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Solid Lipid Microparticles (SLMS): An Effective Lipid Based Technology for Controlled Drug Delivery

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ABSTRACT

The idea that led to this review was conceived after some investigations we carried out showed that solid lipid microparticles (SLMs) have very good prospects as a good and an effective alternative to the traditional colloidal carrier systems like liposomes, emulsions and polymeric microparticles, for the encapsulation, targeting and controlled delivery of drugs and other actives. This was corroborated by reports from several researchers working in other laboratories. Hence, the review aims at showing that SLMs are at the forefront of the rapidly developing field of lipid-based drug delivery and technology with several potential applications in drug delivery, clinical medicine and research. This review presents the various formulation techniques applied as well as relevant issues such as factors considered in drug encapsulation and loading capacity of SLMs, and methods of characterization of SLMs are treated. The important routes of administration of SLMs and examples of candidate drugs incorporated and administered through such routes as well as the various ways SLMs have been applied in drug delivery and clinical medicine. Future areas of research interest are also highlighted. From reported evidences available, SLMs could serve as a good alternative and acceptable method for the controlled delivery of various drug candidates for therapeutic and diagnostic (theranostic) purposes.

Keywords: Solid lipid Microparticles, Drug Delivery, Lipid-based, Drug Encapsulation, Loading Capacity, Drug Entrapment.

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INTRODUCTION

Over the past years, the fraction of new drug products that are new chemical entities has steadily decreased, reflecting the tremendous cost required to bring new drugs to the marketplace. Increased understanding of drug metabolic and toxicological factors, such as the effect of the patient age on drug distribution, the genetic factors that may result in dramatic inter subject variability in metabolism, short-term versus long-term exposure toxicities, and the potential for teratogenic, mutagenic and embryotoxic effects, has increased the scrutiny under which governmental agencies view the chemical entity. This increased emphasis on safety has placed an additional burden on those who are involved in the development of new drugs, while increasing financial pressures have led to the need for decreased development time. The investigation of approved drugs has resulted in enhanced patient safety and therapeutic efficacy by directing research efforts toward the more efficacious delivery of known pharmacologically active agents to the appropriate physiologic site. This trend has caused pharmaceutical researchers to seek the most suitable methods to deliver both new and existing compounds in the most pharmacologically appropriate manner. The methods may be designed to optimize bioavailability, minimize toxicity and side effects, and improve stability. This led to the advent of novel drug delivery system. There is growing interest and investment in the use of lipid-based systems in drug discovery and product development to overcome the limitations associated with traditional formulations such as poor aqueous solubility and stability, membrane permeability, drug efflux and availability[1]. These systems offer large variety of options such as solutions, suspensions, emulsions, microemulsions, self-emulsifying drug delivery systems (SEDDS), liposomes, self-microemulsifying drug delivery systems (SMEDDS), self-nanoemulsifying drug delivery systems (SNEDDS), dry emulsions, solid lipid microparticles (SLMs), and solid lipid nanoparticles (SLNs).

SOLID LIPID MICROPARTICLES (SLMs)

Microparticles or microspheres, as they are interchangeably called, are fine spheres usually less than 1000 um in diameter. Microparticles can be prepared by well-established manufacturing processes. An incorporated drug can be distributed homogenously throughout the polymer matrix (microparticles), or it can be encapsulated into a polymer surrounding to form a drug reservoir (microcapsules) [2] Solid Lipid Microparticles (SLMs) are defined as solid lipid, approximately spherical particles ranging in size from 1 to 1000 um. They are made of polymeric, waxy or other protective materials, that is, biodegradable synthetic polymers and modified natural

products such as starches, gums, proteins, fats and waxes. In recent years, biocompatible lipid microparticles have been reported as potential drug carrier systems, and as alternative materials to polymer[3] They can be considered as physiologically compatible, physicochemically stable and allowing a large scale production at a relatively low production cost than liposomes[4] These micrometer-sized particles consist of a solid fat core based on naturally occurring lipids and stabilized by surfactant molecules [5]

