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Review Article

Solid Lipid Nanoparticle for the Delivery of Docetaxel: A Review

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ABSTRACT

Solid lipid nanoparticles are the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and research. Due to its solid state it has greater stability than other nanocarrier systems. There are several other advantages like sustained release, improves bioavailability and delivery of poorly water soluble drugs, helps in control of several pharmacokinetic parameters of drugs due to which use of SLN is increasing day by day. Various techniques can be used for the formulation of SLN i.e. solvent evaporation, microemulsification technique, high pressure homogenization and supercritical fluid method. It has several applications like it is used in gene transfer therapy, also used in different drug delivery systems like oral and pulmonary drug delivery system. Due to several advantages SLNs are widely used in chemotherapy for the treatment of cancer. The use of SLN for the delivery of Docetaxel to tumor site has several benefits like site specific delivery, less toxic effect, more cell cytotoxicity and more bioavailability which leads to decrease in the dosing frequency. Docetaxel is an anticancer agent extracted from plant *Taxus Baccata* which is widely used in chemotherapy to treat cancer. This article contains the detail information of about the advantages, disadvantages, different methods of preparation and several SLN loaded with Docetaxel.

Keywords: Solid lipid nanoparticles, drug delivery, clinical medicine, poorly water soluble drugs

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Introduction

Colloidal particles ranging in size between 10 and 1000nm are known as nanoparticles. They are manufactured from synthetic or natural polymers and ideally suited to optimized drug delivery and reduce toxicity. Over the years, they have emerged as a variable substitute to liposome as drug carrier. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate across the cell membrane, sustained release of their contents and their stability¹. There are several disadvantages of liposome or traditional nanoparticles like stability, leakage of drug from the dosage form, etc. to overcome these problems solid lipid nanoparticles were developed. SLN are colloidal carriers developed in the last decade as an alternative system to existing traditional carriers such as emulsion, liposomes and polymeric nanoparticles. They are a new generation of submicron-sized lipid emulsion where the liquid lipid has been substituted by solid lipid. SLN offer unique properties such as small size, large surface area, high dose loading and the interaction of phases at the interfaces and are attractive for potential to improve performance of pharmaceuticals, nutraceuticals and other materials as well

as increase stability is the most important advantage of SLN. SLN are sub-micron colloidal carriers which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. The use of solid lipid instead of liquid lipid is beneficial as it has been shown to increase control over the release kinetics of encapsulated compounds and to improve the stability of incorporated chemically-sensitive lipophilic ingredients. The benefit of using solid lipids is due to several physicochemical properties of lipid. Firstly, the mobility of reactive agents in solid matrix is lower than in a liquid matrix and so the rate of chemical degradation reactions may be retarded. Secondly, micro phase separations of the active ingredients and carrier lipid within individual liquid particles can be controlled, thereby preventing the accumulation of active compounds at the surface of lipid particles where chemical degradation reactions often occur. There is also another benefit; the absorption of poorly absorbed drugs has been shown to be increased after incorporation into solid lipid nanoparticles².

Due to several benefits SLN are used for various types of drugs like antineoplastic agents, delivery of several proteins and peptides, antiepileptic agents, etc. Cancer is one of the

