IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Solid Lipid Nanoparticles. (A Review)

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ABSTRACT:

Solid lipid nanoparticles were developed in early 1990s as an alternative to other traditional colloidal carriers like liposomes, polymeric nanoparticles and emulsions as they have advantages like controlled drug release and targeted drug delivery with increased stability. This paper gives an overview about the potential advantages and also the disadvantages of solid lipid nanoparticles, the excipients and all the different methods involved in their production including the membrane contractor method. Aspects of SLN stability and the influence of various excipients (used in SLN production) on stability with other secondary steps involved in their stabilization like freeze drying, spray drying etc. Problems associated with SLN production and instrumental techniques used in production are thoroughly discussed. Special attention is given to models of drug incorporation in SLN and the release pattern of SLN. Analytical methods involved in SLN evaluations are discussed in detail and the major applications of SLNs mainly targeted drug delivery are discussed. Keywords: Colloidal drug carriers, Solid lipid nanoparticles, Solid lipid, Surfactants, Drug incorporation.

INTRODUCTION:

The field of Novel Drug Delivery System is emerging at an exponential rate with the deep understanding gained in diversified fields of Biotechnology, Biomedical Engineering and Nanotechnology. Many of the recent formulation approaches utilize Nanotechnology that is the preparation of Nanosized structures containing the API. Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100 nm. The overall goal of nanotechnology is the same as that of medicine: to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using controlled and targeted drug delivery approach. Some of the important Drug Delivery System developed using Nanotechnology principles areNanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion, Nanocrystals. In this article the main focus is on Solid Lipid Nanoparticles (SLNs). SLNs introduced in 1991 represent an alternative and better carrier system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles.

SLNs are colloidal carrier system composed of a high melting point lipid as a solid core coated by aqueous surfactant and the drugs used are of BCS Class II and IV. In SLNs as compared to other colloidal carriers liquid lipid is replaced by solid lipid. The use of solid lipid as a matrix material for drug delivery is well known from lipid pellets for oral drug delivery (eg. Mucosolvan® retard capsules). The term lipid in a broad sense includes triglycerides, partial glycerides, fatty acids, hard fats & waxes. A clear advantage of SLN is the fact that the lipid matrix is made from physiological lipids which decreases the danger of acute and chronic toxicity. 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. These potentially beneficial effects are because of a number of physicochemical characteristics associated with the physical state of the lipid phase. Firstly, the mobility of reactive agents in a 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. Thirdly, the absorption of poorly absorbed bioactive compounds has been shown to be increased after incorporation into solid lipid nanoparticles. As a result of various research works it has also been shown that the use of a solid matrix instead of a liquid matrix can slow down lipid digestion thereby allowing for a more sustained release of the encapsulated compound. Other major excipients of SLNs are surfactants

of aqueous type. They mainly act as emulsifier to form o/w type emulsion and stabilizer for SLNs dispersion and their choice depends on mainly the route of administration. They are generally made up of a solid hydrophobic core containing the drug dissolved or dispersed[8]. SLNs are mainly prepared by high pressure homogenization or micro emulsification. SLNs prepared by any technique are in dispersion form which on long term storage results in instability mainly because of hydrolysis reactions so to increase their stability they can be converted into solid dry reconstituable powders through lyophilisation and a cheap and easy variant to lyophilisation is spray drying technique.

POPULATION & SAMPLE:

Rainer H.Müller *et.al.* (2000): This paper reviews the present state of the art regarding production techniques for SLN, drug incorporation, loading capacity and drug release, especially focusing on drug release mechanisms. Relevant issues for the introduction of SLN to the pharmaceutical market, such as status of excipients, toxicity/tolerability aspects and sterilization and long-term stability including industrial large-scale production are also discussed. The potential of SLN to be exploited for the different administration routes is highlighted. References of the most relevant literature published by various research groups around the world are provided [5] .

S.AWissing *et.al.* (2004) : This review describes the use of nanoparticles based on solid lipids for the parenteral application of drugs. Firstly, different types of nanoparticles based on solid lipids such as "solid lipid nanoparticles" (SLN), "nanostructured lipid carriers" (NLC) and "lipid drug conjugate" (LDC) nanoparticles are introduced and structural differences are pointed out. Different production methods including the suitability for large scale production are described. Stability issues and drug incorporation mechanisms into the particles are discussed. In the second part, the biological activity of parenterally applied SLN and biopharmaceutical aspects such as pharmacokinetic profiles as well as toxicity aspects are reviewed [6].

