INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Solid Lipid Nano Particle - A Therapeutic Approach In Cancer Treatment

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ARTICLE INFO

Received: 10 March 2024
Accepted: 14 March 2024
Published: 15 March 2024

Keywords:
Solid, Liquid, Nano, Particle, Cancer, Treatment.

DOI:
10.5281/zenodo.10827164

ABSTRACT

Cancer is a family of diseases that which lead uncontrolled cell proliferation. Continues chemotherapy has lead side effect on healthy tissues, long term chemotherapy has been resistance to drug and treatment cost is high .Nano technology based cancer treatment best approaches for the cancer treatment . Solid lipid nanoparticle based cancer treatment is best approaches in cancer chemotherapy ,it has lead sustain releases of drug and increases solubility of drug or decreases side effect of drug.Now a day solid lipid nano particle is widely used , it has good therapeutic efficacy.

INTRODUCTION

Human cancer is a complex disease caused by genetic instability because of accumulation mutant alleles of proto-oncogene, tumour-suppressor genes, and other genes that control, directly or indirectly, cell proliferation. Most current anticancer agents do not greatly differentiate between cancerous and normal cells, leading to toxicity and major side effects. In addition, cancer is often diagnosed and treated too late, when the cancer cells have already invaded and metastasized into other parts of the body. At this stage, therapeutic modalities are limited in their effectiveness .(7)Nanotechnology enables increased delivery of poorly water soluble drugs, targeted delivery, co-delivery of two or more therapeutic agents, increase in half-life, controlled and sustained release of drug, reduced multidrug resistance, and multimodality treatment by co-delivery of chemotherapeutic, radiotherapeutic, thermotherapeutic and biotherapeutics agents.(2)Among various novel colloidal carriers present today, solid lipid nanoparticles (SLNs) have versatile potential for safe and nontoxic formulation of cytotoxic drugs, and achieves site-specific drug release.(3)SLNs are well-known nanomaterials that have now presented the maximum level of commercialisation . SLNs can

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

be used to deliver numerous hydrophilic and lipophilic therapeutic factors. These NPs offer no residual contamination and prolonged physical stability, are inexpensive, and can be produced on a large scale . Solid NPs, either alone or in combination with loaded therapeutics such as doxorubicin and ascorbic acid, can induce apoptosis in tumour cells or boost the effectiveness of conventional therapies. (8) SLNs have radically gained the attention of several researchers with its exceptional properties and benefits over other conventional dosage forms, and other colloidal counterparts of SLN have proved to be a significant discovery in nanotechnology because of their effective performance and as a safe vehicle in pharmaceutical drug delivery. (30)Solid lipid nanoparticles are also referred to as "zerodimensional" nanomaterials.(42)

Role of solid lipid nano particle in cancer

Colorectal cancer (CRC) ranked second in females and third in males among all type of cancers diagnosed..Kuldeep Rajpoot et al develop and optimize oxaliplatin (OP) loaded solid lipid nanoparticles (SLNs).SLNs containing tristearin, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), Lipoid S75, and Tween 80 was developed.Anticancer activity on HT-29 cell line.(1)

Breast cancer

Is the second leading cause of cancer deaths presently after lung cancer and is the most common cancer in women. World health organization predicts nearly 11.5 million deaths by the year 2030.Folic acid functionalized long-circulating co encapsulated docetaxel (DTX) and curcumin (CRM) solid lipid nanoparticles (F-DC-SLN) to improve the pharmacokinetic and efficacy of DTX therapy.The cytotoxicity and cell uptake of the SLN formulations were evaluated in MCF7 and MDA-MB-231 cell lines. The in vivo pharmacokinetic and biodistribution were studied in Wistar rats.(2) SLNs, as anti-cancer agents, using a green method. For this purpose, SLNs were prepared using homogenisation and ultrasound methods .Solid lipid nanoparticles (SLNs) comprise non-toxic surface-active lipidic agents combined with appropriate ratios of drugs or essential oils. The goal of this research was to investigate the effects of the SLN synthesised using essential oils of Foeniculum vulgare on the MCF 7 breast cancer cell line.(8),docetaxel-loaded solid lipid nanoparticles (DSNs) were developed to reduce systemic toxicity of docetaxel while still keeping its anticancer activity. To evaluate its anticancer activity and toxicity, and to understand the molecular mechanisms of DSNs, different cellular, molecular, and whole genome transcription analysis approaches were utilized. The DSNs showed lower cytotoxicity compared with the commercial formulation of docetaxel (Taxotere®) and induced more apoptosis at 24 hours after treatment in vitro. DSNs can cause the treated cancer cells to arrest in the G2/M phase in a dose-dependent manner similar to Taxotere. They can also suppress tumour growth very effectively in a mice model with human xenograft breast cancer. Systemic analysis of gene expression profiles by microarray and subsequent verification experiments suggested that both DSNs and Taxotere regulate gene expression and gene function, including DNA replication, DNA damage response, cell proliferation, apoptosis, and cell cycle regulation. Some of these genes expressed differentially at the protein level although their messenger RNA expression level was similar under Taxotere and DSN treatment. Moreover, DSNs improved the main side effect of Taxotere by greatly lowering myelosuppression toxicity to bone marrow cells from mice. (11)Geeta S. Bhagwat et al -transferrin-conjugated solid lipid nanoparticles (SLNs) were successfully prepared to enhance the active targeting of tamoxifen citrate in breast cancer. Developed formulations were evaluated for particle size,

