Review Article

Strategies in overcoming the challenges of cytotoxic agents using smart colloidal solid lipid nanoparticles and nanostructured lipid carriers - A review

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Received: 18 February 2019 Revised: 20 March 2019 Accepted: 30 March 2019

Abstract

Cancer is one of the most leading causes of morbidity and mortality worldwide causing 9.6 million deaths in 2018. However, for a variety of cancers the efficacy of current standard treatments is suboptimal. For, most of the cytotoxics are highly toxic which restrains their use in cancer treatment. Second, almost all cancer treatments lack specificity, affecting both the cancerous cells and their normal counterparts. Finally, hydrophobicity and short half lives exhibited by a number of chemotherapeutic agents restrict their efficacy. However, application of nanotechnology has led to the development of effective nanosized drug delivery systems known commonly as nanoparticles. Amid the different lipid based oral delivery systems, Solid lipid nanoparticles (SLN) and Nanostructured lipid carriers (NLC) specifically, have shown to be quite effective in manifesting the potentiality to; a) enhance selectivity of cytotoxics b) reduce the cytotoxicity to normal tissues c) improving the solubility of hydrophobic cytotoxics and d) offer a sustained and controlled release of agents. The current review summarizes the strategies using SLN's and NLC's in overcoming the challenges and enhancement of anticancer efficacy of cytotoxic agents to specific tumor targeting, including active and passive targeting, long circulating and MDR reversing.

Keywords: Cytotoxic agents, solid lipid nanoparticles, nanostructured lipid carriers, intracellular lipid transfer, tumor targeting

Introduction

Globally, cancer is the second leading cause of death, nearly 1 in 6 deaths is due to cancer. The increasing global burden of cancer and worldwide prevalence in the last decade, posed an extraordinary threat to the healthcare society. As per the recent WHO statistical report, around 45% enhancement in the global cancer mortality rate by 2030, of which 70% would be from developing countries like India (Plummer et al., 2016). Over the past two decades, great effort had been undertaken in order to ameliorate cancer therapy. Chemotherapy plays a major role in the malignancy treatment which is metastasized (Roland, 2007). Conventionally, cancer chemotherapy has focused on the identification and isolation of cytotoxic agents which includes antimetabolites, topoisomerase inhibitors, alkylating drugs, plant alkaloids, cytotoxic antibiotics, and other antineoplastic agents (Boyle and Levin, 2008; Mesri et al., 2014). Most of these cytotoxic agents can cause mitosis impairment, thus, effectively targeting the rapid cell division. As tumor cells undertake high rate of growth fractions, they are more sensitive to chemotherapy (Roland, 2007). But, unfortunately these agents are also effective in targeting the healthy cells. Owing to the low specificity, these cytotoxic agents are inclined to have a narrow therapeutic window with high dose limiting toxicities. Additionally, they are traditionally administered near to their maximum tolerated dose (Pérez-Herrero and Fernández-Medarde, 2015). The above factors critically restrict the clinical applications of the cytotoxic agents. Consequently, a great deal of attention is being dedicated for the improvement of the antitumor efficacy and safety profile of the anticancer drugs, and exploring alternative methods for delivery of both old and new therapeutic agents.

Cancer Nanotechnology is an emerging field of research with

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DOI: https://doi.org/10.31024/ajpp.2019.5.4.1

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great promise involving alliance among various disciplines such as chemistry, biology, medicine and engineering. Its primary goal is to design and develop novel technologies for advanced cancer diagnosis, detection, and treatment (Nie et al., 2007; Wang and Thanou, 2010; Begarani et al., 2018; Latini et al., 2018; Li et al., 2018; Sayour et al., 2018; Shen et al., 2018; Thurner and Debbage, 2018). The second half of the last century was experienced by a massive development in the pharmaceutical industry, with much importance being given to the advancement of biopharmaceutics and enhanced pharmacokinetics (Bazak et al., 2015). Due to which, the thought of a targeted, sustained and controlled drug delivery system was introduced for the first time.

With nanotechnology becoming more involved in the field of medicine, such a drug delivery system was made possible in the shape of submicron particles called nanoparticles (also known as nanospheres or nanocarriers) (Yingchoncharoen et al., 2016). The size range of nanoparticles varies between 100 to 1000 nm, normally composed of various matrix materials, and has varying mechanical properties as well as surface and physiochemical properties. The application of nanoparticles in drug therapy particularly in the field of oncology has been increasingly explored. Thus, nanoparticles can be designed with high selectivity to the tumor cells and showing prolonged release of active anticancer agents, both of which enhance the distribution, improve circulation time and reduce systemic toxicity of the anticancer agents in the biological system. Drug delivery systems comprising of nanoparticles can be designed in various systems such as nanosuspension, nanocrystals, nanotubes and nanowires, liposomes, ceramic nanoparticles, hydrogel nanoparticles, polymeric nanoparticles, polymeric micelles, copolymerized nanoparticles (CPP), functionalized nanocarriers, dendrimers, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC_s) (Conniot et al., 2014; Khodabandehloo et al., 2016; Sau et al., 2018).

Lipid based drug delivery systems are emerging to be an encouraging oral drug carrier systems because of their potential to enhance the solubility and improve the oral bioavailability of lipophilic drugs or poorly water soluble drugs (Patil-Gadhe and Pokharkar, 2014). The application of lipid nanocomposites has captivated the attention of many researchers especially in cancer treatment. The combination of lipids with the nanoparticulate delivery systems resulted in the development of a relatively new formulations of nanocomposites commonly known as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC's) (Muller et al., 2000; Chen et al., 2016). Lipids used to prepare lipidic nanoparticles are physiological lipids (i.e., biocompatible and biodegradable) with low acute and chronic toxicity (Alkurashi et al., 2014; Mak et al., 2018). In comparison to other drug delivery systems, SLN's and NLC's are emerging as a promising one due to their natural constituents and their potentiality to be produced on an industrial scale (Weber et al., 2014). They are composed of large variety of lipids which includes lipid acids or hard fats, glyceride mixtures, triglycerides, stabilized surfactants like polysorbates, poloxamers, soybean phospholipid or lecithin. Additionally, both of these lipid nanocomposites have important advantages, features which make them excellent delivery systems of anticancer agents (Karmakar et al., 2018; Soleimanian et al., 2018). In addition, different strategies of tumor targeting and recent trends involving the utilizations of SLNs and NLCs as anticancer drug delivery systems so as to enhance the efficacy of the anticancer agents need to be emphasized.