most dangerous disease that threaten the health of human around the world. There are various therapeutic options for the treatment of cancer like surgery, radiation, immunological, hormone, chemotherapy and stem cell transplant. From all of this option chemotherapy is the choice of therapeutic treatment option due to several benefits³. In chemotherapy cancer treatment one or more antineoplastic agents are used according to individual's factors. The various classes of drugs used in chemotherapy are Taxanes (paclitaxel, docetaxel), antibiotics (doxorubicin, mitoxantrone), EGF receptor inhibitors (gefitinib, cetuximab), Glucocorticoids (prednisolone), Folate antagonist (methotrexate, pemetrexed) and Monoclonal antibody (rituximab)⁴. The various side effects includes hair loss, nerve pain, anemia, appetite loss, edema, lymphedema, sexual health issues, skin and nail change, sleep problem, urinary and bladder problem, fertility issues, etc. The major side effect of chemotherapy is the inability to deliver specific drug to the target which cause drug to affect both healthy as well as cancerous cells⁵. Among all the taxane derivative paclitaxel (PTX) and docetaxel (DTX) is the most widely used anticancer agents. PTX is a potent antineoplastic agent frequently used for the treatment of wide variety of human malignancies such as breast, ovarian, lung and other cancer⁶. However, the use of PTX and DTX was limited due to its acquired drug resistant, side effect and poor aqueous solubility⁷. To minimize this problems many formulation has been developed such as use of liposomes of DTX⁸, self-assembled micelles of DTX⁹, nanoemulsion of DTX¹⁰, nanoparticle of PTX¹¹ and solid lipid nanoparticles using PTX¹².

Advantages^{13,14,15}

1. SLN helps to achieve controlled as well as sustained release of several drugs.
2. It has better control over release kinetics of encapsulated compound small particle size and narrow size distribution helps in site specific drug delivery.
3. It improves bioavailability as well protect light sensitive drugs from outer environment.
4. It also helps in delivery of poorly water soluble drugs
5. Encapsulation of drug helps in control over the several pharmacokinetic parameters.
6. Much easier to manufacture than biopolymeric nanoparticles.
7. It improves the stability of pharmaceuticals.
8. The transporter lipids are biodegradable and consequently protected. Avoidance of natural solvents. Enhanced bioavailabilities of inadequately water dissolve atoms.

Disadvantages¹⁶

1. Poor loading capacity
2. Drug expulsion after polymeric transition during storage
3. Due to partitioning effect during the production process it has low capacity to load hydrophilic drugs.

Different techniques for the preparation of SLN

1. High pressure homogenization (HPH)¹⁷

In high pressure homogenization it uses high pressure of 100-200 bar through narrow gap. The fluid is accelerated from a very short distance at very high velocity rate. This

results in decrease of particle size to submicron range due to high rate of velocity. Two general approaches of HPH are hot homogenization and cold homogenization work on the same concept of mixing the drug in bulk of lipid melt.

a. Hot homogenization-

Hot homogenization is generally carried out at high temperature more than melting point of lipid. A pre emulsion of drug loaded lipid melt and the aqueous emulsifier at the same temperature is obtained by high-shear mixing device. In general, high temperature helps in obtaining lower particle size due to the decrease in viscosity of the inner phase.

b. Cold homogenization-

There are various problems associated with hot homogenization techniques like temperature induced drug degradation, etc. To overcome these problems cold homogenization method is developed. In this technique the drug containing lipid melt is cooled, this solid lipid is reduced in size which is further this micro particles are dispersed in a cold surfactant solution yielding a pre-suspension. This pre-suspension is homogenized at or below room temperature; the gravitational force breaks the solid micro particle to solid lipid nanoparticles.

2. Micro emulsion based SLN preparation¹⁸

This technique is developed by Gas co and other scientist in 1993 for developing SLN having nanosize distribution (Gas co. 1993). In this method hot micro emulsion is dispersed in cold water usually in the ratio of 1:25 to 1:50. Ultra filtration is used for the removal of excess amount of water increasing the concentration of particle. Considering micro emulsion, the temperature gradient and pH value fix the product quality in addition to composition of micro emulsion. High temperature gradient helps in rapid lipid crystallization and prevents aggregation.

3. Solvent evaporation¹⁹

In this technique, lipid and hydrophobic drug were dissolved in water immiscible solvent like cyclohexane, dichloromethane, toluene, etc. and that is emulsified in an aqueous phase using high speed homogenizer. This emulsion is further passed through microfluidizer to improve the efficiency of fine emulsification. The organic solvent is evaporated using mechanical stirring at room temperature and reduced pressure. This solvent evaporation will result in the formation of solid lipid nanoparticles.