surface charge, surface morphology and in vitro dissolution studies. Developed formulations exhibited more cytotoxicity as compared to pure Tamoxifen citrate solution in time as well as concentration dependent manner on human breast cancer MCF-7 cells.(12)Mariana S. Oliveira et aldevelop solid lipid nanoparticles (SLN) co-loaded with doxorubicin and a-tocopherol succinate (TS) and to evaluate its potential to overcome drug resistance and to increase antitumoral effect in MCF-7/Adr and NCI/Adr cancer cell lines. The SLN were prepared by a hot homogenization method and characterized for size, zeta potential, entrapment efficiency (EE), and drug loading (DL). The cytotoxicity of SLN or penetration was evaluated in MCF-7/Adr and NCI/adr as a monolayer or spheroid cancer cell model .The combination of doxorubicin and a vitamin E analogue, a-Tocopherol succinate (TS), has been shown to improve Dox anticancer activity. TS is a lipophilic ester of vitamin E that showed the most effective anticancer activity, causing inhibition of proliferation and apoptosis of several cancer cells.(14). To overcome the toxic side effects and multidrug resistance (MDR) during doxorubicin (DOX) chemotherapy, an arginine-glycine-aspartic (RGD) tripeptide modified, pH-sensitive solid lipid nanoparticles (SLNs) is employed in this study. In this study, a RGD conjugated, pH sensitive lipid was synthesized using glycerin monostearate (GMS) and adipic acid dihydrazide (HZ) as lipid materials and named RGD-HZ-GMS. RGD-HZ-GMS was applied to encapsulate DOX to construct a RGD modified, DOX loaded SLNs (RGD-DOX-SLNs). To evaluate the anticancer effect of RGD-DOX-SLNs, breast cancer cell line (MCF-7 cells) and DOX resistant cell line (MCF-7/ADR cells) were used. In vivo tumor suspension and toxicity effects were evaluated on mice. Talozoparib (BMN 673), which is a novel PARP inhibitor, has drawn attention as monotherapy or in combination therapy against different cancers in the recent clinical trials as no sustainable response was achieved (adverse effects and short disease-free survival, etc.) to PARPi including olaparib and iniparib in TNBC treatment. BMN 673 is currently in randomized phase II/III clinical trials for BRCA1/2-related cancer types and is recently approved by FDA for treatment of or gBRCAm HER2-negative locally advanced or metastatic breast cancer bearing MCF-7/ADR cells breast cancer model. RGD-DOX-SLNs had a uniformly spherical shape. (27).Resveratrol-loaded solid lipid nanoparticles (Res-SLNs) were successfully designed to treat MDA-MB-231 cells. The Res-SLNs were prepared using emulsification and low-temperature solidification method. The Res-SLNs were spherical, with small size, negative charge, and narrow size distribution. Compared with free resveratrol, the Res-SLNs displayed a superior ability in inhibiting the proliferation of MDA-MB-231 cells. In addition, Res-SLNs exhibited much stronger inhibitory effects on the invasion and migration of MDA-MB-231 cells. Western blot analysis revealed that Res-SLNs could promote the ratio of Bax/Bcl-2 but decreased the expression of cyclinD1 and c-Myc. These results indicate that the Res-SLN may have great potential for breast cancer treatment.(31)Curcumin was loaded into solid lipid nanoparticles (SLNs), in order to improve the therapeutic efficacy for breast cancer.The Cur-SLNs showed a stronger cytotoxicity against SKBR3 cells. In vitro cellular uptake study demonstrated a high uptake efficiency of the Cur-SLNs by SKBR3 cells. Moreover, Cur-SLNs induced higher apoptosis in SKBR3 cells, compared to cells treated by free drug. In addition, Western blot analysis revealed that Cur-SLNs could promote the ratio of Bax/Bcl-2, but decreased the expression of cyclin D1 and CDK4. These results suggested that Cur-SLNs could be a potential useful chemotherapeutic formulation for breast cancer therapy.

