Available online on 25.12.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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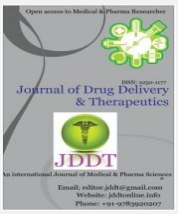

Open Access Research Article

FORMULATION OF PACLITAXEL LOADED NANOSTRUCTURED LIPID CARRIERS TO STUDY THE EFFECT OF CONCENTRATION OF LIQUID LIPIDS ON DRUG RELEASE

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ABSTRACT

In the present study, stearic acid (SA) nanostuctured lipid carriers (NLC) with different proportions of oleic acid (OA) were successfully prepared by solvent diffusion method in an aqueous system. OA was taken in the concentration of 10%, 20%, 30%, 40% and 50%. Prepared NLCs were evaluated for various parameters like drug entrapment efficiency, drug loading and *in vitro* release. A biphasic drug release pattern was observed; initially a fast release was obtained followed by sustained release at a constant rate. The drug release from nanoparticles was found to be significantly influenced by OA content.

Cite this article as: Majumdar A, Dubey N, Formulation of paclitaxel loaded nanostructured lipid carriers to study the effect of concentration of liquid lipids on drug release, Journal of Drug Delivery and Therapeutics. 2017; 7(7):26-28

INTRODUCTION:

The exponential development in the field of nanotechnology has revolutionized the research in the field of advanced drug delivery. Many times problems such as poor solubility, normal tissue toxicity, poor specificity, high incidence rate of pharmaceutical resistance and the rapid degradation, need of large-scale output procedures, a fast release of the pharmaceutical from its carrier, steadiness issues, the residues of the organic solvents utilized in the formulation method, the toxicity from the polymer and sometimes drug expulsion are encountered in the delivery of anticancer drugs through other colloidal delivery systems. These shortcomings are anticipated to be overcome through use of the nanostructured Lipid Carriers along with the advantage of high drug loading capacity and stability. Many nano delivery systems have been studied for the treatment of skin cancers, including liposome, polymersomes, carbon-based nanoparticles, inorganic nanoparticles, protein-based nanoparticles, nanostructured lipid carriers[1], dendrimers[2] and Self-nano emulsifying drug delivery[3, 4].

Lipid-based drug delivery systems have been proved as promising carriers for cytotoxic drugs because of their potential to increase the solubility and bioavailability of poorly water-soluble and/or lipophilic drugs[1]. The combination of nanoparticulate delivery system with lipids resulted in the development of a new class of NPs commonly known as solid lipid NPs (SLN). As SLN are composed of solid lipids only. Therefore, during formulation a part of the lipid crystallizes in a higher energy modification (α or β). Further on storage, these modifications can transform to more organized lower energy, β modification which further leads to drug expulsion. Apart from polymorphic transition, SLNs also show some disadvantages as drug carriers including an unpredictable gelation tendency, and low incorporation due to the crystalline structure of solid lipids. To overcome these limitations of the SLNs, second generation encapsulation systems have been developed by incorporating liquid carrier oil into the solid lipid matrix to form nanostructured lipid carriers (NLCs) thus NLCs were introduced. NLCs have shown to have improved active drug encapsulation and delivery properties compared to SLNs. The major advantage of nanostructured lipid carrier as drug delivery system is its ability to accommodate large quantities of drugs as a result of formation of a less ordered lipid matrix with many imperfections[5, 6].

MATERIALS AND METHODS:

Materials:

Stearic acid (LobaChemie, India) was used as solid lipid material of NLC. Oleic acid (LobaChemie, India) was

used as liquid lipid material for NLC. Paclitaxel was kindly donated by Intas Pharmaceutical Ltd., Ahmedabad. The surfactant, sodium lauryl sulfate, was provided by Merck Specialities Pvt. Ltd., Mumbai. Ethanol, acetone and other chemicals were analytical reagent grade.