Prof. R. H. Muller and Prof. M. Gasco investigated the potential of a new nanoparticle based formulation called as solid lipid nanoparticles (SLNs). Their formulation was based on the lipids, contrary to existing organic nanoparticles (e.g. PLGA nanoparticles), with an advantage of avoiding an organic solvent during the precipitation method, and extending a high stability *in vivo* as they remained solid at body temperature. The succeeding feature made them an alternative not only to organic nanoparticles but also to the preceding lipid based formulations such as liposomes. But, low drug loading lead to a major drawback which seemed to compromise the future applicability and acceptability particularly with regard to anticancer agents of the formulation. Further investigations on the formulation showed an improvement of the SLNs. The inclusion of a liquid lipid to the solid matrix of the nanoparticle appeared to facilitate the number of imperfections in the core solid matrix, thus enhancing the incorporation of an increased amount of drug, while preserving the stability of the nanocarriers. This new unstructured matrix SLN was designed as nanostructured lipid carriers (NLCs). The primary cause of success was due to its ability to overcome hindrance in the development of lipid based nanoparticles and newly emanating applications for NLC formulations (e.g., P-gp efflux inhibition, colitis, theranostics).

Challenges to the oral delivery of cytotoxic agents to tumors

Aqueous solubility, stability in gastrointestinal tract, rate of dissolution from the dosage form, intestinal epithelium permeability, stability against liver cytochrome P450 metabolic enzymes, high toxic effects on the normal healthy cells, lack of stability, low specificity, P-gp efflux pump and the chances of developing MDR are some of the primary factors affecting the oral bioavailability of cytotoxic agents. These agents are highly reproducible in rapidly multiplying and dividing tumor tissues. Whereas,

healthy tissues such as bone marrow, lining of GI tract, oral mucosa and hair cells also multiply and divide rapidly which, may be affected by the anticancer agents leading to toxic effects. Due to which, symptoms such as nausea and vomiting, mouth soreness, loss of appetite, fatigue, anaemia, loss of hair, constipation or diarrhoea and pain or nerve changes are found in patients undergoing anticancer therapy. Few cytotoxic agents show extreme tissue specific toxicity called as dose-limiting toxicity (DLT) which make it impractical to achieve increased anticancer efficacy by dose escalation of the drug. For instance, cardiotoxicity is widely known dose limiting normal tissue toxicity for doxorubicin, epirubicin etc. (Curigliano et al., 2016). Due to these toxicities, increase in the dosage strength of cytotoxics is restricted to what there is an immediate requirement of the development of a suitable drug carrier for the cytotoxic agents which can diminish the toxicity on normal healthy tissues and enhance the therapeutic effect and its bioavailability in the malignant cells or tissues. The major challenges to the oral delivery of drugs to tumors are affected by the inherent and induced physiological barriers posed by the body and the physicochemical properties of the cytotoxics and the drug carriers.

Physiological barriers to the delivery of cytotoxics to tumors

Uncontrolled cellular proliferation leads to abnormal tumor architecture and composition resulting in malignant tumors. These abnormalities cause to be a major setback restricting the uptake and permeation of the cytotoxics (Khawar et al., 2015) (Figure 1). The circumference of the tumor is highly vascularised whereas the centre region is avascular. This diversity of the tumor vessels causes irregular distribution of the drug thus restraining the distribution of cytotoxics to the interior areas. The blood vessels in the tumor are enlarged, non-uniform, defective, and the endothelial cells are broken with large openings. In the vascular wall, the perivascular cells are frequently absent or abnormal, and the lymphatic network is always impaired (Pérez-Herrero and Fernández-Medarde, 2015). The swift proliferation of the tumor cells causes blood vessels to detach resulting in collapsed vessels which reduces the total vascular density (Golombek et al., 2018; Stylianopoulos et al., 2018; Yu et al., 2018). Therefore, nutrients and blood borne oxygen gets restricted to these cells. Hence, tumor cellular proliferation decreases as the distance from vessels increases. These unique tumor abnormities causes enhanced accumulation of high molecular weight compounds or nanocarriers (such as liposomes, niosomes and SLNs/NLCs) in the tumor vasculature, known as the enhanced permeability and retention (EPR) effect. The tissues devoid of enhanced permeability and retention effects, lesser amount of therapeutics are delivered ultimately offering more opportunity for the cytotoxics into tumor tissue. Thus, in passive tumor targeting of therapeutic drug delivery this EPR effect is believed to play an important principle. This EPR effect also acts as a hurdle as it offers scope for the high extravasation and retention of macromolecules in the tumor interstitium. Thereby, a tumor shows a high interstitial fluid pressure and reduced transvascular gradient. All these changes show a negative effect on the uptake and penetration of therapeutics, while transvascular and interstitial transport is regulated by convection (Kalaydina et al., 2018; Libutti et al., 2018; Nielsen et al., 2018).

The extracellular matrix (ECM) of a solid tumor comprises of a denser network of fibers, such as collagen, elastin and an increased number of fibroblasts and polysaccharides (such as glycosaminoglycan, hyaluronan) which provides opportunity for frictional resistance to drug transport (Ferreira et al., 2016; Alimoradi et al., 2018). These components form a gel-like extracellular environment that impairs the interstitial transport of drugs. Furthermore, a higher density tumor cell can reduce the interstitial transport of drugs. The penetration resistance primarily occurs as the uptake by the primary tumor cell layers encountered restricts the diffusion of cytotoxics to the succeeding layers (Bertrand et al., 2014).

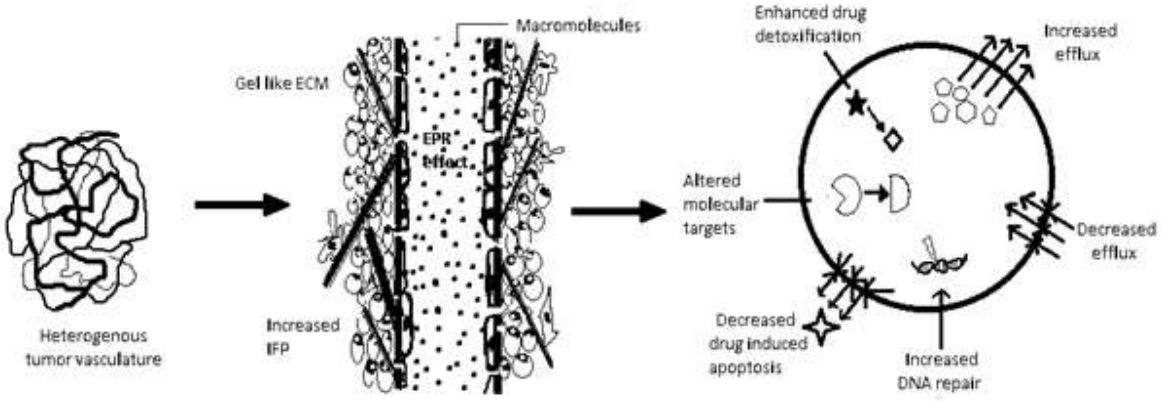

Figure 1. Different physiological barriers curbing the delivery of cytotoxics to the tumors (Khawar et al., 2015).