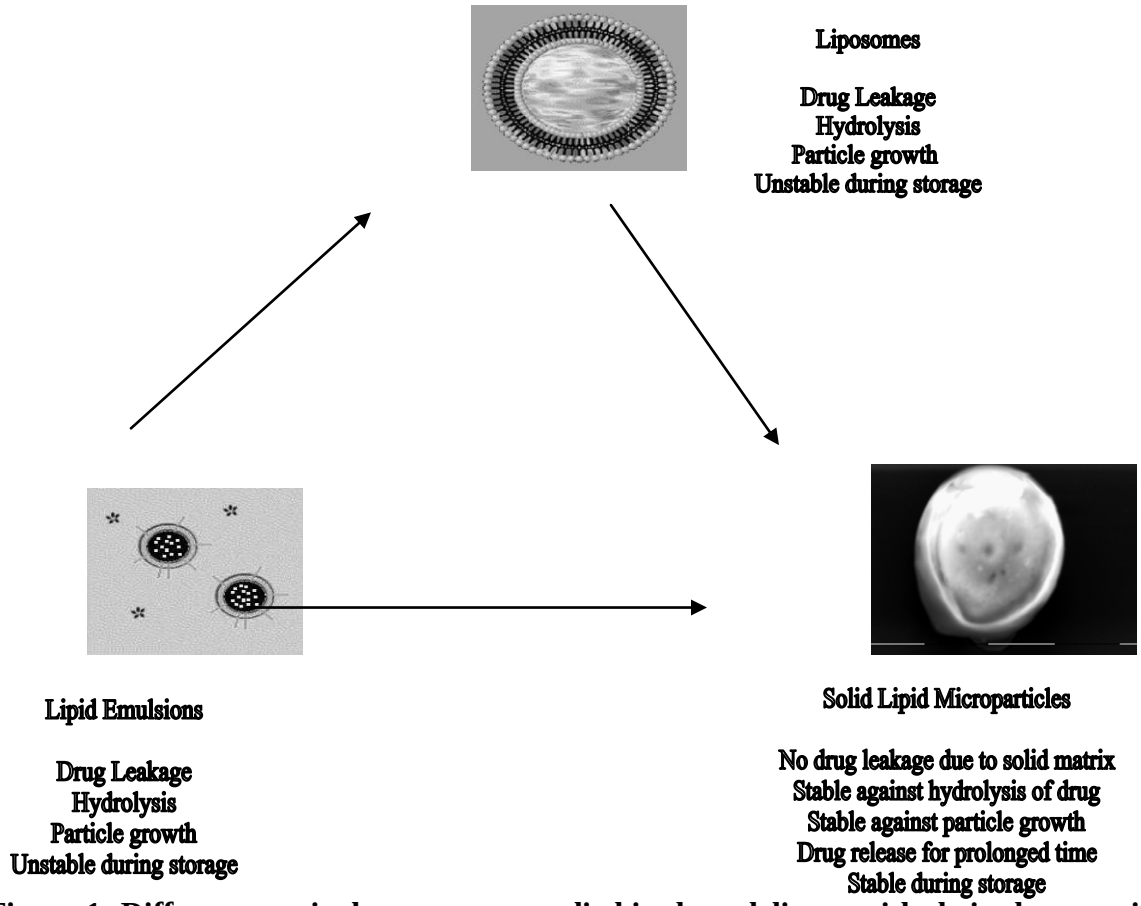

Figure 1: Different particulate systems applied in drug delivery with their characteristics.

Advantages of Solid Lipid Microparticles (SLMs)

SLMs offer some of the following advantages to drug molecules:

1. Possibility of controlled drug release and drug targeting
2. Protection of incorporated labile drug against chemical degradation
3. There is chemical and physical storage stability (for both drug and carrier system)
4. Use of biodegradable lipids
5. Allow hydrophilic and/or hydrophobic drugs to be incorporate

Disadvantages of Solid Lipid Microparticles (SLMs)

1. Possibility of particle growth

2. SLMs dispersions have high water content

3. They adjust the release profile of the incorporated drug.

4. Safety profile may be uncertain

5. Drug loading may be limited due to the solubility and miscibility of the drug in the melted lipid, chemical and physical structure of lipid materials, and their polymorphic state.

The figure below shows a schematic representation of some particulate drug delivery systems with their characteristics. From the figure 1, it can be seen that SLMs show better prospects of an effective technology for controlled drug delivery.

TECHNIQUES IN THE PREPARATION OF SLMs

High Pressure Homogenization (HPH)