4. Solvent emulsification-diffusion method²⁰

This technique can be carried in both the phase i.e. aqueous phase as well as oil phase using partially miscible with water. Firstly, both the solvent and water were mutually saturated in order to achieve thermodynamic equilibrium of both liquid. After this drug and lipid are dissolved in water saturated solvent the organic phase was emulsified with solvent saturated aqueous solution containing stabilizer using mechanical stirrer. Water is added in a particular ratio once the o/w emulsion is formed in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles. The diffusion step was carried out either at room temperature or at the temperature under which the lipid was dissolved. Throughout the process constant stirring was maintained. Finally the diffused solvent was eliminated by vacuum distillation or lyophilization.

5. Supercritical fluid method¹⁸

In this method, a fluid is qualified as supercritical when its pressure and temperature exceed their respective critical value. Above the critical temperature, it is not possible to liquefy a gas by increasing the pressure. The supercritical fluid has unique thermo-physical properties. As the pressure is raised, the density of the gas increases without significant increase in the viscosity while the ability of the fluid to dissolve compounds also increases. A gas may have little to no ability to dissolve a compound under ambient condition can completely dissolve the compound under high pressure in supercritical range. Therefore, its solvent power is altered by careful changes in temperature and pressure. many gases like CO₂, ammonia, ethane and CH₂FCF₃ were tried, but CO₂ is the best option for SCF technique because, it is generally regarded as safe, easily accessible critical point, does not cause the oxidation of drug material, leaves no traces behind after the process, is inexpensive, noninflammable, environmentally acceptable and easy to recycle or to dispose off. In this technique generally, organic solvents are used because they are fully miscible in SCF-CO₂. This process comprises several processes for nanoparticle production such as rapid expansion of supercritical solution, particles from gas saturated solution, gas/supercritical antisolvent, aerosol solvent extraction solvent, solution enhanced dispersion by supercritical fluid, supercritical fluid extraction of emulsion.

Application of SLN-

1. Oral drug delivery applications²¹

Oral drug administration is the most preferable route of administration due to good patient compliance, non-invasiveness and therapeutic success, but poor water solubility of drug is limiting step for the absorption of them. Thus an approach is needed to improve the bioavailability of drugs.

2. Lipid-based delivery system-

In the recent decades have shown many advance for this purpose. Since in this system drug is dissolved in lipid which leads to increase in the solubility of poorly water soluble drug especially lipophilic drug. It also helps in decreasing the toxic effect of several drugs.

3. Pulmonary drug delivery application²²

SLN have several advantages in pulmonary drug delivery i.e. it can be easily incorporated into carriers which inhaled to the lungs, therefore able to provide a deep lung deposition, good adhesion and elongated retention in the lung. Also due to improved and prolonged therapeutic effects, SLN have a longer dosing interval and better patient

compliance. Many studies are available about SLN as local delivery carriers or as systemic delivery carriers for small molecules and for macromolecules respectively by pulmonary administration.

4. Gene transfer applications²³

Phospholipid is the most important component of cell membrane which helps SLN to penetrate across the membrane easily. This enhances the uptake of several genetic materials. Cationic SLN are interesting and proper nonviral gene delivery vector for systemic delivery. Genospheres have large potential for targeted gene delivery. Genospheres generally carry material such as plasmid DNA, DNA and other nucleic acids.

5. Cosmetic application²⁴

SLN are widely used in the cosmetic preparation due to several advantages. They are used as carrier in sunscreen, anti-acne and antiageing preparations. In fact due to high control behavior of SLN on skin penetration of active substances, they have UV-blocking and skin hydration behavior.

6. Food application-

SLN are excellent potential carriers for sensitive compounds in food industry because they improve the industrial and the nutritional quality of a lipid containing food. Quality of them is affected by the lipid oxidation at storage and processing. Therefore, oxidants are used to prevent this problem.