Multidrug resistance (MDR), a phenomenon where the tumor cells which show resistance to a diverse range of functionally and structurally unassociated therapeutics after treatment with a cytotoxic occur simultaneously or subsequently during the course of the therapeutic treatment. Increased incidence rate of MDR were being projected as the primary cause for the chemotherapy treatment failure. The most scrutinised mechanisms with their clinical importance includes i) activation of transmembrane proteins effluxing different chemical substances from the cells; ii) activation of the enzymes of the glutathione detoxification system; iii) alterations of the genes and the proteins involved into the control of apoptosis (especially p53 and Bcl-2) (Housman et al., 2014). The acquired MDR is attributed to a variety of mechanisms, including increased drug efflux due to overexpression of drug efflux transporters, reduced drug influx, increased DNA damage repair, altered molecular targets, decreased drug-induced apoptosis, enhanced drug detoxification or elevated glycolipid levels (Wang et al., 2010; Goldman, 2018; Casals et al., 2017; Jaiswal et al., 2017; Song et al., 2018). One of the most important mechanisms of MDR is the overexpression of transmembrane efflux transporters, such as P-glycoprotein (P-gp) (most typical efflux pumps in the cell membrane) (Callaghan, 2015; Hano et al., 2018) and multidrug resistance-associated protein 1 (MRP1) (Blanco et al., 2015).

P-gp, encoded by the multidrug resistance-1 (MDR1) gene usually gets localized in enterocytes leading to the excretion of drug back in to the intestinal lumen. Over expressions of P-gp and MRP1 constitutively dispersed in the tumor cells originating from various organs, including colon, liver, kidneys, brain and pancreas, intestinal epithelia, hepatocytes, various glands and capillary endothelial cells comprising blood–brain and blood–testis barriers. Also, expressed in normal cells in the digestive system including the small intestine, large intestine, liver, and pancreas; epithelial cells in the kidneys, adrenals, brain, and testes; and endothelial cells. These efflux transporters are membrane associated protein belonging to the superfamily of ATP- binding cassette (ABC) transporters with the molecular weight of 170 kDa and N-terminal glycosylation and from the aspect of the tissue distribution, ATP- binding cassette (ABC) transporters participate in the absorption and secretion of endogenous and exogenous substances (Table 1). Especially, the ABC transporters function as an efflux pump for a broad range of cytotoxic drugs out of cancer cells, resulting in a lower intratumoral drug concentration of lipid, multiple drugs, natural products and peptides. Consequently, tumor cells become cross-resistant and survive the cytotoxic insult even though a cytotoxic drug has marked with a great degree of *in vitro* efficacy. The ABC transporters driven by the energy of ATP hydrolysis, acts as a hydrophobic vacuum cleaner thereby effluxing non-polar compounds from the membrane bilayer to the exterior (Rizwanullah et al., 2016). Its structure is made up of two equal length homologous chains, each comprising six units of transmembrane domains and two ATP binding sites separated by a flexible linker polypeptide region between the two homologous chains (Nanayakkara et al., 2018;

Table 1. Physiological distribution and cytotoxic substrates for various membrane efflux proteins.

ABC transporters	Physiological distribution	Cytotoxic substrates	Endogenous substrate
MDR1 (ABCB1, P-GP)	Apical membrane of epithelial cells of proximal tubule of kidney, luminal membrane of endothelial cells in blood brain barrier, canalicular membrane of liver, endothelial cells of capillary in testis, trophoblast of placenta.	Paclitaxel, Vincristine, Docetaxel, Doxorubucin, Teniposide, Methotrexate.	Aldosterone, Estriol, Cortisol
MRP1 (ABCC1)	Brain and many other organs.	Vincristine, Vinblastine, Doxorubucin, Daunorubicin, Epirubicin, Etoposide.	Glucuronosyl bilirubin, Glutathione S-conjugate leukoetriene C4.
MRP2 (ABCC2, cMOAT)	Kidney, Liver, Placenta, Gut.	Vincristine, Vinblastine, Doxorubucin, Cisplatin, CPT-11, Methotrexate, SN-38 ((active metabolite of irinotecan), Epirubicin, Etoposide	Estradiol-17beta(beta-D-glucuronide), Glutathione Sconjugate Leukoetriene C4.
MRP3 (ABCC3)	Adrenal Cortex, Placenta, Gut, Liver.	Cisplatin, Methotrexate, Doxorubucin, Teniposide	S-(2,4-dinitrophenyl) glutathione
MRP4 (ABCC4)	Many tissues.	6-Thioguanine, Methotrexate, 6-Mercaptopurine.	Glucuronide and conjugates of glutathione.
MRP5 (ABCC5)	Brain and many other tissues.	6-Mercaptopurine, Cisplatin, Doxorubicin, Methotrexate, Oxaliplatin, Thioguanine, 5-Flurouracil.	Glutamate and conjugates of phosphate.
MRP6 (ABCC6)	Kidney & Liver.	Etoposide, Teniposide, Doxorubicin, Cisplatin.	Cyclic nucleotides (cAMP, cGMP), conjugates of glutathione
MRP8 (ABCC11)	Testes & Breast.	5'-Fluorouracil.	Leukotriene C4, cyclic nucleotides, 17beta-estradiol-(17-beta-D-glucuronide).
BCRP (ABCG2, MXR1, ABCP)	Canalicular membrane of the Liver, Gut, Epithelium of the Intestine, Syncytiotrophoblasts of the Placenta, Ducts and Lobules of the Breast.	Gefitinib, Genistein, Imatinib, Irinotecan, Methotrexate, Methotrexate diglutamate, Methotrexate triglutamate, Mitoxantrone, Quercetin, SN-38 (active metabolite of irinotecan), Daunorubicin, Doxorubicin, Epirubicin, Epirubicin.	Porphyrin or Heme.

MRP: Multiple resistance protein; BCRP: Breast cancer resistance protein.

Waghray and Zhang, 2018).

It mainly operates at three major locations, luminal (apical) membrane enterocytes where the drug is limited by entering in the body i.e., canalicular membrane of hepatocytes with an increased elimination in to bile and urine and sensitive tissues such as brain, lymphocytes, testis, and fetal circulation limiting the drug penetration (Xu et al., 2018; Fu et al., 2019). Most of the anticancer drugs are the substrates for P-gp including, docetaxel, paclitaxel, vinblastine, vincristine, etoposide, doxorubicin etc..

Two kinds of ATPase activity expressed by P-gp includes basal stimulated by endogenous lipids, other hydrophobic peptides and drug stimulated ATPase activity. Based on the unique binding property, the drugs impart different kind of ATPase activities on the P-gp. Basing on this property of the drug substance, ATPase activity on P-gp can be classified into three categories (Lee et al., 2013; Sharom, 2014). Class I agents (e.g., verapamil, vinblastine and paclitaxel) activate ATPase activity at low concentrations but inhibit the activity at high concentrations. Class II compounds (e.g., valinomycin, bisantrene and tetraphenylphosphonium) stimulate ATPase activity in a dose dependent manner without any inhibition. In contrast, Class III compounds (e.g., cyclosporin A, gramicidin D and rapamycin) inhibit both basal- and verapamil-stimulated ATPase activities. The mechanism of drug efflux by P-gp can be measured on the basis of various models such as pore model, flippase model, and hydrophobic vacuum cleaner (HVC) model, among which HVC model has gained wider acceptance (Renukuntla et al., 2013).