R.H.Müller et.al. (2002): The paper reviews advantages—also potential limitations—of SLN for the use in topical cosmetic and pharmaceutical formulations. Features discussed include stabilisation of incorporated compounds, controlled release, occlusivity, film formation on skin including in vivo effects on the skin. As a novel type of lipid nanoparticles with solid matrix, the nanostructured lipid carriers (NLC) are presented, the structural specialities described and improvements discussed, for example, increase in loading capacity, physical and chemical long-term stability, triggered release and potentially supersaturated topical formulations. For both SLN and NLC, the technologies to produce the final topical formulation are described, especially the production of highly concentrated lipid nanoparticle dispersions >30–80% lipid content. Production issues also include clinical batch production, large scale production and regulatory aspects [7] .

SlavomiraDoktorovova *et.al.* (2014) : . In this review, we collected the available data from cytotoxicity, oxidative stress and hemocompatibility studies in vitro and analysed their outcomes [8] .

Ho LunWong *et.al.* (2007) : This review focuses on the current use of SLN for the encapsulation and delivery of cytotoxic anticancer compounds. It also discusses more recent trends in the use of SLN as vehicles for delivery of chemosensitizers and cytotoxic therapeutic molecules. It is anticipated that, in the near future, SLN will be further improved to deliver anticancer compounds in a more efficient, specific and safer manner [9].

Anna Radomska-Soukharev (2007): The paper is devoted to the investigation of chemical stability of lipids used as excipients in the production of Solid Lipid Nanoparticles (SLN). Different lipids and amounts of surfactants were considered. Most of the formulations were produced using identical binary surfactant mixtures and concentrations to analyze the effect of the chemical nature of the lipids on their stability in SLN. In some formulations, surfactants were exchanged or their concentration was increased to assess the contribution of surfactants on stability of lipids particles. Solid Lipid Nanoparticles were characterized by photon correlation spectroscopy, laser diffractometry, zeta potential determination and differential scanning calorimetry. Potential effects of lipid crystallinity and modifications were assessed [10].

Melike Üner and **Gülgün Yener (2007):** This paper basically reviews types of SLN, principles of drug loading and models of drug incorporation. The influence of PEG coating on particle size and surface characteristics is discussed followed by alteration in pharmacokinetics and bioavailability of drugs in order to target the site of action via SLN. The future direction of research and clinical implications of SLN is also considered [11].

Wolfgang Mehnert *et.al.* KarstenMäder (2007): This paper presents an overview about the selection of the ingredients, different ways of SLN production and SLN applications. Aspects of SLN stability and possibilities of SLN stabilization by lyophilization and spray drying are discussed. Special attention is paid to the relation between drug incorporation and the complexity of SLN dispersions, which includes the presence of alternative colloidal structures (liposomes, micelles, drug nanosuspensions, mixed micelles, liquid crystals) and the physical state of the lipid (supercooled melts, different lipid modifications). Appropriate analytical methods are needed for the characterization of SLN [12] .

Catherine Charcosset *et.al.* (2005): Solid lipid nanoparticles (SLN) were introduced at the beginning of the 1990s, as an alternative to solid nanoparticles, emulsions and liposomes in cosmetic and pharmaceutical preparations. The present study investigates a new process for the preparation of SLN using a membrane contactor. The lipid phase is pressed, at a temperature above the melting point of the lipid, through the membrane pores allowing the formation of small droplets. The aqueous phase circulates inside the membrane module, and sweeps away the droplets forming at the pore outlets. SLN are formed by the following cooling of the preparation to room temperature. The influence of process parameters (aqueous phase and lipid phase temperatures, aqueous phase cross-flow velocity and lipid phase pressure, membrane pore size) on the SLN size and on the lipid phase flux is investigated [13] .

Paolo Blasi *et.al.* (2007): The present review discusses the potential use of solid lipid nanoparticles for brain drug targeting purposes. The state of the art on surfactant-coated poly(alkylcyanoacrylate) nanoparticles specifically designed for brain targeting is given by emphasizing the transfer of this technology to solid lipid matrices. The available literature on solid lipid nanoparticles and related carriers for brain drug targeting is revised as well. The potential advantages of the use of solid lipid nanoparticles over polymeric nanoparticles are accounted on the bases of a lower cytotoxicity, higher drug loading capacity, and best production scalability [14] .

Nina Pedersen *et.al.* (2005) : Cationic solid lipid nanoparticles (SLN) have recently been suggested for non-viral gene delivery, as these particles consist of well tolerated substances, can bind DNA directly via electrostatic interactions and mediate gene transfer in vitro. We here report the development of SLN complexes, which can be targeted to specific surface receptors. A formulation of SLN was prepared by the microemulsion technique comprising of stearylamine and the matrix lipid Compritol ATO 888 with a size of approximately 100 nm and a zeta-potential of +15. These SLN are able to condense DNA in complexes, which are very stable under physiological conditions, and they display low cytotoxicity in cell culture [15] .