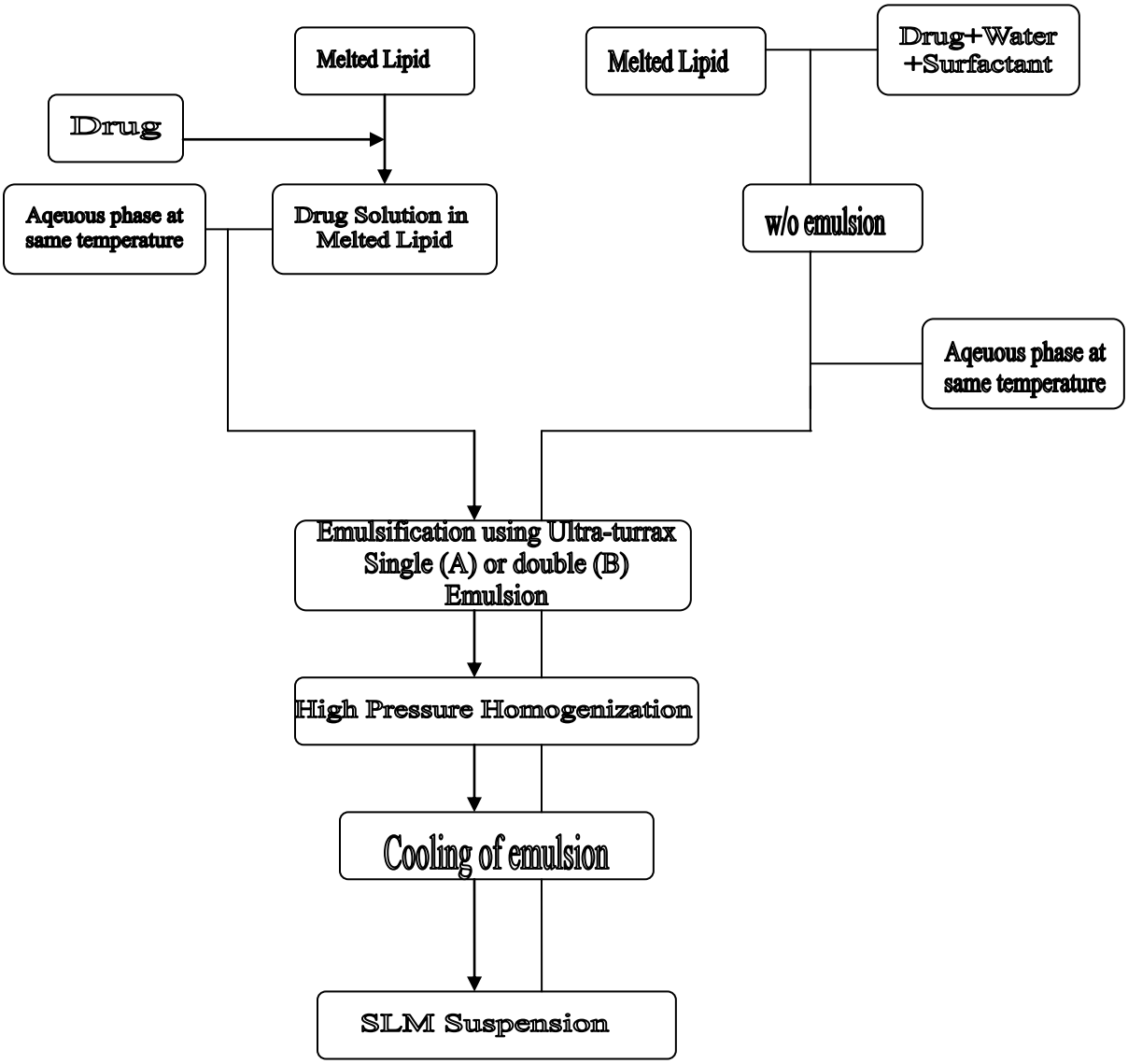

Figure 2: Hot homogenization technique of SLMs preparation

This foremost technique has gained wide acceptability and reliability in the preparation of SLMs because it presents many advantages compared to the other methods applied in SLMs preparation. Some of the advantages include avoidance of organic solvents, it has short production time, and easy scale up. HPH is sub-divided into hot homogenization and cold homogenization. The high temperature applied in hot homogenization is important because higher temperatures result in lower particle sizes as a result of the decreased viscosity of the lipid phase[6] The untoward effect of this method is that high temperatures might increase the degradation rate of the drug especially thermolabile drugs, and the carrier system. This technique is illustrated in Figure 2.

Cold homogenization is most suitable for thermolabile drugs and hydrophilic drugs. This is because these drugs would partition between the melted lipid and the aqueous phase during hot homogenization process. This process minimizes the melting of the lipid phase and hence, the loss of hydrophilic drugs to the aqueous phases[7]. This technique is illustrated in the diagram below in figure 3.