ATP binding and hydrolysis are the most important processes for the drug efflux where two molecules of the ATPs, one molecule of the drug is effluxed. The first cycle begins with the binding of the drug to the ATP at their respective sites subsequently by the conformational change which is regained in the second cycle by the hydrolysis of another ATP molecule (Mitra and Dash, 2018). P-gp plays an important role in the ADME of the drug molecules as it's widely distributed throughout the biological system. This has been proven experimentally with the help of anticancer drugs such as paclitaxel whose oral bioavailability has been enhanced significantly in mice with MDR 1 knocked out and in mice administered with the P-gp inhibitor, PSC-833 (Kim et al., 2018).

First pass effect of drugs

Gastro-intestinal and hepatic availability is defined as the bypassing of therapeutics from the metabolizing effects of the GI-tract and the liver. The luminal metabolism also known as gastro-intestinal metabolism, is discharged by digestive enzymes secreted by pancreas such as lipase, amylase and peptidases and from the bacterial flora located primarily in the lower part of the gastrointestinal tract. Brush border and the intracellular metabolism also takes a major role for first pass intestinal metabolism. The brush border metabolism is especially maximum in the proximal small intestine and is performed by the enzymes such as alkaline phosphatase, isomaltase sucrase and various peptidases (Yun et al., 2013).

Extrahepatic microsomal enzymes located inside the cytoplasm on the endoplasmic reticulum performs the intracellular metabolism in the gut. Cytochrome P450 3A family, especially CYP 3A4, phase I metabolizing enzymes, located in the enterocytes which leads to the metabolism of the drug substances at the gastrointestinal wall. Phase II metabolizing enzymes such as glutathione-S transferases, esterases, etc. were also been reported to be located in the intestine (Jones et al., 2016). The drug after passing absorption stage in GI-tract, through the entero-hepatic portal vein is collected in the liver, where a portion of the drug absorbed is metabolised as it a hub of various enzymes, which is termed as First Pass Hepatic Metabolism (FPHM). This first pass metabolism plays a significant role in lowering oral bioavailability of many drugs e.g. tamoxifen (Dalasanur et al., 2018; Pangeni et al., 2018). Liver is also called as metabolic clearing house for both endogenous chemicals (e.g., cholesterol, steroid hormones, fatty acids, and proteins) and xenobiotics (Gonzalez and Tukey, 2006). The drugs which are substrates for cytochromes usually have an incidence of being substrates for P-gp simultaneously, thereby leading to further lowering the bioavailability. Both of these work are done simultaneously and requires careful consideration while designing of oral drug delivery system for their substrates, e.g. level of CYP 3A4 reduces from proximal to small intestine on the other hand P-gp expression increases in same flow (Lin and Wong, 2017).

Physicochemical characteristics of the anticancer drugs

Lipinski reported the prototypical connection between solubility, permeability and potency. It stated that the amount sufficient for the solubility of a therapeutics can be known on the basis of the permeability and potency of a therapeutics (Bhakay et al., 2018). *In vivo* bioavailability of a therapeutic agent is based on its pharmacokinetics (what the *body* does with the *drug*) and pharmacodynamic (action of *drugs* on the human *body*) response. The absorption segment of the pharmacokinetics can be determined by the Fick's First law of diffusion, which states that which states that flux (J) of therapeutic for physiological exposure is directly proportional to the permeability coefficient (inclusive of drug efflux) and concentration of therapeutic in the gastrointestinal lumen (inclusive of solubility, dissolution and stability of drug within the GIT) (Quan et al., 2017). Therefore, the restricted oral bioavailability of the drugs could therefore be designated as

solubility limited, permeability limited and both permeability and solubility limited. According to BCS (Biopharmaceutics Classification System) classification, these candidates with dose number much greater than 1 are categorized as Class II (high permeability, low solubility) and requires attempt for the enhancement of solubility in order to increase the bioavailability. Classical examples include busulfan, gefitinib, imatinib, regorafenib monohydrate etc. Candidates with adequate solubility and low permeability are categorised under Class III of the BCS system which includes methotrexate, gimeracil, examestane, doxorubicin etc. Permeability values 10×10−6 cm/s are considered as poorly permeable and requires improvement in its permeability (Cao et al., 2018; Ferraretto et al., 2018). More than 65% of anticancer drugs are available as oral dosage forms for clinical usage but practically, only few of them are used due to their poor physicochemical characteristics and efflux mechanisms restricting oral bioavailability. In order to propagate research in the field of oral anticancer drug delivery and to develop a rationalised drug delivery system, the exact usage should be identified.

Absorption mechanism of lipid drug delivery systems

Lipid based nanocarriers have been extensively used for the enhancement of the oral bioavailability of many difficult to administer hydrophilic and liphophilic drugs. The excipients primarily consists of glycerides (monoacylglycerols, diacylglycerols and triacylglycerols), liquid lipids consisting of oils of various combinations of phospholipids, glycerides, sphingolipids etc. (Batchelor, 2015). The major problem of drug molecules is either poor aqueous solubility or low intestinal permeability which needs to be overcomed for maximim efficacy in the body. Lipids are widely used as a carrier for drug delivery systems due to their unique properties such as biocompatibility, higher degree of solubilization, specific mode of absorption bypassing different physiological barriers such as GI degradation, pre-systemic metabolism, P-gp efflux and permeability, industrial adaptability, and manufacturing scalability (Kalepu and Nekkanti, 2015).

The solubility of the drug molecule in the lipidic system and the subsequent processing of the lipid carrier loaded with drug in order to attain sufficient bioavailability are the two most important features which attributes for the design and development of the lipid based drug delivery system (Figure 2). Inside the stomach, gastric and lingual lipases digest the fatty acids, glycerides thereby generating crude lipidic emulsions stabilised by dietary proteins, polysaccharides etc. The partially digested crude lipidic emulsions subsequent to gastric emptying comes in contact with the bile salts, cholesterols and phospholipids mainly phosphatidylcholine which is secreted by gall bladder and pancreatic lipase secreted by the pancreas which is then adsorbed on the periphery of the droplets of crude lipidic emulsion. This adsorption on the surface leads to digestion and formation of small sized emulsion droplets which again comes in contact with fatty acids and 2- monoglycerides (lipid digestion products), as a result of which the process of lypolysis is self promoted (Talegaonkar et al., 2010). The micelles which is formed gets absorbed on the enterocytes, which on re-esterification by monoacyl glycerol or phosphatidic acid pathway gets converted into chylomicrons. These chylomicrons then enters into the lymphatic transport system through the mesenteric lymph, finally available in the systemic circulation by lymphatic drainage at the thoracic duct (Feeney et al., 2016; Yasmin et al., 2016; Talware et al., 2018).