(37)Metastasis causes the most breast cancer-related deaths in women. Here, we investigated the anti tumoreffect of solid lipid nanoparticles (SLN-DTX) when used in the treatment of metastatic breast tumors using 4T1-bearing BALB/c mice. Resultis Solid lipid nanoparticles (SLNs) were produced using the high-energy method. Compritol 888 ATO was selected as the lipid matrix, and Pluronic F127 and Span 80 as the surfactants to stabilize nanoparticle dispersion. The particles had high stability for at least 120 days. (45)Surface modified targeted solid lipid nanoparticles (SLNs) were fabricated by nano-homogenizer using tripalmitin glyceride and stearic acid as lipid constituents.MTT test was used to evaluate the viability of the MCF-7 cells upon treatment with Epirubicinloaded SLNs and Lysine-SLNs.(49) 5-azacytidine -loaded solid lipid nanoparticles were produced by double emulsification (w/o/w) method by using stearic acid as lipid matrix, soy lecithin and poloxamer 407 as surfactant and co-surfactant respectively5-azacytidine into the lipid nanoparticles was investigated and in vitro effect of encapsulated 5-azacytidine studied on MCF-7 cell lines The developed SLN showed promising 5-azacytidine encapsulation probably due to the ion-pair interaction of the negatively charged lipid with the positively charged drug. In vitro cell cytotoxicity experiments proved the better performance of 5-azacytidine-loaded SLN than free 5-azacytidine, which may attributed to better endocytosis of nanoparticulate carriers and higher drug stability.(52)the toxic effects of gefitinib-loaded solid lipid nanoparticles (GFT loaded SLNs) upon human breast cancer cell lines (MCF-7) were investigated. GFT-loaded SLNs were prepared through a single emulsification–evaporation technique using glyceryl tristearate (Dynasan™ 114) along with lipoid® 90H (lipid surfactant) and Kolliphore® 188 (water-soluble surfactant).(54)

Gastric carcinoma

Is one of the most common cancers and the second most frequent cause of cancer-related deaths. Although surgery is a preferred method of gastric carcinoma removal, it cannot remove the tissue completely and is required to be supplemented by multidrug chemotherapy and/or radiation as preferred treatment of choice.VP16 loaded SLNs (VP16-SLNs) to enhance antitumor activity. VP16-SLNs were prepared using the emulsification and low-temperature solidification method ,hypothesized that the anticancer activity of VP16-SLNs would be different from free drug; thus, the in vitro cytotoxicity as well as the effect on cell apoptosis and cell cycle with SGC7901 cells were further investigated.

Prostate cancer (PCa)

Is one of the most prevalent male malignancies and the second leading cause of death by cancer in industrialized countries. The advancement of PCa not only means the long-range metastasis but also the development of the autonomic nerves into the tumour microenvironment. Solid lipid nanoparticles (SLNs) containing docetaxel (DTX) for prostate cancer treatment. The goal has been achieved by locating anisamide (Anis) ligand on the surface of SLNs, which can interact with the overexpressed sigma receptor on the prostate cancer cells. DTX loaded SLNs were prepared by high shear homogenization and ultra-sonication method and optimized by applying experimental design.The drug release pattern of the nanoparticles follows the Higuchi model. The prepared SLNs have been tested on 2 cell lines in order to evaluate the cytotoxicity effects. The results have shown the notable cytotoxicity effect on PC3 cell line. However, this effect was not considerable on HEK293.(6)

Pancreatic cancer (PCa)