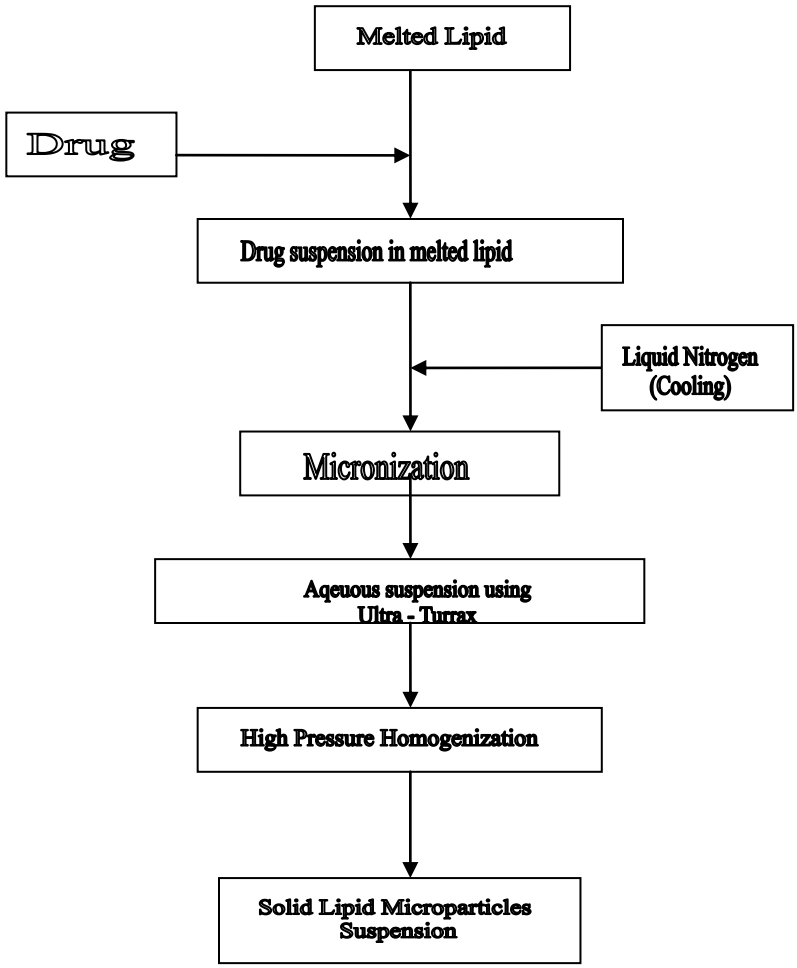

Figure 3: Cold homogenization technique of SLMs preparation

Solvent Evaporation

This is a common method for the preparation of microparticles and nanoparticles. Much of the researches that are currently carried out on proteins antigen microencapsulation, including solid lipid particles, are based on this method which avoids any thermal or pressure stress on the incorporated proteins [8, 9] Solvent evaporation method and a melt-dispersion technique without the use of organic solvents were compared for protein incorporation in lipid microparticles using insulin, thymocartin and somatostatin as model drugs. The resulting microparticles were characterized with respect to particle size and morphology, biocompatibility, encapsulation efficiency and *in vitro* release behaviour. The encapsulation efficiency was high and release was influenced by the physicochemical properties of the proteins. Both methods were found to be suitable for the preparation of microparticles for subcutaneous and intramuscular injection [10] This process is shown in the diagram below in figure 4.