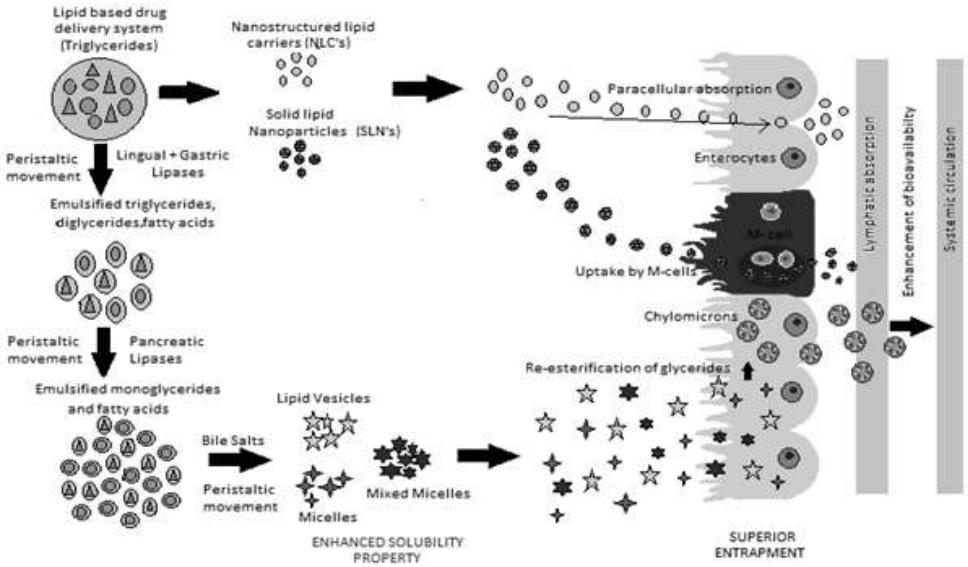

Figure 2. Processing of the lipid carrier loaded with drug and its absorption mechanism for the enhancement of oral bioavailabilty (Talegaonkar et al., 2010).

Rationale behind the use of SLN's and NLC's in cancer chemotherapy

A malignant growth or tumor is a leaky, flawed vascular architecture because of imperfectly regulated nature of tumor angiogenesis and inadequate drainage of the interstitial fluid from the tumor tissue by a poorly formed lymphatic system. Due to which the submicronic particulates preferentially gets extravasated into the tumor tissue, it is called as the enhanced permeability and retention (EPR) effect (Fernandes et al., 2018). The drawback of this EPR effect can be taken advantage of by a well designed and developed nanostructured drug carrier system such as SLN and NLC in order to achieve passive tumor targeting. Due to which, the aforementioned irregular tissue specificity issue gets partially resolved. The systemic availability of SLN and NLC could be further be regulated by modifying the surface physicochemical features of the carriers only to target them to the tissue of interest ultimately maximising the drug amount at the targeted tissue and reducing systemic drug toxicity. Cytotoxics are highly heterogenic comprising a class of molecules with diverse physicochemical properties and molecular structure (Ewesuedo and Ratain, 2003; Li et al., 2016). The versatility of carrier polymers is thus exceedingly inevitable for the encapsulation of incompatible cytotoxic mixtures with the use of nanocomposites.

Similar to other nanocomposite drug carriers, SLN possess various advantages as protection of the labile drugs, physical stability, sustained release, high tolerability and economical production process. Subsequently avoiding issues related to low drug loading, immediate release of drug from the emulsion, drug leakage from the carrier and high cost of for large scale production (eg., liposomes) (Muller et al., 2000; El-Say and Hosny, 2018; Ghasemiyeh and Mohammadi-Samani, 2018). SLN improves the anticancer activity of the cytotoxics thereby enhancing the pharmacokinetic and bioavailability of the cytotoxics and reducing the toxic side effects of the drugs.

SLN possess a perfect lipid crystal lattice which reduces the drug loading percentage and drug expulsion from the carrier on storage. An advanced generation of SLN known as NLC, composed up of both liquid and solid lipids has as imperfect crystal structure or an amphorous lipid lattice. This imperfect structure allows loading of drug both in molecular form and also in clustered aggregates at the lattice imperfections thereby showing higher drug loading and stable formulation minimising expulsion of drug during the preparation and also on storage (Muller et al., 2002; Doktorovova et al., 2014).

Emerging trends based on SLN and NLC to overcome the chemotherapeutic challenges

Lipid nanocomposite carriers such as SLN and NLC are greatly emerging as an potential carrier for cytotoxics. Reports from tissue culture and *in vivo* studies have also proved that there is tremendous progress in the anticancer activity of the cytotoxics and reducing tissue toxicity. Summary of the cytotoxics formulated in NLC and SLN till date and their improvement in oral bioavailability is listed in table 2. The cytotoxics are delivered at the target site through various mechanisms which is discussed below.

Passive targeting of SLN and NLC loaded with cytotoxics

When SLN and NLC's are administrated parentally, they immediately bind with opsonins in blood which is then cleared subsequently by the reticuloendothelial system (RES). Passive targeting to tumors is highly conducive only when the tumor is loacted in this system and also it diminishes the toxicity effects as lesser amount of cytotoxics are distributed to other tissues. Doxorubicin, a broad spectrum anticytotoxic agent with therapeutic effect especially on lymph tumor shows severe cardiac toxicity. After encapsulating Doxorubicin in SLN when administered parentally, lower amount of drug was accumulated in the heart in thereby reducing cardiac toxicity. This leads to the conclusion that SLN encapsulated doxorubicin by passive targeting minimises the unwanted normal healthy cell toxicity (Yingchoncharoen et al., 2016).

The EPR effect of a tumor helps SLN and NLC to differentiate between the malignant cells and normal healthy tissues. SLN and NLC show improved effect on the tumor in comparison to the solution formulations. Docetaxel encapsulated in NLC showed improved cytotoxicity activity against A549 cells (Liu et al., 2011). Novel C-substituted diindolylmethane (DIM) derivatives DIM-10 and DIM-14 in aggressive Triple negative breast cancer (TNBC) models showed 4.73 and 11.19-folds increase in maximum serum concentration (Cmax) and area under the plasma drug concentration time curve (AUC) values respectively in comparison to DIM-10, DIM-10 suspension (Chandraiah et al., 2016). Long chain lipid based tamoxifen loaded nanostructured lipid carriers was assessed in human estrogen receptor expressing breast cancer cell lines viz. MCF-7 and ZR-75-1 exhibited an increment in the bioavailability by 2.71-fold and sustained the half life by 7.10-fold in comparison to the Tamoxifen suspension (Shetea et al., 2013).