Preparation of Paclitaxel loaded NLCs dispersion:

PTX-loaded NLCs were prepared by solvent diffusion method in an aqueous system as reported earlier with slight modification[5]. Briefly,290 mg selected lipid (SA and OA) with varing content of OA (0%, 10%, 20%, 30%, 40% and 50%) and 10mg drug were dissolved completely in a 16 ml mixture of acetone and ethanol (1:1, v/v) in water bath at 70 ◦C. This lipid solution was poured into 100 ml of an aqueous phase containing 10mg of SLS under continuous mechanical agitation (Remi Instruments, Mumbai, India) with 3000 rpm at room temperature (25–28 ◦C) for 5 min. The pH value of the acidic aqueous phase was adjusted to 1.20 by addition of 0.1 M hydrochloric acid to form aggregation of nanoparticles. The aggregate of nanoparticle dispersion was then centrifuged 25,000 rpm for 20 min, to get the precipitate of nanostructuered carriers. The precipitate was collected for drug entrapment efficiency determination.

Particle size measurement:

The volume average diameter of drug-free or drug-loaded nanoparticles in dispersion was determined with Particle Mastersizer 2000 (Malvern Instruments, UK) after diluted 20 times with distilled water.

Drug entrapment efficiency determination

The precipitate of drug-loaded nanoparticles were dispersed in 100 ml of 1 wt% sodium lauryl sulfate solution and shaken for 3 min to dissolve the free drugs. The resulting dispersions were centrifuged for 20 min at 25,000 rpm. The drug content in the supernatant was analyzed by UV-VIS spectrophotometer (UV-1800 Shimadzu Spectrophotometer) at 228nm. The entrapment efficacy and drug loading of nanoparticle was calculated using:

$EE = (W\alpha - Ws) / W\alpha \times 100$…….....(i)

$DL = (W\alpha - Ws) / (W\alpha - Ws + Wl) \times 100$……(ii)

Where, EE is entrapment efficiency, DL is Drug loading, Wα stands for the weight of PTX added to the formulation and Ws is the analyzed weight of drug in supernatant and Wl is weight of lipid.

In Vitro release assay

The drug release profiles from nanoparticles were measured in vitro. 100mg of powdered nano structured lipid carriers were dispersed in 30 ml sodium lauryl sulfate solution (1 wt %) in 50 ml glass test-tube. The resulting samples were shaken for 3 min, and one milliliter of the dispersion was withdrawn from the system at definite time interval and filtrated with 100 nm filter. The filtrate was determined by UV-VIS spectrophotometer (UV-1800 Shimadzu Spectrophotometer) at 228nm as described above.

RESULTS AND DISCUSSION:

Preparation of stearic acid SLN (0%OA) and NLC by solvent diffusion method in an aqueous system

The stearic acid SLN (0% OA) and NLC with 10, 20, 30, 40 and 50wt% OA content, respectively, were prepared by solvent diffusion method in an aqueous system.

Drug entrapment efficiency and Drug loading capacity

The effects of OA on drug entrapment efficiency and loading capacity of formulations of all the batches were investigated. The curves of drug entrapment efficiency and loading capacity against OA content are given in Figure.1 and Figure.2. It is clear that the drug entrapment efficiency and drug loading capacity of nanoparticles were increased from 48.92 to 82.86% and from 1.65 to 2.78%, respectively, with increasing the percentage of OA from 0 to 50 wt%.

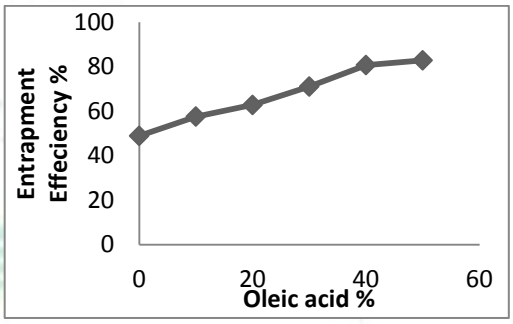

Figure 1: Drug entrapment efficiency (EE) of various batches NLC against oleic acid (OA) content (*n* = 3).