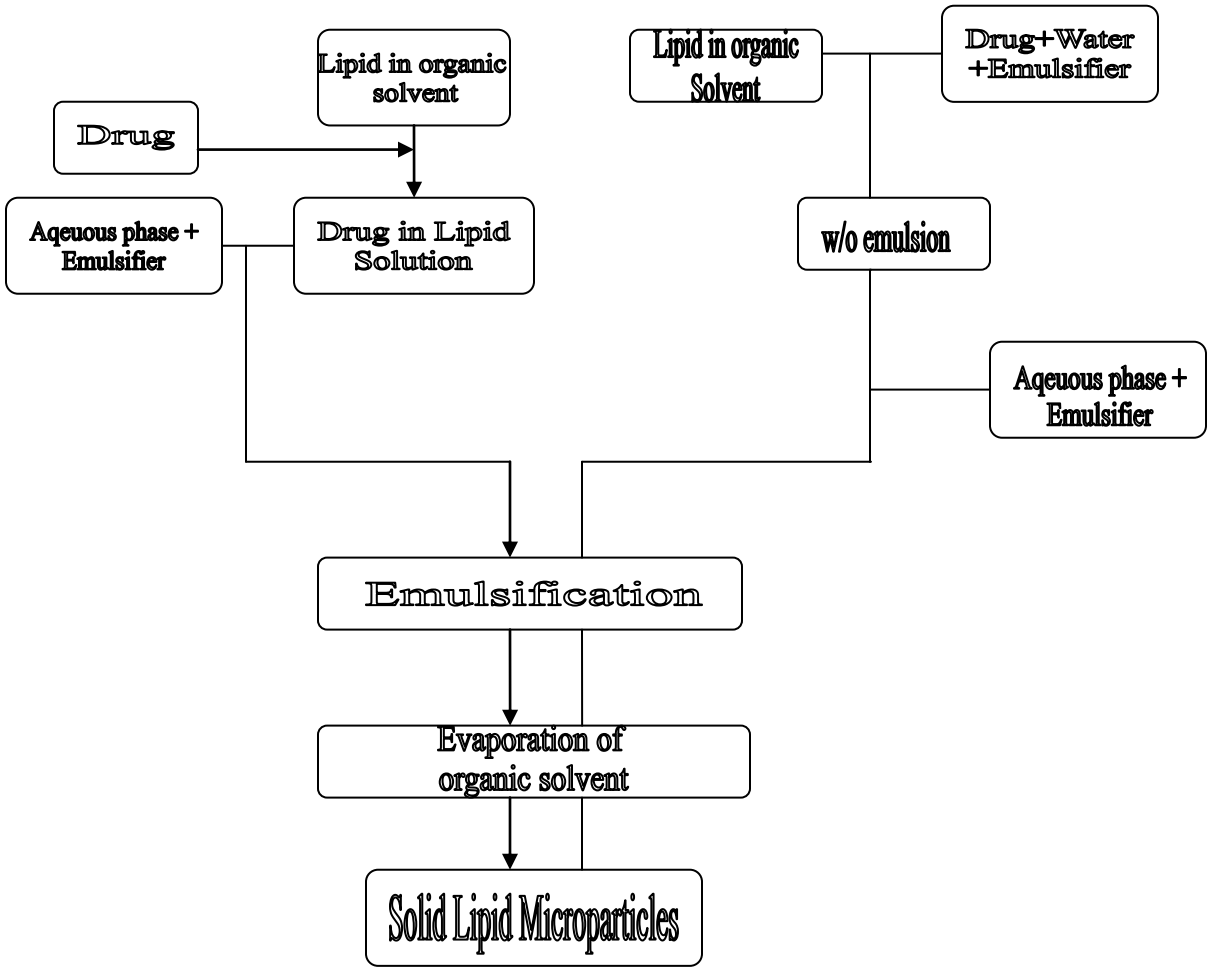

Figure 4: Solvent evaporation method of SLMs preparation

Spray Drying

Spray drying is a method of producing a dry powder from a liquid or slurry by rapidly drying with a hot gas. This is the preferred method of drying of many thermally-sensitive materials such as foods and pharmaceuticals. A consistent particle size distribution is a reason for spray drying some industrial products such as catalysts. Air is the heated drying media; however, if the liquid is a flammable solvent such as ethanol or the product is oxygen-sensitive, nitrogen is used. All spray dryers use some type of atomizer or spray nozzle to disperse the liquid or slurry into a controlled drop size spray. The most common of these are rotary disks and single-fluid high pressure swirl nozzles. This method is most suitable for poorly water-soluble drugs. The drug is dispersed in lipid solution, and then this dispersion is atomized into an airstream. The air, usually heated, supplies the latent heat of vaporization required to remove the solvent and forms the solid lipid microparticles [11].

DRUG ENCAPSULATION AND LOADING CAPACITY IN SLMs

The selection of a drug carrier system and its effectiveness in the encapsulation of a drug depends on the loading capacity of the carrier system. The loading capacity is usually expressed as the ratio of the weight of entrapped drug and the total weight of the lipids in percentage as follows:

$$\text{Loading Capacity, LC} = \frac{Wa}{W_1} \times 100\ \% \qquad (1)$$

W_a = Weight of active pharmaceutical ingredient (API) or drug entrapped by the lipid

W_1 = Weight of lipid added in the formulation [12, 13, 14].

Some of the factors which affect the loading capacity of a drug in a lipid are the solubility of the drug in the lipid melt, the miscibility of the drug and the lipid melt, the chemical and physical orientation of the solid lipid matrix, and the polymorphic state of the lipid material.

CHARACTERIZATIONOF SOLID LIPID MICROPARTICLES (SLMs)

It is very essential to carry out adequate and proper characterization of the SLMs to ensure their quality. The following parameters are considered because they have direct effect on the stability and release kinetics of the particles.

Measurement of Zeta potential

This study could be carried out on the SLMs immediately either after production, after lyophilization, or after sterilization for SLMs meant for intravenous or pulmonary administration. Suspensions of SLMs are used for performing the analyses. Zeta potential is an important product characteristic of SLMs since its high value is expected to lead to de-

aggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by using a zeta meter. The measurement of the zeta potential allows predictions about the stability on storage of colloidal dispersion [15]

Evaluation of Surface Morphology

This is usually done using Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) or photomicroscope, but the most commonly used method is SEM, which is an electron optical imaging technique that provides photographic images and elemental information. Interaction of the electron beam with the specimen produces a variety of physical phenomena, which, when detected, forms images and provides elemental information about the specimen as shown in the figure below [16] In our study in which gentamicin SLMs were formulated, majority of the particles have spherical shape and smooth surface with minor irregularity. This was paramount when the drug to lipid matrix ratio was 1:1. But as the lipid ratio increased, the observed irregularity becomes more pronounced with increase in the collapse of the spherical shape and smooth surface of the particles [12]. This shows that processing variable such as drug to lipid ratio influences the appearance of SLMs.