The ability of camptothecin loaded solid lipid nanoparticles (SLN) targeted to deliver into the brain parenchyma after crossing the blood–brain barrier was investigated. Camptothecin-loaded SLN demonstrated induced cell death with the lowest maximal inhibitory concentration (IC_{50}) values, revealing higher antitumor activity against glioma and macrophage human cell lines. *In vivo* biodistribution

Table 2. List of cytotoxics loaded in SLN and NLC thereby improving their cytotoxic activity

Cytotoxic agent	Type of carrier	Solid and Liquid lipids	Particle size (nm)	Zeta (mv)	Cytotoxicity study	*In vivo* study	Therapeutic effects	Ref.
Docetaxel	SLNs	Trimyristin, 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-2000] (DOPE-PEG-2000)	182.8± 2.0	-30	TC-1 cells (murine lung cancer cell line) and Human breast adenocarcinoma cells (MDA-MB-231)	Female C57BL/6 mice	Concentration of drug in male albino rats was higher in tumor tissues but decreased in liver, spleen, heart, lung and kidney.	(Naguib et al.2014)
Docetaxel	NLCs	Glyceryl monostearate, Miglyol 812N	-	-	-	Eighteen male pathogen-free Sprague–Dawley rats (220–250 g) and 54 male Kunming mice (20–25 g)	The pharmacokinetics in rats and tissue distribution in mice-bearing sarcoma-180 cells showed increased AUC_{0-t} of docetaxel and prolonged MRT. Concentration of docetaxel in tumor and kidney for folate-PEG-NLCs were significantly higher than for the solution.	(Zhao et al.2011; Mosallaei et al. 2013)
Doxorubicin	SLNs	Emulsifying wax	<100	−5 to −15	P388/ADR	Six-week-old male athymic NCr-nu/nu mice	In comparison to the free drug solution, *in vitro* cytotoxicity study against P388/ADR cancer cell lines showed around nine fold increase.	(Kapse-Mistry et al. 2014; Coburn et al. 2015)
Doxorubicin	NLCs	Monostearin, Oleic acid	368.9± 35.7	−33.2 ± 2.2	MCF-7/ADR cells, SKOV3-TR30	-	Reversal potencies of MCF-7/ADR cells and SKOV3-TR30 in the *in vitro* cytotoxicity study were increased 6.4- and 2.2-fold respectively.	(Zhang et al.2008; Doktorovova et al 2014)
Emodin	SLN	Compritol 888 ATO, glycerol monostearate (GMS), stearic acid , lauric acid	28.6± 3.1	-15 to -20	MCF-7 and MDA-MB-231	-	Higher *in vitro* cytotoxicity of SLN against MCF-7 and MDA-MB-231 cancer cell lines in comparison to free drug solution.	(Wang et al.2012)
Etoposide	SLN	Compritol® 888 ATO, Stearic Acid, DSPEPEG 2000-CA	125–210	−13 to −32	HBMECs, U87MG	-	Increased permeability of Etoposide loaded SLN through Blood brain barrier.	(Kuo and Lee 2016)
5-fluorouracil	Ferritin - SLNs	Triolein, cholesterol, Hydrogenated soya phosphatidylc-holine (HSPC), Distearoylpho-sphatidylethan-olamine (DSPE)	152.12±3.52	2.5 ±0.52	MDA-MB-468	BALB/c mice	IC_{50} of Ferritin-SLNs was 1.28 µM, while non-targeted SLNs had an IC_{50} of 3.56 µM. Effective reduction in tumor growth of MDA-MB-468 tumor-bearing BALB/c mice compared with free 5-FU.	(Jain et al.2008; Patel et al. 2014; Wang et al. 2016)
Hydroxy camptothecine	Octreoti-de PEG-NLCs	Soybean phospholipids, Trilaurin, Labrafac CC and vitamin E	113.7 ±2.4	-3.74 ±1.25	SMMC-7721	Sprague-Dawley (SD) rats	The pharmacokinetics in rats showed 10 fold longer t1/2 in comparison to free solution. *In vitro* cellular uptake in SMMC-7721 cells was the highest.	(Su et al.2011)
Methotrexate	SLN	Stearic acid	215 ± 3.5	-17 ± 0.24	MCF-7, Mat B-III cell lines	Adult Wistar male rats (weight 500 g)	MTX-SLN showed a significant enhancement in $t_{1/2}$ and mean residence time in comparison to free drug solution. The life span of Ehrlich Ascites Carcinoma bearing mice was increased upon treatment with MTX-SLN as compared to free drug solution.	(Moura et al. 2011; Ezzati et al.2015)
Paclitaxel	Brij 78-SLNs, F68-SLNs	Stearic acid, Cremophor EL	103.5± 29.2 and 220 ±98	-16 to -28	-	Male KM mice	Brij 78-SLN and F68-SLN showed slow drug elimination with $t_{1/2}$ values of 4.88h and 10.06h in comparison to paclitaxel injection whose $t_{1/2}$ value was 1.36h.	(Chen et al.2001; Bernabeu et al. 2016)
Paclitaxel	NLCs	Monostearin, Oleic acid	501.6± 41.9	−38.7 ± 2.7	MCF-7/ADR, SKOV3-TR30	-	MCF-7/ADR cells and SKOV3-TR30 cells exhibited 34.3 and 31.3 fold reversal power respectively.	(Zhang et al.2008; Yang et al. 2013)
Tamoxifen citrate	SLNs	Glycerol behenate, Tristearin, tripalmitin	232± 2.7	-30±2	-	Albino rats	In comparison to free drug solution, tamoxifen citrate loaded formulation showed a 3.5-fold enhancement in the mean residence time.	(Reddy et al.2006; Thanki et al. 2013)
Tocotrienol	NLCs	Compritol® 888 ATO, Dynasan® 118, Precirol® ATO	113.6	-27 to -36	+SA mammary epithelial cells	-	Drug loaded NLC exhibited 2-fold lower IC_{50} in comparison to free drug solution.	(Ali et al.2010; Agrawal et al. 2016)

studies performed in rats showed significant higher brain accumulation of camptothecin, compared to non-encapsulated counterparts. These results give an indication that they have bypassed the blood--brain barrier (BBB) (Susana et al., 2013). By modifying the surface hydrophilicity, surface charge, surface mobility, particle size and surfactant ratio, brain targeting efficiency was enhanced using SLN. After half an hour of treatment with doxorubicin-loaded PEG-modified SLNs, there was fivefold higher doxorubicin concentration in brain. Whereas, no detectable doxorubicin concentration of doxorubicin in the brain in case of suspension (Ezzati et al., 2015; Yingchoncharoen et al., 2016; He et al., 2018). Some commonly used hydrophilic emulsifying agents like tween 80, pluronics improve the drug uptake to the brain thereby reducing the efflux activity of P-gp in BBB. Thus it can be concluded that both SLN and NLC act as excellent carrier by enhancing the ability of a drug to bypass the blood brain barrier and targeting the brain and disorders of CNS.

