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Review Article

SOLID LIPID NANOPARTICLES: A PROMISING APPROACH FOR COMBINATIONAL DRUG THERAPY IN CANCER

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ABSTRACT

Combination therapy for cancer treatment is accepted worldwide due to the generation of synergistic anticancer effects; restrain in multidrug resistance (MDR) or tumor resistance by different mechanisms of action and minimization of dose-dependent toxicity. Recently developed Solid lipid nanoparticles (SLNs) are matrix composed of lipid which is solid at both room and body temperature and hence it is as an alternative to other nanocarrier systems. SLNs after oral administration get absorbed by lymphatic pathway due to stimulation of chylomicron formation. Thus, it avoids all consequences related to an oral drug delivery system and improves oral bioavailability. SLNs based combination drug delivery to tumor tissues reduces the problems associated with chemotherapy. The targeted and sustained delivery of chemotherapeutic agents reduces the dose by achieving high concentrations at the target site, without altering the normal tissues. In this article, we have reviewed and focused on SLNs as a drug delivery system; ingredients used in formulating SLNs and developed two or more drugs in a single formulation of SLNs as drug delivery. This article also focuses on the fact that SLNs as a combination drug delivery provides an attractive approach in future prevention and beneficial for the treatment of cancer by increasing its therapeutic efficacy.

Keywords: Nanodrug delivery, Solid Lipid Nanoparticles, Tumor, Combinational Chemotherapy, Multidrug Resistance

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INTRODUCTION

Cancer has been listed as one of the most challenging to treat diseases. Genetic alterations and cellular abnormalities are noticed in cancer. The aggressive growth of cancer cells promoted by the intricacy and heterogeneity of abnormal and altered cells leads to significant morbidity and mortality in patients [1, 2]. Cancer studies show that the survival rates improved but mortality rates still remained high for some specific tumors. To enhance the effectiveness of cancer treatment, effective therapeutic methods with the least side effects along with and precise diagnostics are essential [3]. In anticancer therapy, various chemotherapeutic agents are used which are targeted on specific multiple pathways. Nevertheless, a single agent prescribed repetitively in the treatment consequences in resistance to chemotherapy (specific drug) or development of MDR [4].

Problems associated with conventional single-drug chemotherapy include limited accessibility of the drug to tumor tissues requiring an additional dose and leading to intolerable cytotoxicity with specific targeting not being achieved. To avoid these hindrances in cancer therapy, combinatorial chemotherapy is preferred clinically. Combinatorial therapy consists of two or more therapeutic agents administered concurrently or use of different therapies in combined form. Currently, four therapies are preferred in cancer-chemotherapy, hormone therapy, immunotherapy, radiotherapy. Simultaneously chemotherapy or hormones or immuno-suppressants are given together in combinatorial therapy [5]. Combinatorial therapy decreases the side effects of individual drug therapy by taking into consideration synergistic effect of two drugs administered in a single dosage form, countering different biological signaling pathways in a synergistic manner, possibly minimizing dosage of each drug or accessing specific multi-target mechanisms, insufficient transportation through membrane, inadequate bio-availability and least biodistribution can thus be overcome [5]. This approach may be helpful in enhancing the therapeutic efficacy of drugs since it attacks different stages of cancer cell growth cycles [6].

Currently, nanotechnology is developing into a rapidly growing field with applications in health and drug therapy. Nanoparticles have a small size and high surface area. The nano-size distribution effect is due to some physical and chemical properties [7]. Various types of nano drug delivery systems are nanoparticles, dendrimers, nanotubes, micelles and liposomes. Nanotechnology-based combinational drug delivery systems increase the bioavailability by enhancing permeability, retention and reaching the cancers tissues target site [8]. It helps to conquer the systemic toxicity towards normal tissue and adverse effects which result from conventional cancer therapeutic agents [5]. SLNs are a drug delivery system consisting of a drug carrier which helps in increasing bioavailability and reducing erratic absorption [7, 9]. In this review, we discuss nanotechnology based SLNs for combinational drug delivery in cancer therapy as a novel promising drug delivery system. This article is an updated and comprehensive review discussing the progress and applications of SLNs from various published reviews and research (national and international) in the field in the last two decades.

