exhibited a key role in cell internalisation as compared to the uncoated particles which exhibited negative charge

The *in vitro* release profile showed 36.9% meloxicam release from the formulation. On other hand, the results obtained from the *in vitro* cytotoxicity showed 34.7% of cell proliferation inhibitory effect. Hence, from the cell toxicity study it is very evident that the particle size of the MSN was appropriate to ease internalisation. As well as the polymeric coating of polyethyleneimine exhibited a key role in cell internalisation. The treatment with Meloxicam for 48 hours with the concentration of 80 µg/ml showed the highest cell growth inhibition indicating a positive possibility to outlook on the use of Meloxicam as anti-angiogenic and anticancer agent. These obtained results confirm the fact that there is an exceptional effect of Meloxicam as a COX-II inhibitor responsible to inhibit cell proliferation of cancer cells. That is to say Meloxicam can be delivered through silica nanoparticle drug delivery system.

CONCLUSION: Mesoporous silica nanoparticles were synthesized and loaded with meloxicam to target metastatic colorectal cancer. Synthesis and evaluation of MSN loaded Meloxicam was successfully carried out. Evaluation results of the product shows promising approach for the development of a delivery like MSN. Moreover, the cell viability studies also provide positive results indicating the activity of Meloxicam for colorectal cancer. Further studies are necessary to investigate the therapeutic potential of the nanoparticle system containing Meloxicam and develop a suitable dosage form.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interest regarding the publication of this paper.

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