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*Review*

# Solidified reverse micellar solutions (SRMS): A novel approach for controlling drug release from various lipids based drug delivery systems

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**Solidified reverse micellar solutions (SRMS) are reverse micelles containing lecithin and a triglyceride, for example, SOFTISAN®142, which is hydrogenated coco glyceride. SRMS transform into a lamellar mesophase after melting on contact with water; this transformation enables controlled release of solubilized drugs. They offer potentials for sustained drug delivery of both hydrophilic and lipophilic drugs. SRMS have the advantage of providing more flexibility in controlling the drug release and protecting the encapsulated ingredients from chemical degradation. SRMS based systems influence the absorption of active ingredients through different mechanisms to modify the release of active ingredients, and improve drugs bioavailability. The types of SRMS-based drug delivery systems include solid lipid nanoparticles (SLN), solid lipid microparticles (SLM), tablets and suppositories amongst others. The work exhaustively reviews the advances in SRMS based carriers. Its formulation methods, characterisation and delivery systems were discussed in details.**

**Key words:** Solidified reverse micellar solutions (SRMS), lipids, wide angle X-ray diffraction analysis (WAXD), small angle X-ray diffraction analysis (SAXD), lipid absorption.

## INTRODUCTION

There is growing interest and investment in the use of lipid-based systems in drug discovery and product development to effectively overcome physical and biological barriers related to poor aqueous solubility and stability, membrane permeability, drug efflux and availability (Westesen and Siekmann, 1998). Solid lipids have the advantage of providing more flexibility in controlling the drug release and protecting the encapsulated ingredients from chemical degradation. Also, they allow for the incorporation of hydrophilic as well as hydrophobic drugs (Lippacher et al., 2001; Hu et al., 2020). Many waxes (for example, stearic acid, mono-, di- and tri-glycerides, glyceryl behenate, glyceryl monostearate, hydrogenated castor oil, among others) have been extensively investigated for sustaining the release of various drugs (Wadher et al., 2010).

Reverse micellar solutions (RMS) are lipidic solutions consisting of lecithin (30% w/w) dissolved in an oily

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**Abbreviations: RMS,** Reverse micellar solutions; **LRMS,** liquid reverse micelles; **SRMS,** solidified reverse micellar solutions; **LDDS,** lipid based drug delivery system; **P-gp,** P-glycoprotein; **WAXD,** wide angle X-ray diffraction analysis; **SAXD,** small angle X-ray diffraction analysis; **TEM,** transmission electron microscopy; **PCS,** photon correlation spectroscopy; **SLN,** solid lipid nanoparticles; **m.p.,** melting points; **SLM,** solid lipid microparticles; **NSAIDs,** non-steroidal anti-inflammatory drugs; **CMC,** critical reverse micelle concentration.

vehicle, for example, isopropylmyristate or middle-chain trigly-cerides and transform into a lamellar mesophase on contact with water (Papantoniou and Müller-Goymann, 1995; Friedrich et al., 2000). This application-induced transformation into a semisolid system of liquid crystals enables controlled release of solubilized drugs (Müller-Goymann and Hamann, 1993; Schneeweis and Müller-Goymann, 1997; Friedrich and Müller-Goymann, 2003). On contact with water, the liquid reverse micelles (LRMS) exhibits an application induced transformation into a semi-solid system of liquid crystalline microstructure. The structure of the liquid crystal has been identified by polarized light microscopy as a lamellar mesophase (Friedrich and Müller-Goymann, 2003). Solidified reverse micellar solutions (SRMS) are reverse micelles containing lecithin and a solid lipid such as the triglyceride (softisan® 154), and softisan® 154, which is a completely hydrogenated palm oil. SRMS offer potentials for sustained drug delivery of both hydrophilic and lipophilic drugs and also transform into a lamellar meso-phase after melting on contact with water. This trans-formation enables controlled release of solubilized drugs. Both LRMS and SRMS offer a high solubilization rate of different types of drugs (Friedrich and Müller-Goymann, 2003). SRMS based carriers have been investigated, and successfully employed to achieve controlled release of hydrophilic and lipophilic drugs (Schneeweis and Müller-Goymann, 2000; Friedrich and Müller-Goymann, 2003; Umeyor et al., 2012 a; Chime et al., 2012; Chime et al., 2013a,b). SRMS can also be formed using modified natural lipids containing lecithin and dika wax (Chinaeke et al., 2013), lecithin and Moringa oil, lecithin and goat fats (Uronnachi et al., 2013), lecithin and beeswax (Momoh et al., 2012) and lecithin and soy oil respectively at the ratios that could yield SRMS (Chinaeke et al., 2013).