Is projected to be the second leading cause of cancer deaths by 2030 .Systemic cytotoxic and kinase-targeted regimen represent the standard of care for most patients presenting with PCa. Most

tumors, however, develop rapid resistance to these regimens and continue to progress by unknown mechanisms . As a result, both the median survival and annual death rate for patients with PCa have remained unchanged over the past 20 years .The cytotoxic effects of gemcitabine-loaded solid lipid nanoparticle (Gem-SLN) on the patient-derived primary pancreatic cancer cell lines (PPCL-46) and MiaPaCa-2 pancreatic cancer cells. Different SLN formulations were prepared from glyceryl monostearate (GMS), polysorbate 80 (Tween® 80) and poloxamer 188 (Pol 188) as surfactants using a cold homogenization method. Gem-SLN was characterized for particle size and charge distribution, entrapment efficiency and loading capacity. Fourier Transform Infra-Red (FTIR) spectroscopy was used to verify Gem and SLN interaction while differential scanning calorimetry (DSC) was used to acquire thermodynamic information on Gem-SLN. Cytotoxicity studies was conducted on PPCL-46 cells and MiaPaCa-2 cells.(13).C. A new docetaxel-loaded hepatoma-targeted solid lipid nanoparticle (tSLN) was designed and prepared with galactosylateddioleoylphosphatidyl ethanolamine. The cellular cytotoxicity, cellular uptake, subcellular localization, in vivo toxicity, therapeutic effect, biodistribution and histology of tSLNs were investigated. The tSLNs showed the particle size about 120 nM with encapsulation efficiency >90%, a low burst effect within the first day and a sustained release for the next 29 days in vitro. Cytotoxicity of tSLNs against hepatocellular carcinoma cell line BEL7402 was superior to Taxotere and non-targeted SLNs (nSLNs). The tSLNs also showed better tolerant and antitumor efficacy in murine model bearing hepatoma compared with Taxotereor nSLNs. The studies on cellular uptake and biodistribution indicated that the better antitumor efficacy of tSLNs was attributed to both the increased accumulation of drug in tumor and more cellular uptake by hepatoma cells. The histology demonstrated that tSLNs had no detrimental effect on both healthy liver and liver with fibrosis.(35)

Lung cancer

Is one of the deadliest types of malignancy worldwide, with poor response to conventional treatments and presents serious resistance to classical chemotherapy, leading to a high mortality rate . A nano-drug delivery system to the lung cancer tumor mass may decrease the associated systemic adverse effects with conventional chemotherapeutic and increase the response rates ,the antineoplastic activity of gemcitabine (GM) and oxaliplatin (OXA) co-loaded into oleic acid-based solid lipid nanoparticle (OA-SLN) in A549 non-small cell lung cancer cells. OA-SLN was synthesized using homogenization and physically characterized using the dynamic light scattering techniques.(22)Solid lipid nanoparticles with hyaluronan (HA-SLNs)would allow targeted delivery of paclitaxel (PTX) to CD44-overexpressing B16F10 melanoma cells. First, we developed a model system based on melanoma stem-like cells for experiments in vitro and in mouse xenografts, and we showed that cells expressing high levels of CD44 (CD44+) displayed a strong CSC phenotype while cells expressing low levels of CD44 (CD44-) did not. This phenotype included sphere and colony formation, higher proportion of side population cells, expression of CSC-related markers (ALDH, CD133, Oct-4) and tumorigenicity in vivo. Next we showed that administering PTX-loaded HA-SLNs led to efficient intracellular delivery of PTX and induced substantial apoptosis in CD44+ cells in vitro. In the B16F10-CD44+ lung metastasis model, PTX-loaded HA-SLNs targeted the tumor-bearing lung tissues well and subsequently exhibited significant antitumor effects with a relative low dose of PTX, which provided significant survival benefit without evidence of adverse events.(24) Curcumin (Cur) is a promising