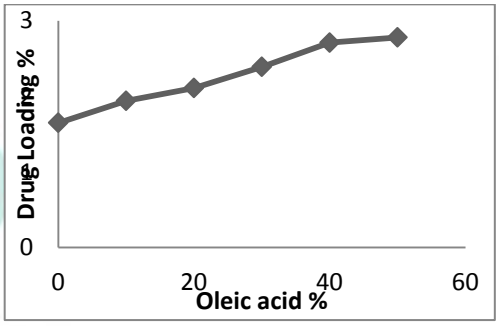

Figure 2: Drug loading (DL) of various batches NLC against oleic acid (OA) content (*n* = 3)

***In Vitro* Drug release**

In Vitro release curves of six type drug-loaded nanoparticles are shown in Fig. 3. A biphasic drug release pattern was observed; initially a fast release was obtained followed by sustained release at a constant rate. The drug released was found to be slowest from stearic acid SLN ie.0% OA formulation. The release rate became faster when the OA was incorporated to nanoparticles and it increased with increasing the OA content. As shown in Table 1, the nanoparticles with less than 20 wt% OA content had almost similar mean size, but the release rate at the initial stage increased with the increasing OA content in nanoparticles. This means the OA content is a main factor affecting the drug release rate at the initial stage when the OA content was lower than 20 wt%. On the other hand, when the OA content

increased up to 50 wt%, the particle size significantly decreased, consequently, the specific surface area was increased. Therefore, the fastest release rate in initial stage, observed in the nanoparticles of 50 wt% OA content, was resulted by both of smaller size and higher OA content. However, later it was noticed that the release profiles of all the batches were almost parallel with each other. This result revealed that the OA almost did not affect the drug release rate of OA incorporated nanoparticles after initial stage. This may be due to nonhomogenous distribution of OA in nanoparticles. When solvent diffusion method at 70 ◦C was applied to prepare NLC, during cooling down process from the melted lipid droplet in dispersed medium to the formation of a nanostructured lipid carrier at room temperature, because of the different melting point between solid lipid and liquid lipid, the solid lipid (stearic acid) having higher melting point could crystallize first forming a liquid lipid free or little liquid lipid core, finally, most of the liquid lipid located at the outer shell of the nanoparticles which led to drug-enriched shell related with drug burst release at the initial stage observed above. The OA-enriched outer layers possessed a soft and considerable higher solubility for lipophilic drugs character, in which the drug was easily loaded to higher amount and could be easily released as well by the drug diffusion or the matrix erosion manners. Therefore, the OA incorporated nanoparticles showed the burst release at the initial stage and sustained release later.

Table1: Particle size of various batches of Drug free and Drug loaded NLCs

OA Wt%	Particle size (nm)	
	Drug –free nanoparticles	Drug loaded nanoparticles
0	412±2.8	476±6.3
10	409±6.2	471±1.8
20	399±7.9	458±2.6
30	209±1.2	265±3.9
40	189±3.8	228±1.3
50	174±9.1	212±5.2

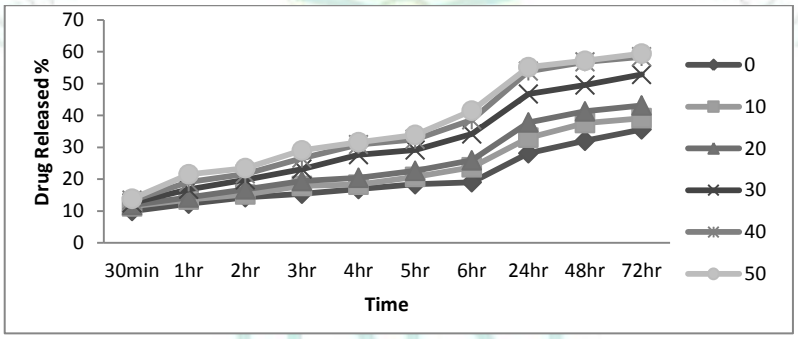

Figure 3: Cumulative *in vitro* drug release from various batches having OA in different proportions

CONCLUSION:

A solvent diffusion method in aqueous system was employed to prepare the OA–SA NLC with improved drug incorporation and release properties. The drug release characteristics from the NLC exhibited a biphasic pattern with burst release at the initial stage and followed by sustained release at a constant rate. The drug release rate at the initial stage and the drug entrapment efficiency of the NLC were increased with increasing the content of liquid lipid (OA). These results proved that the NLC prepared in the present study can be successfully used as a carrier for therapeutic drug delivery.

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