Advantages of combinational drug delivery in cancer therapy mentioned in (fig. 1)

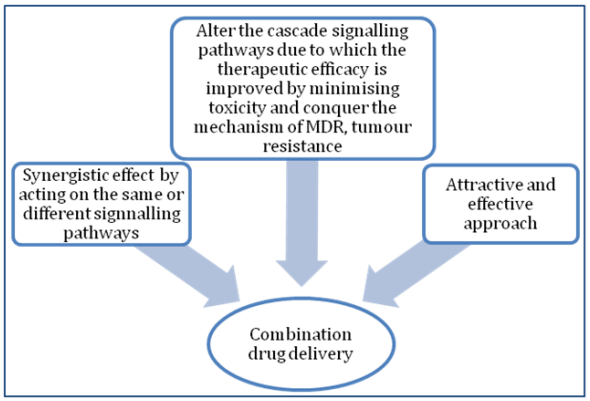

Fig. 1: Advantages of combinational drug delivery [5]

SLNs

SLNs are colloidal nanoparticlate delivery systems with a nano-size distribution (50 to 1000 nm) made from lipids which remain in solid state at room temperature and body temperature, stabilized by surfactants. SLNs can be easily prepared by using several types of lipids including lipid acids which are mono, di or triglycerides,

glycerides mixtures or waxes, and stabilized by using compatible surfactants i.e. Non-ionic or ionic [10]. SLNs can be used for several purposes and overcome the problems associated with other colloidal carriers. They lead to enhancement of drug solubility, controlled drug release, reaching the target site enabling site targeting, reduction in the therapeutic dose regimen, prevention of degradation of incorporated labile drugs, tremendous permissibility, increase the bioavailability of drug [7, 11-13]. SLNs have been developed and recommended for administering to several different routes of administration like oral, topical, parenteral; and pulmonary [7]. Absorption of nanoparticles takes place through mucosa of the intestine by several mechanisms namely through the Payer's patches, by intracellular uptake or by the paracellular pathway [14].

Rationale of SLNs for Cancer: Tumor cells are having defective, leaky vascular structure due to poorly regulated nature of tumor angiogenesis. Due to lymphatic system drained interstitial fluid within a tumor, the submicron-sized particulate matter may preferentially extra vasate into the tumor and be retained there. This is called as "enhanced permeability and retention" (EPR) effect. EPR effect can be considered while designing Nano particulate drug delivery. Thus, SLN system is designed in such a way to achieve passive tumor targeting by taking advantage of EPR effect [10].

Lipids and emulsifiers used in SLN formulations

General ingredients for SLN include solid lipids, emulsifiers and solvent/water. The two phases i.e. lipid and aqueous should be mixed thoroughly to form one homogenous phase with droplet size in the nanometer (nm) range. Subsequently, these particles are allowed to solidify by cooling or solvent evaporation depending on the employed method of preparation. The emulsifiers are preferred on the basis of drug solubility, HLB values as per Griffith scale and type of emulsion being formulated for particular drug or drugs used in combination. Several types of lipids used presently include triglycerides, partial glycerides, fatty acids, steroids and waxes. Emulsifiers and their combinations have been used to stabilize the lipid dispersion. It has been found that a combination of emulsifiers efficiently prevents the agglomeration of particles [15, 16]. Ingredients used in SLNs are given in (table 1).

Table 1: Lipids and emulsifiers used in SLN formulations

Lipids		References
Triglycerides		
Tricaprin		(Glycerol Tricaprate)
Tristearin	(Glycerol Tristearate)	[17]
Trilaurin	(Glycerol Trilaurate)	[18]
Tri-myristin	(Glycerol Trimyristate)	[19]
Tri-palmitin	(Glycerol Tripalmitate)	[20]
Hydrogenated coco-glycerides (Softisan 142)		[21]
Hard fat types		[22]
Witepsol W 35		[23]
Witepsol H 35		[24]
Witepsol H 42		[25]
Witepsol O 85		[24]
Glyceryl monostearate (Capmul GMS-40)		[26]
Glycerylbehenate (Compritol 888 ATO)		[27, 28]
Glycerylpalmitostearate (Precirol ATO 5)		[22]
Cetylpalmitate		[29]
Stearic acid		[30]
Palmitic acid		[27]
Decanoic acid		[31]
Behenic acid		[32]
Emulsifiers/Coemulsifiers		
Soybean lecithin		[32, 33]
(Lipoid S 75, Lipoid S 100)		
Egg lecithin (Lipoid E 80)		[20]
Phosphatidylcholine		
(Epikuron 170, Epikuron 200)		[15, 34]
Poloxamer 188		[35]
Poloxamer 182		[36]
Poloxamer 407		[37]
Poloxamine 908		[37]
Tween 20		
Tween 80		[38]
Span 80		[39]
Sodium cholate		[36] [39]
Sodium glycocholate		[40, 41]
Taurocholic acid sodium salt		[42]
Taurodeoxycholic acid sodium salt		[43]
Butanol		[44]
Butyric acid		[45]
Dioctyl sodium sulfosuccinate		[46]
Monooctylphosphoric acid sodium		[47]