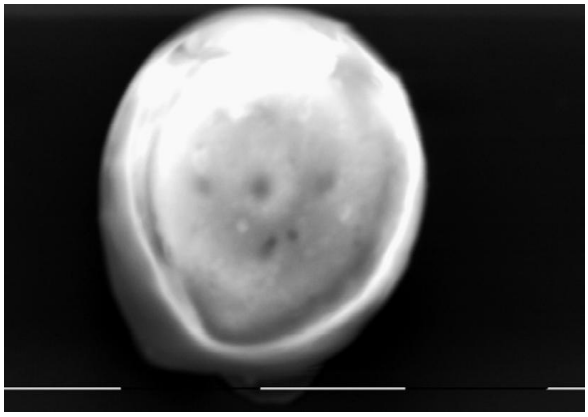

Figure 5: Scanning Electron Microscope (SEM) image of a SLM

Degree of Crystallinity and Lipid modification

The degree of lipid crystallinity and lipid modifications affect the incorporation of drugs in SLMs, and consequently, their release. The physicochemical profile of the lipid used in the formulation of microparticles could be determined using differential scanning calorimetry (DSC) and X-ray scattering techniques. The use of DSC is based on the principle that different lipid modifications possess different melting points and melting enthalpies. In X-ray scattering, it is possible to investigate the length of the long and short spacing of the lipid lattice. In a study to formulate ibuprofen-loaded SLMs using compritol 888 ATO and tripalmitin, compritol was selected as the best excipient for the formulation. The sizes of its microparticles were smaller

than that of tripalmitin because its mono- and diglycerides have surfactive properties, and improve the surfactant properties of the film around the particles. This prevents the aggregation of the particles [17] Glycerides are polymorphic and show three forms such as α, β, β′. Mixtures of glycerides give an intermediate β_i modification. β modification is usually common in triglycerides, but the existence of diglycerides in compritol results in a large number of lattice imperfections and prevents the transformation of the β form.

Drug Entrapment Efficiency, DEE.

Drug entrapment efficiency is a test performed to determine the amount of drug that is actually retained in the microparticles, usually expressed as a percentage. It goes a long way to show the reliability or otherwise, of the formulation technique. A good and reliable formulation method should be able to entrap up to 95 % of the incorporated drug. In a study to formulate the SLMs of the immunosuppressant drug sirolimus, the calculated entrapment efficiency was 98.02 %. This almost perfect encapsulation could be attributed to the high lipophilicity of the formulation resulting in increased accommodation of the drug [18] The entrapment efficiency of any formulation of SLMs could be calculated using the equation:

$$\text{Entrapment Efficiency (EE) \%} = \frac{W_a - W_b}{W_a} \times 100\ \% \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where: W_a = Weight of drug added to the system, W_b = Weight of free drug in the dissolution solvent.

ROUTES OF ADMINISTRATION OF SOLID LIPID MICROPARTICLES

Microparticles can be administered through any of the following routes:

Oral route

Oral administration of SLMs is possible as aqueous dispersion or after transforming into dosage forms like tablets using aqueous SLMs dispersion, pellets, capsules by filling the spray-dried powder in capsule shells or powders for reconstitution. It has being discovered that orally administered microparticles enhance and prolong mucosal and systemic antibody responses, most likely by temporarily protecting antigen from the acidic and enzymatically hostile environments found at mucosal surfaces, facilitating microparticles uptake by M cells overlying Peyer's Patches (PP) [19, 20, 21] and/or mucosal epithelium, [22] thereby promoting antigen transport to local lymphoid follicles and associated lymph nodes [19] P90Gylated-Softisan®142 conjugate, otherwise referred to as SRMS142, was reportedly used to formulate SLMs as an alternative carrier system for oral glibenclamide, and evaluated in diabetic rats. It was shown that SRMS 142 generated an imperfect mix with numerous spaces that accommodated glibenclamide in a

concentration-dependent manner up to 60.58 %. The blood glucose-lowering effect of the SLMs was higher than that of a commercial sample [23]

Parenteral route

SLMs have been administered through the following parenteral routes: intramuscularly, intravenously and subcutaneously, to animals. They are very suitable for systemic delivery because they consist of physiologically well-tolerated ingredients and they have good storage capabilities after lyophilization and/or sterilization. After parenteral administration, the particles are cleared from the circulation by the liver and the spleen. Gentamicin was reportedly encapsulated in SLMs formulated using phospholipon®90G and softisan®154, as P90Gylated-Softisan®154 conjugate, otherwise referred to as SRMS154 [12] Physicochemical characterization showed that the biomaterials used for the formulation are capable of ensuring a high payload of the drug, and pharmacokinetic analysis showed that the formulation released over 90 % of the encapsulated drug after intramuscular administration in rats compared to the commercially available gentamicin injection.