SRMS were believed to be formed by combination of lecithin (30%) and oily vehicle or triglycerides (60 - 70%) (Schneeweis and Müller-Goymann, 2000). However, Friedrich and Müller-Goymann (2003), Umeyor et al. (2012 a), Momoh et al. (2012) Uronnachi et al. (2013) and Chime et al. (2013) demonstrated respectively that SRMS could be formed using 1:1, 2:1, 1:2, 3:1 and 2:3 ratios of lecithin and solid fats.

Most lipid based formulations today are available as normal release formulations, and this poses serious problems of patient noncompliance leading to poor disease management. This led to research into the field of controlled lipid based delivery system with huge success recorded by the discovery of SRMS. SRMS offer high solubilization capacities for different types of drugs in contrast with simple triglyceride systems (Friedrich and Muller-Goymann, 2003). However, the increase in water content causes a change in shape and size and finally a phase transformation from the reverse micellar solution into a lamellar liquid crystal. Solubilization of the drug in its free acid form results in almost spherical micelles, while solubilization of drug in its sodium salt form results in cylindrical micelles. The lamellar liquid crystals which form on contact with aqueous media can be used for sustained release, as the diffusion coefficient of the drug within the liquid crystals is smaller by factor 100 than that within an oily solution. The apparent diffusion coefficient of the drug depends on the thickness of the liquid crystalline interface which is also influenced when either the free acid or the salt is solubilized in the system (Muller-Goymann and Hamann, 1993).

Lipid-based formulations and SRMS based systems influence the absorption of active ingredients through different mechanisms to modify the release of active ingredients, improve drugs bioavailability, stimulate the lymphatic transport of active ingredients, and interact with enterocyte based transport (Fouad et al., 2011). SRMS-based formulations have been shown to enhance the bioavailability of drugs administered orally in addition to controlling the rate of drug release and have been used for once daily sustained release formulations (Umeyor et al., 2012a, Nnamani et al., 2010; Chime et al., 2013, Momoh et al., 2012, Uronnachi et al., 2013). The proven safety (GRAS) of lipid based carriers makes them attractive candidates for the formulation of pharmaceuticals (Attama and Nkemnele, 2005; Attama et al., 2009). Lipid formulations in general, provide increased drug solubilization for water - insoluble drugs. If the drug is dissolved in the lipid matrix (for example, SRMS), the drug absorption is observed to be better. Drug suspended in the lipid matrix has been shown to get absorbed better than the conventional solid dosage forms (Sarkar, 2002; Hou et al., 2003; Gao et al., 2004; You et al., 2005; Obitte et al., 2012; Brown et al., 2013). This could be due to the ease of wetting of the hydrophobic drug particles in the presence of lipid matrix. The presence of surfactant in the formulation may ease the wetting further. Also entrapment of drug in the micelles may be enhanced due to the presence of lipid matrix (Joshi and Shah, 2008). For poorly water soluble drug molecules, whose dissolution in water is likely the rate limiting step to overall oral absorption, the primary role of ingested lipids and their lipolytic products is to impact the drug dissolution step by forming different colloidal particles with bile components, which are able to maintain a larger quantity of hydrophobic drugs in solution via micellar solubilization (Porter, 2007). The primary mechanism of action which leads to improved bioavailability is usually avoidance or partial avoidance of slow dissolution process which limits the bioavailability of hydrophobic drugs from conventional solid dosage form (Pouton, 2000). Lipid-based excipients such as glycerides, fatty acids, ionic and non-ionic surfactants are known permeability enhancers (Aungst et al., 1996; Kuentz, 2012), which may be due to increased membrane fluidity. Permeability enhancement may also be achieved by the interaction of lipid based drug delivery system (LDDS) with efflux transporters. A well-known efflux transporter at the apical membrane of human intestine is the P-glycoprotein (P-gp). Excipients with

inhibiting effects on efflux pumps are found in the group of medium chain glycerides, polyethylene glycols, polysorbates and polyethoxylated castor oil or block copolymers of the type Pluronic. Surfactants have been shown to inhibit P-gp because of their amphiphilic structure (Bogman et al., 2003; Aungst et al., 1996; Pang et al., 2007; Kuentz, 2012).