photosensitizer that could be used in photodynamic therapy. However, its poor solubility and hydrolytic instability limit its clinical use.The Cur-loaded SLNs (Cur-SLNs) were prepared using an emulsification and low-temperature solidification method. The functions of Cur and Cur-SLNs were studied on the non-small cell lung cancer A549 cells for photodynamic therapy.(26)Nanoparticles (200 nm) were radiolabelled with 99mTc using the lipophilic chelator D,L-hexamehylpropyleneamine oxime (HMPAO). Biodistribution studies were carried out following aerosolisation and administration of a 99mTc-HMPAO-SLN suspension to a group of adult male Wistar rats. A 60 min dynamic image acquisition was performed in a gamma-camera, followed by static image collection at 30 min intervals up to 4 h postinhalation.(33)Cationic solid lipid nanoparticles for delivery of RNAi-mediating plasmid DNA in order to down regulate STAT3 in cisplatin resistant lung cancer cells.(34)Phyllanthi Tannin- PTF-SLNs have been successfully developed by the thin film hydration method to enhance therapeutic outcomes in lung cancer. In this research, we used biocompatible and biodegradable constituents to investigate the preparation and prescription process of SLNs and their anti-tumour ability. The optimal PTF-SLNs allowed high drug incorporation with significantly improved aqueous solubility of PTF.(38)Phospho-sulindac (OXT-328)s incorporated into SLNs using the emulsion evaporation technique. We determined the antitumor activity of SLN-PS in cultured lung cancer cells. The performance of SLN-PS was further evaluated by pharmacokinetic studies in mice and in a model of human lung cancer xenografts in nude mice.—SLN-PS was >4-fold more potent than PS in inhibiting the growth of A549 and H510 cells in vitro. SLN-PS enhanced cellular uptake and facilitated PS accumulation in mitochondria, leading to oxidative stress and apoptosis via the mitochondrial-apoptosis pathway.(39)The tumour targeting potential of surface tailored solid lipid nanoparticles (SLNs) loaded with an anti-cancer drug doxorubicin HCl (DOX). DOX encapsulating SLNs were prepared, characterized and further mannosylated. The ex vivo cytotoxicity and cellular uptake studies were performed on A549 cell lines. In vivo studies were conducted to determine pharmacokinetics, tissue distribution pattern and nephrotoxic/ hepatotoxic effect of mannosylated SLNs.(40)The cytotoxicity of paclitaxel solid lipid nanoparticles (SLN) modified with stearic acid octaarginine (SA-R8-PTX-SLN) as well as the cellular uptake of coumarin-6-loaded SLN modified with SA-R8 (SA-R8-C6-SLN) in human lung cancer cells, A549.Curcuminloaded solid lipid nanoparticles (Cur-SLNs) and test its efficacy in the treatment of lung cancer.The erythrocyte toxicity study of Cur-SLNs and its components demonstrated moderate hemolytic potential towards red blood cells (RBCs). The cytotoxic potential of the formulation and plain curcumin was estimated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay against A549 cell line. After 48 h of incubation, Cur-SLNs demonstrated more cytotoxicity (IC50 = 26.12 ± 1.24 µM) than plain curcumin (IC50 = 35.12 ± 2.33 µM). Moreover, the cellular uptake of curcumin was found to be significantly higher from Cur-SLNs (682.08 ± 6.33 ng/µg) compared to plain curcumin (162.4 ± 4.2 ng/µg).(44)Surface-modified, co-encapsulated solid lipid nanoparticles (SLN) containing enhanced green fluorescence protein plasmid (pEGFP) and doxorubicin (DOX) in order to create a multifunctional delivery system that targets lung cancer cells, in an effort to improve the efficacy of cancer therapy. DOX- and pEGFP loaded SLN were prepared separately and then mixed to form co-encapsulated SLN (SLN/DE). Transferrin (Tf)-containing ligands were used for

the surface coating of the vectors. The in vitro transfection efficiency of the modified vectors was evaluated using a human alveolar adenocarcinoma cell line (A549 cells) and the in vivo transfection efficiency of the modified vectors was evaluated using mice bearing A549 tumors. The Tf-modified DOX and pEGFP co-encapsulated SLN (T-SLN/DE) had a particle size of 267 nm with a 42 mV surface charge. The in vitro cytotoxicity of T-SLN/DE was low (cell viability was between 80 and 100% compared with the controls).(46)Gefitinib-loaded solid lipid nanoparticles (GEF-SLN), and GEF-loaded PEGylated SLN (GEF-P-SLN) for targeting metastatic lung cancer through the lymphatic system. The prepared SLNs were characterized in terms of physicochemical properties, entrapment efficiency, and in-vitro release. Furthermore, ex-vivo permeability was investigated using the rabbit intestine. Cytotoxicity and apoptotic effects were studied against A549 cell lines as a model for lung cancer(55). Gemcitabine is a nucleoside analogue used as a form of chemotherapy for non-small cell lung, pancreatic, bladder and breast cancer. Gemcitabine-loaded SLNs prepared by double emulsification technique showed controlled drug release when compared to free drug. In-vivo tissue distribution study of the optimized solid lipid formulation showed increase in cellular uptake by various organs over free drug.(3)The unique composition of the 4-(N)- GemC18-SLNs is critical for their ability to overcome gemcitabine resistance is supported by the following findings: 1) a 3′-(O)-GemC18 ester synthesized by conjugating gemcitabine in the 3′-O position with stearic acid, when incorporated into the same solid lipid nanoparticles engineered from lecithin/glyceroyl monostearate-in-water emulsions, was not significantly more effective than free gemcitabine in controlling the growth of the gemcitabine-resistant TC-1-GR tumor cells in culture and in a mouse model(10) Solid lipid nanoparticles of atovaquone (ATQ-SLN) were prepared by high shear homogenization method using tripalmitin, trilaurin, and Compritol 888 ATO as the lipid matrices and Phospholipon 90H, Tween 80, and poloxamer 188 as the surfactants. Optimization of the formulations was conducted using 6 sets of 24 full-factorial design based on four independent variables that were the number of homogenizing cycles, concentration of the lipid, concentration of the co-surfactant, and concentration of the main surfactant(5) The first invivo studies of SLN containing anticancer compound was carried out by Yang et al in 1999, they have used a chemically reactive compound camptothecin which known for anticarsinojen properties. Amongest various anti cancer drugs, paclitaxel has been studied by researchers to evaluate the potential of SLN . In these studies, they demonstrated that paclitaxel loaded SLN have cytotoxic effect on varios cancer cells (HCT15, U118, A-549 etc.) and revealed the potential application of SLN for therapeutic targeting of cancer. Gasco et al studied the cellular uptake and cytotoxicity of SLN loaded with doxorubicin or paclitaxel by using two different cell lines (MCF-7 and HL-60) . They found that the cytotoxicity of DoxSLN and PTXSLN was higher than free drug solutions on both cell lines. A similar studies found that cholesterol buterate, doxorubicin and paclitaxel loaded SLNs have more effective than free solutions by using colorectal cancer cells (HT29) . Tamoxifen, a anti cancer drug used for breast cancer (MCF7) also used in SLN . They were observed that the activity of tamoxifen-SLN was comparable to free drug, but the usefulness of these SLN in cancer therapy is because of their prolong release of drug. But Reddy et al showed tamoxifan citrate of these SLN as compared to free drug which revealed prolonged circulation time of SLN that is useful for breast cancer therapy. Lu and colleageus evaluated that the therapeutic effect of mitoxantrone loaded solid lipid nanoparticle(