Active targeting of SLN and NLC loaded with cytotoxics

Targeting of all the cancerous cells randomly is not always feasible as the diffusion rate of few cytotoxics through the cells is low which makes it difficult to control the process thereby inducing multiple drug resistance (MDR). Overexpression of the cytotoxics on the surface of cancerous cells by the carrier proteins lowers the therapeutic effect thereby developing resistance to one more or drugs by the cells (Blanco et al., 2015). The permeability vessels in the tumor cell may not be uniformly arranged and the EPR effect is not exhibited by some of the tumors. In order to overcome these limitations, the nano lipid carriers (SLN's and NLC's) can be attached with ligands that will bind only to specific receptors sites located on the tumor surface (Bertrand et al., 2014). Folate receptors, aptamers, ferritin, peptides and monoclonal antibodies are the most commonly used ligands. Paclitaxel-7-carbonyl-cholesterol, a lipophilic prodrug of paclitaxel when loaded in NLC along with a ligand i.e., folate polyethylene glycolcholesterol to target folate receptors present on the tumor cells. There was fourfold reduction in IC_{50} with FR-targeted NLCs compared with non-targeted NLCs (0.61 vs 2.82 μM in folate receptor (FR) and KB (a human oral carcinoma cell line) cells). Increase in both tumor growth inhibition rate and animal survival rate in mice FR (+)M109 tumors was reported when targeted with FR-targeted NLCs in comparison with non-targeted NLCs (Stevens et al., 2004; Mura et al., 2015). Formulation containing paclitaxel encapsulated stearyl-2-amino-2-deoxyglucose (2-DG) modified NLC actively and efficiently accumulated at the site of the tumor and had good antitumor effectiveness and low toxicity in MCF-7 tumor bearing mice (Jing et al., 2012; Mirahadi et al., 2018). Vascular endothelial growth factor receptors (VEGFRs) act as a potential targets for "double targeting" (tumor- and vascular-targeting) tumor therapy. These are overexpressed on the surface of a variety of tumor cells and on tumor neovasculature *in situ*. Developement of an antibody modified docetaxel loaded targeted NLC (tNLC) with DSPE-PEG-NH2 as a linker showed that the tNLC exhibited increased drug accumulation both in tumor and tumor vasculature proved by the cellular uptake and biodistribution studies (Donghua et al., 2011). Transferrin-modified NLC as multifunctional nanomedicine for codelivery of enhanced green fluorescence protein plasmid (pEGFP) and doxorubicin (DOX) was developed by Yiqun et al. *In vivo* transfection efficiency of the modified vectors in mouse bearing A549 cells model demonstrated enhanced antitumor activity when treated with T-NLC. Also coating of active transferrin improved the lung cancer cell-targeting of the carriers (Y Han et al., 2014).

Approaches of SLN and NLC nanocomposite carriers to reverse MDR

As discussed earlier, multi-drug resistance (MDR) is the most perilous cause for incompetency in the treatment of cancer. Due to overexpressions of ABC transporters mainly MRP1 and P-gp, the efflux rate of the drug increases causing MDR. It also has no specific differentiation in the chemical structure and intracellular target of the drug. In order to restrict this MDR effect, researchers are targeting to block specific drug efflux. In the formulation of paclitaxel (PTX) and doxorubicin (DOX) loaded NLC for the application to human breast cancer (MCF-7) cells, human ovarian cancer (SKOV3) cells and their multidrug resistant (MCF-7/ADR and SKOV3-TR30) cells, in comparison to taxol and doxorubicin solution, NLC loading PTX exhibited 34.3 folds high cytotoxicities in both MCF-7 and MCF-7/ADR cells while the NLC loading DOX only indicated 6.4 folds high cytotoxicity in MCF-7/ADR cells. The reversal power in MDR cells was improved when the NLC was modified with folic acid, showing a potential application for reversal multi-drug resistance in human cancer cells (XG Zhang et al., 2008; Shao et al., 2015). SLN formulation prepared by freeze-drying process in order to achieve more stability to the peptide showed considerable cytotoxic effect on cDDP resistant C13* ovarian carcinoma cell line at concentration 50 times lower than that used previously with a marketed drug delivery system. An increase in the apoptosis percentage was observed on SLNs-peptide treated cancer cells, which was calculated from the cell cycle analysis by propidium iodide test. From this study it was reported that the SLNs were able to carry efficiently the peptide until its enzymatic target site (Francesca et al., 2015).

Drug enters into the tumor cells in two different ways; either by simple diffusion or by phagocytosis. The drug carried by

phagocytosis process remains attached to the carrier molecule due to which the drug could bypass the efflux action handles by the membrane associated P-gp. Therefore, at the P-gp overexpressing cells more drug molecules remains confined in comparison to free drug solution. Internalization of drug into the tumor cells occurs due to nano range particle size of the nanocarriers and high membrane affinity. This results in an enhanced drug concentration intracellularly (Kirtane et al., 2013). Hyaluronic acid, a high molecular linear glycosaminoglycan, due to its biocompatiblity, biodegradablity, non-toxic and non-immunogenic property acts as an attractive polymer in the field of active targeting of anticancer drug. The frequent overexpression of HA receptors CD44 and CD168 (RHAMM) on many types of tumors opens new avenues for targeting. P-gp inhibitors such as cremophor EL, polysorbate 80, D-alpha-tocopheryl poly (ethylene glycol 1000) succinate (TPGS), Poloxamers and chitosan derivatives have also proven effective against MDR resistance. Fang Wang et al developed hyaluronic acid (HA) decorated pluronic 85 (P85) coated SLN loaded with paclitaxel (HA-PTX-P85-SLN) and evaluated its potential to overcome MDR in mice bearing cervical and breast tumor (Fang et al., 2017). Poloxamer and 1,2-distearoyl-sn-glycero-3-phosphatidel-ehanolamine (DSPE) conjugate was synthesized. The DSPE terminal (the lipophilic terminal) was encapsulated into the core of SLN, and the Pluronic terminal (the hydrophilic terminal) was covered on the surface of SLN. Paclitaxel loaded SLN showed a mean diameter of 160.3nm and exhibited outstanding sustained release profiles in comparison to free Paclitaxel. The pharmacokinetics biodistribution findings conducted in mice bearing cervical and breast tumor results indicated a 5.5 fold increase in AUC and higher tumor drug concentration respectively.