Techniques of SLNs preparation

The different techniques used to formulate the SLNs, their merits and demerits are mentioned in table 2.

Influence of ingredient composition on product quality

Influence of the lipid

The composition and quality of lipids may be varied from different suppliers and different batches from the same suppliers. Thus, these slight changes in composition might extensively influence the quality of SLN dispersion [15]. The increments in lipid concentration also reduce the leaking of the drug into the external phase, which positively influences entrapment efficiency [48] and however the subsequent increase in particle size with increase in lipid amount significantly causing an increase in viscosity of the dispersion thus resulting in particle agglomeration [43]. Several research studies have reported that increasing lipid concentration results in larger particles, high entrapment efficiency and broader particle size distribution and a higher poly-dispersity index as well [50].

Table 2: Merits and demerits of SLNs preparation methods

Methods	Merits	Demerits	References
High-Speed Homogenisation/Ultra sonication	1. Applicable for Lab Scale 2. Low capital cost	1. The broader range of particle size distribution due to the presence of micro particles. 2. The possibility of agglomeration of the particle after storage hence not suitable intravenous administration. 3. Possibility of metal contamination. 4. Low stability. 5. Time-consuming.	[15, 48]
High-Pressure Homogenisation (Hot homogenization)	1. Lab scale and large scale applicability 2. Narrow particle size distribution 3. Low polydispersity index 4. Greater stability compared to High-Speed Homogenisation/Ultra sonication	1. Temperature-induced degradation of thermolabile drug and lipids. 2. Sample remains in super cooled melt state for months instead of solid state. 3. Increasing the rate of homogenization leads to an increase in particle size due to particulate coalescence which occurs due to the generation of high kinetic energy of particles.	[15, 48]
High-Pressure Homogenisation (Cold homogenization)	1. Prevents temperature induced degradation of thermolabile drug and lipids. 2. Prevents complexity of the crystallization step of nanoemulsion leading to modifications in supercooled melts. 3. Low temperature increases fragility of lipid and therefore favor comminution. 4. High cooling rate favors better distribution of the drug in a lipid matrix.	1. Larger particle size and greater particle size distribution compared to hot homogenization 2. Effective temperature control and regulation is required to ensure the unmolten state of lipid. 3. Higher cost	[15]
Solvent emulsification/evapration	1. Smallest particle size is obtained 2. Lab scale applicability 3. High stability 4. Thermo labile drugs can be successfully incorporated into SLNs without degradation	1. Use of toxic solvents may make the SLNs systemically toxic 2. Inconvenient for large production scale up 3. With increasing lipid content, the difficulty arises in uniform homogenization of SLNs leading to an increase in polydispersity index and particle size distribution.	[15]
Microemulsion-based SLNs by the dilution method	1. Particle size is intermediate between high-pressure homogenization and solvent evaporation technique. 2. Size distribution depends on the quality of microemulsion formed. 3. Intermediate stability	1. SLNs are subjected to thermal stress hence are liable to agglomerate quicker than solvent evaporation and high-pressure hot homogenization technique. 2. High thermal stress 3. Larger particle size is obtained with lipophilic solvents and cosolvents and vice versa in case of hydrophilic solvents.	[15]