SLN loaded with Docetaxel-

Docetaxel is an antineoplastic agent derived from the plant *Taxus Baccata* which is used for the treatment of various types of cancer such as colon cancer, colorectal cancer, small lung cancer, breast cancer and skin cancer. Due to several benefits docetaxel is widely used for the treatment of the cancer. Various types of SLN is formulated containing docetaxel. In 2009, a Chinese scientist developed SLN of docetaxel for the first time. They used homogenization techniques for the preparation of SLN using egg yolk phosphatidylcholine, dioleoylphosphatidyl thanolamine, trimyristin and lactobionic acid. From the results of various evaluation tests, it was found that the cytotoxicity of SLN against hepatocellular carcinoma cell line BEL7402 was superior to Taxotere. It also shows better antitumor efficacy tolerant and antitumor effect in murine model bearing hepatoma. These results implied that this targeted nanocarrier of docetaxel could enhance its antitumor effect in vivo with low systemic toxicity for the treatment of locally advanced and metastatic HCC²⁵. After this many other scientist also worked on the formulation of docetaxel loaded SLN some of them are listed below in Table I.

Table I. Different types of SLN formulation loaded with DTX

| Sr. No. | Drug | Method | Key Ingredients | Conclusion |
|---------|-----------|------------------------------|--|---|
| 1. | Docetaxel | Supercritical Fluid Method | Soya bean lecithin, Poloxmer 188 and Glycerol tristearate | SLN shows elongated $t_{1/2}$ and MRT compared with Taxotere. It also shows potent anti-tumor activity to ovarian carcinoma <i>in vivo</i> with less toxicity ²⁶ . |
| 2. | Docetaxel | Micro Emulsion Technique | Disterayl Phosphatidyl Ethanolamine, soya phosphatidylcholine | It shows better cytotoxic effect on MDA-MB-453 breast cancer cell line. It is also proved for the targeting efficacy for FGFR-1 ²⁷ . |
| 3. | Docetaxel | Emulsion Solvent Evaporation | Betreliesoxybutyric acid, Glycerol monostearate, Vitamin E, soy lecithin | In vitro study sate the control released of drug. Cell uptake study revealed the increase of docetaxel with SLN ²⁸ . |
| 4. | Docetaxel | Super Critical Fluid | Compritol, precirol, H-SPC | In vitro cytotoxicity studies on C-26 and A-375 cells show the increase in cellular uptake as compare with Taxotere. In vivo antitumor inhibitory efficacy was carried out on C-26 implanted BALB/c mice and it showed better tumor inhibitory efficacy and survival rate ¹⁸ . |
| 5. | Docetaxel | High Pressure Homogenization | Soyabean lecithin, Trimyrustin | It showed lower toxicity as compare to Taxotere and induced more apoptosis at 24 hours after treatment in vitro ¹⁷ . |
| 6. | Docetaxel | Solvent Diffusion Techniques | Tween 80, D-alpha-tocopherol-succinate | The oral bioavaibility and intestinal absorption increases as compare to Taxotere ²⁰ . |
| 7. | Docetaxel | Solvent Evaporation | DOPE-PEG-2000, Phosphatidylcholine | It shows higher antitumor activity on mouse as compare to TaxoTer ¹⁹ |
| 8. | Docetaxel | Emulsion Solvent Evaporation | Soyabean Lecithin, Glycerol monosterate, Tween 80 | It shows the higher cellular uptake in Caccp-2 cells as compare to marketed formulation ²⁹ . |

Conclusion

In 1992, SLN was invented by Schwarz which was formulated using Dynasan (melted lipid), soya lecithin and poloxamer. The use of SLN is increasing day by day with several benefits like feasibility of incorporation of lipophilic and hydrophilic drug, improved physical stability, low cost, ease of scale-up and manufacturing. Also, site specific and sustain release of drug can be achieve with the use of SLN. Several methods of preparation has been developed to prepare SLN like emulsion solvent evaporation method, solvent evaporation, high pressure homogenization and microemulsion techniques. SLNs are relatively young delivery systems and hold great promise for their systemic investigation and exploitation.

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