Pulmonary administration

Over the years, SLMs have been shown to be effectively delivered through the pulmonary route. Systemic delivery through pulmonary administration can be facilitated by unique features such as large surface area of the lungs, good vascularisation, large capacity for solute exchange, ultra-thinness of the alveolar epithelium (0.1 to 0.5 mm) and avoidance of first pass metabolism. In a recent study, antitubercular drugs (rifampicin, isoniazid, and pyrazinamide) were incorporated into various formulations of solid lipid particles ranged from 1.1 to 2.1 µm, and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery. Nebulization of solid lipid particles carrying antitubercular drugs was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary tuberculosis [24.]

Topical route

SLMs are becoming more popular for the topical delivery of oily substances, and are already common in a variety of topical pharmaceutical and cosmetic applications. This is because many suitable compounds are soluble in these materials, they do not irritate the skin and they have extremely low acute and chronic toxicities. When SLMs are topically applied, they create a monolayered lipid film of smaller interparticle pores, which are associated with higher occlusiveness, and, therefore, higher hydration and skin emolliency. SLMs have being used because of their UV blocking effects, which is also dependent on lipid composition and the

particle size. The smaller the particle size, the higher the sunscreen activity. They can act as sunscreen carriers and increase the sun protection factor (SPF) obtained after topical application of UV absorbers incorporated within these carriers [25] Researchers have reported intensively on the topical application of SLMs. During the last few years, SLMs have been studied with active compounds such as econazole nitrate [26] octyldimethyl aminobenzoate [27], juniper oil [28] rhodamine [29] and acyclovir [30] for topical application.

Ocular administration

Millions of people suffer from a wide variety of ocular diseases, many of which lead to visual impairment and ocular blindness [31] Ocular bioavailability after topical ocular eye drop administration is less than 5 % and often less than 1 %, and therefore, only the diseases of the anterior segment of the eye can be treated with eye drops [32] Within the group of controlled release intraocular substances developed to date are microparticles. Microparticles, as microspheres, have been developed in ophthalmologic therapeutics for treating a range of pathologies. For instance, adriamicine, 5-fluoracile (5-FU) and retinoic acid microspheres have been developed for treating proliferative vitreoretinopathy, dexamethasone microspheres for preventing ureitis after surgical procedures, acyclovir microspheres for treating retinal necrosis, and ganciclovir microspheres for cytomegalovirus-induced retinitis. The intraocular administration of microparticles is carried out with the injection of a suspension thereof with a needle having a diameter between 25 – 30 G for particle sizes between 1 and 50 µm, and 18 G for particles up to 500 µm [33]. Microparticles are sterilized by using a method based on ionizing radiation with gamma rays which have high penetration capacity, and the necessary dosage for achieving sterilization is comprised between 25 and 20 kGy [34].

Rectal Administration

The rectal route has been frequently exploited for the systemic delivery of drugs in situations where it is desirable to avoid hepatic first-pass metabolism [35] or to prolong drug release [36] Plasma levels and therapeutic efficacy of rectally administered drugs were reported to be higher compared with those given orally or intramuscularly in the same dose [37, 38] Some researchers examined the therapeutic potential of biodegradable meselamine microspheres in the treatment of inflammatory bowel disease (IBD). The microparticles were formulated with poly (lactic-co-glycolic acid) by emulsification solvent evaporation method, and inflammation was induced in wistar rats using acetic acid. After administering the meselamine microparticles rectally and orally once daily for five consecutive days, the clinical parameters employed to determine the therapeutic potential of the microspheres decreased significantly compared to the effect produced

by the free drug. This new delivery system enabled the drug to accumulate in the inflamed tissue with higher efficiency than when given as suspension of drug [39]

Also, microparticles have been shown to have a sustained release effect when administered rectally as suppositories, and hence produce improved patient compliance and reduce the number of doses to be administered. Aceclofenac is a non-steroidal drug having potent analgesic, anti-inflammatory and antipyretic activities due to its prostaglandin synthetase inhibitory action has been used to formulate microparticles, which were used to prepare suppositories. Since it produces serious gastrointestinal complication such as gastric ulcer, severe bleeding and perforation resulting in hospitalization and even death, so rectal administration is used as an alternative to oral route. The microparticles were prepared by solvent evaporation method employing ethylcellulose as the microparticle forming polymer. The suppositories were formed using PEG 4000, PEG 6000 and stearic acid as bases. The sustained release property of the microparticulate suppositories were evaluated comparatively using conventional aceclofenac suppositories, and it was found out that aceclofenac microspheres containing suppositories showed a sustained effect (98 %) up to 8 h *in vitro* while the conventional suppositories released 99 % of the drug within 3 h [40].