Table 3: Developed and formulated combinatorial nanoparticles for cancer therapy

Author name	Drugs	Cell line/type of cancer cells	Results	References
Nazzal Sami *et al.*	Simvastatin, Tocotrienol	Malignant+SA mammary epithelial cells	-*In vitro* studies showed their antiproliferative effects on malignant+SA mammary epithelial cells -The potency of combination therapy was confirmed	[54]
Jayakumar R *et al.*	Curcumin (CUR), 5 Fluorouracil (5 FU)	Colon cancer cells (HT29)	-The collective exposure of the nanoformulations in colon cancer cells (HT 29) proved beneficial. -Enhanced anticancer effects *in vitro* and *in vivo* synergistically.	[55]
Han J *et al.*	All-trans-retinoic acid (ATRA), Paclitaxel (PTX)	HepG2 cells	-ATRA chitooligosaccharide (RCOS) nanoparticles could be rapidly and continuously taken up by HepG2 cells via endocytosis and transported into the nucleus, and the uptake rates increased with particle concentration. -The RCOS nanoparticles have promising potential as drug carriers for co-delivery of both drugs together	[56]
Sahoo SK *et al.*	CUR, Temozolomide	T-98G cells	-The dual drug loaded MNPs formulations showed the higher cytotoxic effect and higher therapeutic efficacy. -The formulation showed a synergistic effect against HepG2 cells.	[57]
Cho CW *et al.*	PTX, Verapamil (VP)	MCF7 cells	-PVSV (PTX and VP co-loaded SLN, later added VP) were prepared to overcome MDR by a combination of PTX and VP. -PVSV showed significantly higher cytotoxicity and cellular uptake, down-regulated the expression of p-gp than PTX solution in MCF-7/ADR resistant cells. -PVSV exhibited great potential for breast cancer therapy	[58]

Wang S *et al.*	CUR, 5 FU	SMMC-7721 cells	-SLN-CUR and LDH (Layered double hydroxides) 5-FU showed a significant synergetic effect on SMMC-7721 cells which was stronger than plain drugs together. -FACS analysis proved that the combination of SLN-curcumin and LDH-5-FU induced 80.1% apoptosis in SMMC-7721 cells, which were 1.7-folds of the sum of the two plain drugs loaded.	[59]
Dianzani C *et al.*	Doxorubicin (DOX), PTX	Colorectal cancer cell line HT-28	-SLNs of cholesteryl-butyrate (aprodrug of butyrate), DOX or PTX and evaluated the antiproliferative effect on human colorectal cancer cell line HT-28. -The combination formulations have higher cytotoxicity than the individual drug treatment.	[45]
Wu Yu Xiao *et al.*	DOX, chemosensitizer, GG918,	MDR breast cancer cell line (MDA435/lCC6/MDR1)	-Polymer–lipid hybrid NPs (PLN) was formulated. -The results confirmed that DOX and GG918 co-encapsulated PLN formulation showed a greater efficiency when compared with the single drug formulation on a MDR breast cancer cell line.	[60]
Thakkar A *et al.*	Ferulic acid (FA) and Aspirin (ASP)	MIA PaCa-2 and Panc-1 human pancreatic cancer cells	-The FA and ASPc-SLN (chitosan coated) combination showed a synergistic inhibition of cell viability and induced apoptosis in MIA PaCa-2 and Panc-1 human pancreatic cancer cells.	[61]
Prabhu S *et al.*	ASP, CUR, Sulforaphane (SFN)	MIA Paca-2 and Panc-1 cell lines	-Cell viability studies and aptosis assay revealed that the formulation showed synergistic effect. -It also proved that a nanoparticulate drug delivery regimen is beneficial for the chemoprevention of pancreatic cancer	[62]
Gulay B *et al.*	PTX, siRNA	HeLa cell line	-Vaginal suppository was prepared by using PTX and genetic material which can be applied locally for cervical cancer. -SiRNA was selected as genetic material which inhibits BCL2 oncogene. This combination were incorporated into SLNs and dispersed separately in vaginal suppositories. -This formulation indicated that vaginal suppository containing SLNs can brought the advantages of the simultaneous delivery of PTX and siRNA via vaginal route.	[63]
Li S *et al.*	Docetaxel (DTX), Baicalein (BA)	Lung cancer cells	-Transferrin tinted DTX and BA loaded SLNS (Tf-D/B-SLNs) were prepared. -(Tf-D/B-SLNs) is having ability to suppress lung cancer cells *in vitro* and *in vivo* was investigated. The best tumor inhibition ability and the lowest systemic toxicity were observed.	[64]
Torchilin VP *et al.*	DOX, α-tocopherol succinate (TOS)	MCF-7/Adr and NCI/Adr cancer cell lines	-Drug-resistant cancer cells in monolayer and spheroid model were selected for study. -The SLN co-loaded with Dox and TS showed a stronger cytotoxicity against MCF-7/Adr and NCI/Adr cells as compared to Single drug. -The co-delivery of both drugs in SLN showed a promising approach for combination cancer therapy.	[65]
Gulay B *et al.*	PTX, Herceptin	MDA-MB-453 cell line	-PTX-loaded cationic SLN/Herceptin complexes were more toxic to MDA-MB-453 cell line. -*In vitro* results proved this combinational therapy is beneficial for the treatment of cervical cancer therapy.	[66]
Bo Liu *et al.*	PTX, α-tocopherol succinate cisplatinprodrug (TOS-CDDP)	HeLa Cells	-Trans-activating transcriptional activator (TAT)-modified SLNs for co-delivery of PTX and TOS-CDDP were formulated. TAT PTX/TOS-CDDP SLNs showed a synergistic effect in the suppression of cervical tumor cell growth. -They showed high tumor tissue accumulation, superior antitumor efficiency, and much lower toxicity *in vivo*.	[67]
Prabhu S *et al.*	Ibuprofen (IBU), sulforaphane (SFN)	Panc-1 and MIA PaCa-2 cells	-IBU-SLN combination with SFN showed a synergistic inhibition of cell viability in human pancreatic cancer cells. -Cell-based assay and formulation studies revealed that low dose of IBU which was encapsulated in SLN formulation to prevent pancreatic cancer.	[68]
Wang X *et al.*	PTX, DOX	NCL-H460 cells	-PTX-DOX NLC achieved the highest cytotoxic effect. -*In vivo* investigation on NSCLC animal models showed that co-delivery of PTX and DOX possessed high tumor-targeting capacity and strong antitumor activity.	[69]