P-gp inhibitors, such as cyclosporine A and verapamil, have been shown to reverse the MDR1 phenotype in a variety of Paclitaxel resistant human cancer cells but during clinical trials, they failed to restore the treatment response in p-gp-expressing tumors. Jong S. B. *et al* (Jong et al., 2012; Baek et al., 2016) examined on Paclitaxel loaded SLNs modified with 2-hydroxypropyl-β-cyclodextrin (HPCD) to overcome the efflux by p-gp in MDR-resistant cells. The cellular uptake of PTX from PTX loaded SLNs modified with HPCD was about 5.8 and 1.5 fold higher than that from PTX solution and unmodified PTX-loaded SLNs in MCF-7/ADR cells, respectively. The cellular uptake of PTX was enhanced by 1.7 fold when PTX loaded SLNs modified using HPCD were incubated for four hours with MCF-7/ADR cells. All the above results suggested that, the active targeting of tumors by the use of SLNs/NLCs helps to overcome the MDR by specifically targeting the tumor cells thereby enhancing endocytocis subsequently, bypassing or avoiding the efflux pump of P-gp.

Design and development of SLN and NLC to bypass mononuclear phagocyte system barrier

Mononuclear phagocyte system also known as reticuloendothelial system plays an important role in human immune system comprising of phagocytic cells which eradicates the drug carriers when identified as foreign particles. These are located in lymph nodes, Kupffer cells in liver and spleen. The functionality of the lipid nanocarriers gets restricted due to their rapid blood clearance and identification by the mononuclear phagocytic system. The low circulation time of the nanocarriers within the body reduces the opportunity to bind to the specific receptors at the tumor site thereby reducing active targeting. Due to which prolongation of the circulation time of SLN's and NLC's should be enhanced by surface modifying with a hydrophilic polymers so that it couldn't be easily recognised by mononuclear phagocyte system (Kim et al., 2017; Sangrà et al., 2017).

Nanocarriers such as NLC or SLN when covered with polymers such as poloxamers or polyethylene oxide (PEO), there occurs enhancement of surface adsorption of proteins which suppress the opsonisation *in vivo*. As a consequence of which the carrier becomes more resistant to the reticuloendothelial system clearance thereby increasing the circulation time within the body. These polymer coated nanocarriers are often referred to as "stealth" as they could seemingly escape the surveillance of the immune system. The half life of these stealth nanocarriers is prolonged in the blood i.e., from few hours in rodent models to as high as 55hours in human subjects (Yan et al., 2016). These stealth nanocarriers coated with hydrophilic polymeric materials and amphipathic materials where the hydrophilic part covering the outer surface and the lipophilic part attached to the interior portion of SLN and NLC are in great use nowadays. The length of the polymer chain and circulating time are directly proportional to each other as the circulation time of PEG-DSPE (distearoylphosphatidylethanolamine) coated Paclitaxel loaded SLN with F-68 was prolonged due to the presence of a longer hydrophilic chain exhibiting a stronger forbidden force on the plasma protein (Chen et al., 2001; Bernabeu et al., 2016).

Tamibarotene (Am80), a poorly water-soluble drug used for the treatment of acute promyelocytic leukemia (APL) showed significant prolongation in Mean Residence Time (MRT) and improved Area Under the Curve (AUC) value when loaded in PEGylated NLC. Am80-PEG-NLC modified with PEG-40 stearate (PEG40-SA, molecular weight 2000 Da) improved the solubility of Am80 and sustained the circulation time in blood (X Liu et al., 2015).

PEG40-SA, an amphiphilic polymeric derivative of hydrophilic PEG modified by attaching a hydrophobic moiety, was easily incorporated into the lipid core of colloidal carriers with the hydrophilic PEG chain on their surface. The biodistribution was notably different in the Am80-PEG-NLC group and the Am80-NLC group. The concentration of Am80 in kidney was much lower for the Am80-NLC group thereby reducing the potential side effects to kidney as PEGylation results in a decrease of the renal clearance. Surface coating with PEG and Poloxamers prevented RES removal of the nanocarriers thereby accumulating higher concentration of Am80 in brain for Am80-PEG-NLC group in comparison with Am80-NLC (Ghasemiyeh and Mohammadi-Samani, 2018).

Conclusion

Drug targeting is the one of the most critically important fields of nanotechnological drug delivery system. As we can deliver the cytotoxic cargo at the target organelles in the body thereby reducing the side effects and cytotoxicity of drugs to other cells and organs. One of the most challenging strategies is the implementation of biodegradable lipid based nanocarrier technologies. Due to their potential to encapsulate therapeutics and input ability, they are capable to deliver drugs to different parts of the body. Beginning with an existing old cytotoxic agent with a known clinical history can significantly reduce the time and cost required for the development of a new cytotoxic molecule for the prevention and treatment of cancer. Classical drug substances could be delivered efficiently through design of specific formulations whereas the newer generations of cytotoxics for oral administration are at priority in developmental pipeline. But poor physicochemical and biopharmaceutical properties, diversity in molecular structure causing variable stability issues, high incidence of MDR, and irregular distribution of cytotoxics due to poor specificity; leads to the failure of cytotoxics in the treatment of cancer which could be overcome by the use of SLN and NLC based nanocarrier composites. Due to its increased cytotoxic delivery at the tumor site for improved anti-tumor efficacy with reduced toxic effects makes them a potential cytotoxics drug carrier. Both SLN and NLC increases the treatment efficacy whereas on the other hand reduce the toxic effects of cytotoxics. The surface modification and utilization of absorption enhancers (P-gp inhibition and functional excipients) have further opened up new dimensions for active targeting of cytotoxics at the tumor sites. Owing to their special properties, these novel nanocomposite carriers such as SLN and NLC could bypass different gastointestinal barriers. Oral delivery of the cytotoxics loaded SLN and NLC for passive targeting using enhanced permeation and retention is of great interest for the improvement of the quality of life of cancer patients.

Future Scope

Target specific with reduced toxic effects is the need of the hour for the delivery of therapeutic cargo. Major advantage of these nanocarriers is the safety profile dedicated for chronic treatment which are already under consideration. The results so far seem to be quite promising which is evident from the fact that there are numerous nanotechnolgical products which have been approved by the regulatory agencies. The increasing number of these nanotechology based products which are under clinical trials clearly shows the thrust in the scientific community in this field. Sincere efforts are made in the field of understanding the mechanism of cellular trafficking of these nanocarriers, its correlation with the therapeutic efficacy and its toxicity profile is one of the most important research areas. The insight of these will lead to development in the newer technologies that would be able to exploit the physiological principles for drug delivery purposes without compromising the safety profile. Furthermore, more attempts can be made for translation of the laboratory developments in to product development on a commercial scale. This could be achieved by efforts in the area of improving the drug payload within the nanocarriers, simple manufacturing steps, usage of inexpensive excipients and robust formulation design.

Acknowledgements

Authors are thankful to Jadavpur University for providing infrastructure and facilities in Department of Pharmaceutical Technology.

Disclosure statement

The authors report no conflict of interest.

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