CLINICAL APPLICATIONS OF SOLID LIPID MICROPARTICLES (SLMs)

1. SLMs have been used as a carrier system for the delivery of drugs in the treatment of inflammatory bowel disease using curcumin [41]
2. Budesonide loaded solid lipid microparticles have been demonstrated to be of potential benefit in the treatment of pulmonary diseases *in vitro* [42.]
3. SLMs have been demonstrated to be effective as carriers for solid lipid nanoparticles (SLNs) e.g. inhalable microparticles were used as carriers for the pulmonary delivery of thymopentin-loaded SLNs [43.]
4. SLMs are also employed in imaging e.g. imagent, a perflexane lipid microparticles is used in clinics or hospitals to determine gastrointestinal problems through magnetic resonance imaging (MRI). It is used to differentiate the problems from the normal structures. It affects the bowel contents, showing on the MRI image as a black spot [44]
5. Lipid microparticles of cosmetic ingredients such as glycolic acid have shown decreased irritation potential, while incorporation of quercetin in lipid microparticles improved photo and chemical stability of the flavonoid [45]
6. Lipid microparticles have been developed by many researchers as carrier systems for the delivery of proteins and peptides such as antide [46], somatostatin [47], thymocartin[10],

Japanese encephalitis antigen (JEAg)[9], Fluorescein-5-isothiocyanate (FITC) [48] bovine serum albumin (BSA) [8, 49], Hepatitis B surface antigen (HBsAg) [8] and insulin [10, 50]. This is shown in the table below.

Table1: Some examples of proteins and peptides encapsulated in solid lipid microparticles.

Peptide/Protein	Method of Preparation	Incorporation Efficiency (%)	Cumulative Release	Protein Stability/Biological Activity
GnRH Antagonist (Antide)	Milling of drug-lipid solid solutions (Co-melting)	> 85	≤ 60 %/24 h	100 % Biological Activity
GnRH Antagonist (Antide)	Milling of drug-lipid solid solutions (Solvent stripping)	> 85	≤ 40 %/24 h	100 % Biological Activity
Insulin	Solvent Evaporation (o/w)	45-94	< 60 %/3 days	Some aggregation
Insulin	Melt-dispersion (o/w or w/o/w)	≈ 50 or > 80	< 60 %/3 days	Some aggregation
Insulin	Solvent Diffusion (w/o/w)	78-84	≈ 30 %/24 h	Intact Protein
Somatostatin	Solvent Evaporation (o/w or w/o/w)	< 75	n.a	n.a
Somatostatin	Melt Dispersion (o/w)	65-97	70-80 %/14 h	Intact Protein
BSA	Solvent Evaporation (w/o/w)	58.1-69.5	≈ 30 %/24 h	93 % intact
BSA	Coating with lipid using SCF	13-62 protein content	≈ 80 %/24 h	10 % intact
BSA-FITC	Adsorption onto Lipid Microparticles	n.a	n.a	n.a
Thymocartin	Solvent Evaporation (o/w or w/o/w)	< 10 or < 50	65-90 %/5 days	Intact Peptide
Thymocartin	Melt Dispersion (o/w or w/o/w)	< 90 or 90-100	65-90 %/5 days	Intact Peptide
JEAg	Solvent Evaporation (w/o/w)	73.8	≈ 20 %/10 days	Biological Activity proved *in vivo*
HbsAg	Solvent Evaporation (w/o/w)	58.2-67.9	n.a	> 98 % intact; Biological activity proved *in vivo*

Note: *BSA – Bovine Serum Albumin; FITC – Flourescein-5-isothiocyanate; HBsAg – Hepatitis B surface Antigen; JEAg – Japanese Encephalitis Antigen; n.a. – non-available; SCF – Supercritical Fluid Technology*

CONCLUSION AND FUTURE PROSPECTS

Lipid carriers have bright future due to their inherent property to enhance the bioavailability of lipophilic and hydrophilic drugs. These are the types of carriers which not only combine the

advantages of other colloidal systems but also avoid their disadvantages. The incorporated drugs enter the systemic circulation through the lymphatic route which avoids hepatic first pass metabolism. SLMs constitute an attractive colloidal drug carrier system due to successful incorporation of active compounds and their related benefits. Their benefits are still being demonstrated and new approaches are introduced. SLMs offer an economical and patient-friendly device for administration of drugs by various routes. Reports on surface modification of SLMs by PEG and/or PLGA coating have created great and increased attention of various research groups with the aim of improving drug bioavailability. Certainly, further researches have to be carried out to fully understand and demonstrate the pharmacokinetic profiles and interactions of SLMs with their biological environment. These may include their absorption and desorption processes, enzymatic degradation, agglomeration interactions, and interactions with endogenous lipid carrier systems. No breakthrough would be recorded for any delivery system if it is left for those in academic research alone. Huge success can only be recorded if pharmaceutical industries could fund development of these research findings. To guarantee a broad application of a carrier system, it is highly desirable that companies specialized in drug delivery systems engage themselves in the new technology. This would encourage the various research groups to continue to develop new technologies for solving problems related to drug delivery and bioavailability.

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