Influence of the emulsifier

The selection of the emulsifiers and their concentration has great importance on the dispersion quality of SLNs [51]. The surface tension reduces and supports the particle partitioning during homogenization when the concentration of the emulsifier is higher. During high pressure homogenization, the surface area increases very rapidly due to high pressure being applied on the dispersion leading to particle size reduction. Hence, the kinetic aspects have to be considered [15]. To some extent, the concentration of surfactant does affect, but once

the optimal concentration is reached, it may not significantly influence the particle size [52]. The primary process covers the new surfaces which compete with the agglomeration of uncovered lipid surfaces. The primary dispersion should contain an excessive quantity of emulsifier, which should cover the new surfaces rapidly. It has been reported that SLNs stabilized using combination of surfactants having lower particle size range and higher stability as compared to formulations having only one surfactant [15]. As per the reported studies, Tween 80 and Poloxamer 188 in combination showed lowest particle size and polydispersity index when it compared with Tween 80 alone. The presence of two surfactants i.e. Tween 80 and Pol-188 rapidly covered the new lipid surfaces generated during the shearing process thereby, avoiding aggregation and increasing surface area. Also the combination of emulsifiers and their HLB values could lead to different surface absorption [53].

Developed and formulated combinatorial nanoparticles for cancer therapy

Some research has been carried out on the combinatorial SLNs these literatures mentioned in table 3.

CONCLUSION

The goal of cancer treatment in the modern era is to target the cancerous cell without affecting normal cells selectively. Cancer therapy is extremely complicated, thus to overcome the problems with conventional therapy. Nano drug delivery is focused on SLNs combinatorial formulations having an optimal effect on tumor cells and can be delivered in a more effective way. SLNs have the potential to reduce the dose by reaching the target site, emphasizing on the synergistic effect of drugs used together thus the normal cells are not affected or only to a lesser extent resulting in a reduction of the dose associated toxicity of both drugs. The combinatorial approach in oncology with chemotherapeutic drugs using SLNs as a suitable Nano carrier could improve therapeutic efficacy, increase bioavailability and prevent tumor resistance. This approach could be considered as an innovative, promising, beneficiary approach for cancer therapy and supportive of achieving the desired therapeutic effect in a minimal dose of chemotherapeutic agents.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors have declared no conflict of interest

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