MTO-SLN) was promising in terms of either the breast cancer weight or the percent inhibition of the tumor.(7) Caffeic acid-loaded solid lipid nanoparticles (CA-SLNs) were constructed, and were characterized to determine their properties followed by their evaluation for in vitro cytotoxic properties. The SLNs were prepared by using hot homogenization method. The treatment of H-Ras 5RP7 and NIH/3T3 cell lines with CA and CA-SLNs suggested that CA-SLNs are less toxic to NIH/3T3 normal cells but have more cytotoxic effects on H-Ras 5RP7 as compared with free CA by using MTT assay. In addition, CA-SLNs can increase the cytotoxic effect and accelerate cellular uptake of CA on H-Ras 5RP7 cells(9) Cisplatin loaded solid lipid nanoparticles was prepared by microemulsion technique. Stearic s SLNs loaded with paclitaxel (PTX) were prepared using the film ultrasonication method, followed by conjugation with a PEGylated peptide (Pp) that can specifically interact with matrix metalloproteinases (MMPs) that is over-expressed by tumor cells. The physicochemical characteristics of the Pp-PTX-SLNs were studied and the in vitro drug release, cytotoxicity and cell uptake of the formulations were investigated acid was used as lipid. The other excipients were used as DPPG, Soya lecithin and Poloxamer P407 and acidic buffer pH4. Probe sonication was used for 10 min at 79 Amplitude.(16)PTX-loaded SLNs were successfully conjugated with PEGmatrix metalloproteinase (MMP)-substrate peptide. The PEG peptide was cleaved specifically by MMPs overexpressed in the tumor microenvironment, facilitating the uptake of the nanoparticles by tumor cells. Pp-PTX-SLNs accumulated to a greater extent in tumor tissue than did the non-cleavable Pp'-PTXSLNs, leading to better efficacy in a mouse tumor model. PpPTX-SLNs also persisted much longer in the circulation than did non-PEGylated PTX-SLNs. Compared with Taxol®, Pp-PTXSLNs showed lower distribution in heart, lung, and liver, suggesting that encapsulating PTX in SLNs may decrease the major side effects of PTX. The Pp-SLN delivery system may be suitable for other lipophilic chemotherapeutic drugs.(17)Berberine hydrochloride (BH) is an isoquinolin alkaloid with promising anticancer efficacies. Nevertheless, further development and application of this compound had been hampered by its poor aqueous solubility, low gastrointestinal absorption, and rapid metabolism in the body. In this study, a solid lipid nanoparticle (SLN)-based system was developed for efficient incorporation and persistent release of BH.(18)Hyaluronic acid (HA)-decorated solid lipid nanoparticles (SLNs) were developed for 28 tumor. targeted delivery of vorinostat (VRS), a histone deacetylase inhibitor. HA, a naturally occurring polysaccharide, which specifically binds to the CD44 receptor, was coated on a cationic lipid core through electrostatic interaction Hyaluronic acid was successfully attached onto the surface of cationic SLNs by electrostatic attraction. The resultant particles were spherical in shape, uniform in size with a visually clear outer shell. HA-VRS-SLNs exhibited favorable characteristics that suggested their capability for efficient drug delivery and targeting. First, VRS was released slowly in order to maintain drug concentration in control, leading to reduced toxicity on normal cells. The HA-VRS-SLNs penetrated rapidly into cancer cells, especially on high level CD44 overexpression cells. In addition, the better performance of HA-VRS-SLNs clarified the role of HA in selective targeting to tumor cells. As expected, the HA-VRS-SLNs showed more potency in inhibiting the growth of all cancer cells: A549, SCC7, and MCF-7, compared to that for the VRS and VRS-SLNs.(19)Camptothecin incorporated into the SLN-P showed a higher in vitro cytotoxicity against melanomas compared to the free drug form.(20)Oridonin (ORI),ORI-loaded SLNs were