Nicolas Anton *et.al.* (2008): This requires the nanoparticle formulation processes (and thus the nano-emulsion formation methods) to be more adapted to the nature of the encapsulated drugs, as well as to the chosen route of administration. Offering a comprehensive review, this paper proposes a link between nano-emulsion formulation methods and nanoparticle generation, while at the same time bearing in mind the above-mentioned parameters for active molecule encapsulation. The first part will deal with the nano-emulsion template through the different formulation methods, i.e. high energy methods on the one hand, and low-energy ones (essentially spontaneous emulsification and the phase inversion temperature (PIT) method) on the other. This will be followed by a review of the different families of nanoparticles (i.e. polymeric or lipid nanospheres and nanocapsules) highlighting the links (or potential links) between these nanoparticles and the different nano-emulsion formulation methods upon which they are based

[16] .

Neda Naseri *et.al.* (2015): Lipid nanoparticles (LNPs) have attracted special interest during last few decades. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are two major types of Lipid-based nanoparticles. SLNs were developed to overcome the

limitations of other colloidal carriers, such as emulsions, liposomes and polymeric nanoparticles because they have advantages like good release profile and targeted drug delivery with excellent physical stability. In the next generation of the lipid nanoparticle, NLCs are modified SLNs which improve the stability and capacity loading. Three structural models of NLCs have been proposed. These LNPs have potential applications in drug delivery field, research, cosmetics, clinical medicine, etc. This article focuses on features, structure and innovation of LNPs and presents a wide discussion about preparation methods, advantages, disadvantages and applications of LNPs by focusing on SLNs and NLCs [17].

Medha D.Joshi *et.al.* Rainer H.Müller (2008) : The present review compiles the applications of lipid nanoparticles mainly solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugates (LDC) in parenteral delivery of pharmaceutical actives. The attempts to incorporate anticancer agents, imaging agents, antiparasitics, antiarthritics, genes for transfection, agents for liver, cardiovascular and central nervous system targeting have been summarized. The utility of lipid nanoparticles as adjuvant has been discussed separately. A special focus of this review is on toxicity caused by these kinds of lipid nanoparticles with a glance on the fate of lipid nanoparticles after their parenteral delivery in vivo viz the protein adsorption patterns [19] .

Roberta Cavalli *et.al.* (2002) : Aim of this study was to evaluate solid lipid nanoparticles (SLN) as carriers for topical ocular delivery of tobramycin (TOB). The SLN were in the colloidal size range (average diameter below 100 nm; polydispersity index below 0.2) and contained 2.5% TOB as ion-pair complex with hexadecyl phosphate. The preocular retention of SLN in rabbit eyes was tested using drug-free, fluorescent SLN (F-SLN): these were retained for longer times on the corneal surface and in the conjunctival sac when compared with an aqueous fluorescent solution. A suspension of TOB-loaded SLN (TOB-SLN) containing 0.3% w/v TOB was administered topically to rabbits, and the aqueous humour concentration of TOB was determined up to six hours. When compared with an equal dose of TOB administered by standard commercial eyedrops, TOB-SLN produced a significantly higher TOB bioavailability in the aqueous humour [19] .

Methods of preparation of solid lipid nanoparticles:

1. High pressure homogenization A. Hot homogenization B. Cold homogenization

2. Ultrasonication /high speed homogenization A. Probe ultrasonication B. Bath ultrasonication

3. Solvent evaporation Method

4. Solvent emulsification-diffusion method

5. Supercritical fluid method

6. Microemulsion based method

7. Double emulsion method

8. Precipitation technique

9. Film-ultrasound dispersion

10. Solvent Injection Technique

11. Using Membrane Contractor

1. High pressure homogenization (HPH):

It is a reliable and powerful technique, which is used for the production of SLNs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated.

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 carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.

B. Cold homogenization:

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the Nano emulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.

OBJECTIVES OF STUDY:

The Present study is to carried out to study on Solid Lipid Nanoparticles with following objectives :

- Possibility of controlled drug release.
- Increased drug stability.
- High drug pay load.
- No bio-toxicity of the carrier.
- Avoidance of organic solvents.
- Incorporation of lipophilic and hydrophilic drugs.

CONCLUSION:

SLN as colloidal drug carrier combines the advantage of polymeric nanoparticles, fat emulsions and liposome; due to various advantages, including feasibility of incorporation of lipophilic and hydrophilic drugs, improved physical stability, low cost, ease of scale-up, and manufacturing. SLNs are prepared by various advanced techniques. The site specific and sustained release effect of drug can better achieved by using SLNs. Nanoparticles have been used extensively for applications in drug discovery, drug delivery, and diagnostics and for many others in medical field. They are relatively novel drug delivery systems, having

received primary attention from the early 1990s and future holds great promise for its systematic investigation and exploitation. We can expect many patented dosage forms in the form of SLNs in the future

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