prepared by hot high pressure homogenization with narrow size distribution and good entrapment efficacy. MTT assay indicated that ORI-loaded SLNs enhanced the inhibition of proliferation against several human cancer cell lines including breast cancer MCF-7 cells, hepatocellular carcinoma HepG 2 cells, and lung carcinoma A549 cells compared with free ORI, while no significant enhancement of toxicity to human mammary epithelial MCF10A cells was shown. Meanwhile, flow cytometric analysis demonstrated that ORI-SLNs induced more significant cell cycle arrest at S and decreased cell cycle arrest at G1/G0 phase in MCF-7 cells than bulk ORI solution.(21)PEGylated SLNs to overcome the insolubility of PK-L4 and established its physiochemical properties and biodistribution behavior. The main advantage of PEGylated SLNs is that they can successfully encapsulate hydrophobic PK-L4 in the inner core of SLNs. The size, in the range of 10–200 nm, is small enough to avoid filtration by the liver and spleen, ensuring the potential passive targeting of tumors through an enhanced permeability and retention effect.(23)Solid lipid nanoparticles containing cholesteryl butyrate (cholbut SLN) can be a delivery system for the anti-cancer drug butyrate. Cholbut SLN inhibited tumour cell line viability, clonogenic activity, Akt phosphorylation and cell cycle progression. In mice injected i.v. with PC3-Luc cells and treated with cholbut SLN, . in vivo optical imaging and histological analysis showed no metastases in the lungs of the treated mice. In another set of mice injected s.c. with PC-3 cells and treated with cholbut SLN when the tumour diameter reached 2 mm, analysis of the tumour dimensions showed that treatment with cholbut SLN substantially delayed tumour growth.(25).Curcumin (Cur) is a promising photosensitizer that could be used in photodynamic therapy. However, its poor solubility and hydrolytic instability limit its clinical use. vorinostat (VOR), by using solid lipid nanoparticles (SLNs) enhanced its bioavailability and effects on multidrugresistant cancer cells. Methods VOR-loaded SLNs (VOR-SLNs) were prepared by hot homogenization using an emulsification-sonication technique, and the formulation parameters were optimized. The cytotoxicity of the optimized formulation was evaluated in cancer cell lines (MCF-7, A549, and MDA-MB-231), and pharmacokinetic parameters were examined following oral and intravenous (IV) administration to rats.(28)Curcumin reduces Hodgkin's lymphoma (HL) cell growth in vitro, but its unfavorable pharmacokinetics highlight the need for novel in vivo delivery systems. Thus, we explored whether formulation of curcumin in solid lipid nanoparticles (SLN-curc) or d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) nanoparticles (TPGScurc) could enhance its efficacy in mice. Curcumin formulated in SLN and in TPGS resulted in higher curcumin plasma levels in mice.(29).These therapeutic nanoparticles contained water-insoluble paclitaxel in the core with tumor-targeting ligand covalently conjugated on the polyethylene glycol (PEG)-modified surface (targeted PtSLNs). In preclinical human cancer xenograft mouse model studies, the paclitaxel-containing tumor-targeting SLNs exhibited pronounced in vivo stability and enhanced biocompatibility. Furthermore, these SLNs had superior antitumor activity to in-class nanoparticular therapeutics in clinical use (Taxol and Genexol-PM) and yielded long-term complete responses. The in vivo targeted antitumor activities of the SLN formulations in a mouse tumor model suggest that LDL-mimetic SLN formulations can be utilized as a biocompatible, tumor-targeting platform for the delivery of various anticancer therapeutics. (32)Aloe-emodin (AE) is a promising anti-tumor candidate for its significant activity against various tumors such as lung cancer, hepatic cancer, breast cancer and so

on. Nevertheless, AE is clinically limited due to its poor water solubility and low bioavailability. This study was designed to prepare AE-loaded solid lipid nanoparticles (AE-SLNs) in an attempt to improve the anti-cancer efficacy of AE. The AE-SLNs were prepared with optimized prescription using high pressure homogenization (HPH) technique , in vitro cytotoxicity against human breast cancer MCF-7 cells and human hepatoma HepG2 cells as compared to the AE solution, while they showed no significant toxicity on human mammary epithelial MCF-10A cells.(36)Paclitaxel (PTX) is one of the well-known choice as antineoplasitic agent used for the treatment of different types of human cancers such as non-small-cell lung, head and neck cancers, leukemia, breast, ovarian and melanoma. Lactoferrin (Lf), a ‘‘multifunctional protein’’ is crucial for natural immunity which is secreted by exocrine glands. Lf receptors are expressed on the apical surface on bronchial epithelial cells. These over-expressed LF receptors can be utilized for the transportation of Lf-conjugated drug or nanocarrier devices. The present study was aimed to develop PTX-loaded Lf-coupled solid lipid nanoparticles (SLNs) for the treatment of lung cancer. PTX-loaded SLNs were prepared, characterized and then coupled with Lf using carbodiimide chemistry.(41)

Lycopene belongs to the carotenoids that shows good pharmacological properties including antioxidant, anti-inflammatory and anticancer. However, as a result of very low aqueous solubility, it has a limited systemic absorption, following oral administration. Methods: Here, we prepared a stable lycopene-loaded solid lipid nanoparticles using Precirol® ATO5, Compritol 888 ATO and myristic acid by hot homogenization method with some modification,(51)

Albendazole (ABZ) is an antihelminthic drug used for the treatment of several parasitic infestations. In addition to this, there are reports on the anticancer activity of ABZ against a wide range of cancer types. However, its effect on glioma has not yet been reported. In the present study, cytotoxicity of ABZ and ABZ loaded solid lipid nanoparticles (ASLNs) was tested in human glioma/astrocytoma cell line (U-87 MG). Using glyceryl trimyristate as lipid carrier and tween 80 as surfactant spherical ASLNs with an average size of 218.4 ± 5.1 nm were prepared by a combination of high shear homogenization and probe sonication methods. A biphasic in vitro release pattern of ABZ from ASLNs was observed, where 82% of ABZ was released in 24 h. In vitro cell line studies have shown that ABZ in the form of ASLNs was more cytotoxic (IC50 = 4.90 µg/mL) to U-87 MG cells compared to ABZ in the free form (IC50 = 13.30 µg/mL) due to the efficient uptake of the former by these cells.

CONCLUSION

Cell-specific targeting can be achieved by attaching drugs to individually designed carriers. Recent developments in nanotechnology have shown that nanoparticles (particles with diameter).The cancer nanotherapeutics using nanocarriers based drug delivery has emerged as an advanced tool to provide a solution to formulation challenges and a better cancer therapy by overcoming the limitations in conventional cancer therapy. (47)The SLNs have the potential to maintain high stability during their storage period. A varied range of lipids (oils) and fatty acids are accessible for tuning the release kinetics. SLNs are very flexible lipid carriers that can be easily tailored with the terminal groups of solid lipid to attain efficient improvement for a given treatment. Drug expulsion and targeting problems can be efficiently addressed by surface modification. SLNs are not only used for treatments, imaging agent or diagnostic agent potential are also explored. A front line of research should merely be focused on the development of surfacemodified SLNs for future

perspectives.(48)Solid lipid nanoparticles (SLNs) are popular research topics recently introduced as nano-scale drug carriers; they have shown numerous merits in drug delivery. Size is the most important index in a nanocarrier affecting its drug delivery efficiency. The influence of preparation conditions and type of lipidic components on the size of SLN and NLC in comparable states seems to be interesting for researchers who investigate these types of carriers.(50)

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HOW TO CITE: Jamuna Mekaliya, Dharmesh Sisodiya, Kamlesh Dhashora, Solid Lipid Nano Particle - A Therapeutic Approach In Cancer Treatment, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 3, 502-515. https://doi.org/10.5281/zenodo.10827164