## MATERIALS USED FOR SRMS FORMULATION

Basically, SRMS are formed mainly using lecithin (for example, Phospholipon® 90G, a purified soybean lecithin with at least 90% (w/w) phosphatidylcholine, phospholipon® 90H, completely hydrogenated soybean lecithin with at least 90% (w/w) phosphatidylcholine) and a triglycride (softisan® 100, 133, 134, 138, 142, a hydroge-nated coco-glycerides and softisan® 154, a hydrogenated palm oil) at ratios 1:1, 1:2 and 2:1 (Friedrich and Müller-Goymann, 2003; Umeyor et al., 2012; Chime et al., 2013). Oils like soy oil, isopropyl myristate, coco nut oil and Moringa could be used in the right ratio in formulating SRMS (Schneeweis and Müller-Goyman, 2000; Chinaeke et al., 2013). Some waxes like bees wax, dika wax and fats from animals for example, goat fat may also be used in the formulation of SRMS (Momoh et al., 2012; Uronnachi et al., 2013).

## FORMULATION OF SRMS

SRMS are normally formulated by fusion using a magnetic stirrer hot plate. A binary mixture (usually, 1:1, 1:2 and 2:1) of lecithin and triglycerides for example, softisan, respectively are normally used for SRMS preparation. The lipids are melted together and stirred with a Teflon coated magnet at a temperature of about 60 - 90°C, depending on the SRMS composition. The molten lipids are stirred until a transparent melt is obtained. Then, the homogeneous mixture will be stirred at room temperature until solidification (Friedrich and Müller-Goymann, 2003).

## CHARACTERISATION OF SRMS

### Differential scanning calorimetric analysis

Melting transitions and changes in heat capacity of the SRMS could be determined using a differential scanning calorimeter. About 1-5 mg of SRMS could be placed in the aluminum pan, hermetically sealed and the thermal behaviour determined in the range of 10-190°C at a heating rate of 5 or 10°C/min (Nnamani et al., 2010; Umeyor et al., 2012 a).

Depending on a variety of factors, lipids may exist in one crystalline form or it may be a mixture of several different crystal modifications. Lipids are polymorphic and transform systematically through a series of successive crystalline forms without change in chemical structure (O'Brien, 1998). The polymorphic transitions may be influenced by the addition of one or more substances (or other fats) to the SRMS (Attama et al., 2006). Consequently, certain properties necessary for improved performance as drug delivery bases may be influenced. It is important to know the thermal characteristics, crystal habit, texture, and appearance of a new lipid matrix when determining its suitability for use in certain food or pharmaceutical application. DSC is the most widely used thermo-analytic technique for studying lipids and their mixtures. It gives information about the temperatures and energy associated with their fusion and crystallization, phase behavior, polymorphic transformations, and data to estimate solid fat contents (Tan et al., 2000; Solís-Fuentes et al., 2005; Attama et al., 2006). Figure 1 shows the DSC thermograms of SRMS 100 (lecithin softisan 100 mixtures), (b) SRMS 142 (lecithin S142 mixtures, with 0, 30, 40, 50 and 60% (w/w) bottom to top) (Friedrich and Müller-Goymann, 2003). The crystallinity index (CI%) of the SRMS could be calculated using the Equation (1) (Freitas and Müller, 1999; Attama et al., 2006):

$$\mathrm{CI}(\%) = \frac{\mathrm{Enthalpy}_{\mathrm{SRMS}}\left(\frac{\mathrm{J}}{\mathrm{g}}\right)}{\mathrm{Enthalpy}_{\mathrm{PL}}\left(\frac{\mathrm{J}}{\mathrm{g}}\right)} 100\, f_{PL} \quad (1)$$

Where, $\mathrm{enthalpy}_{PL}$ is the fusion enthalpy of pure lipid for example, softisan, $\mathrm{enthalpy}_{SRMS}$ is the fusion enthalpy of the lipid matrix admixture (SRMS) and $f_{PL}$ is a correction factor which takes into account the concentration of pure lipid. The SRMS with lower CI are preferable due to presence of spaces in the SRMS for drug localization therefore, leading to high payload of drug.

### Wide angle X-ray diffraction analysis (WAXD)

WAXD analysis of lipid matrices gives information on the crystalline state of the matrices, as it reveals the dimensions of the short spacing of the unit cells. WAXD analysis gives further insights on the preferred orientation and crystallinity of the samples with emphasis on the orderliness of the crystal arrangement (preferred orientation) and the ratio of the crystalline properties to the non-crystalline properties (Attama et al., 2006). Distorted crystal arrangements of the individual lipids within the SRMS are desirable in order to create spaces for drug localization. This is a desirable quality in particulate drug delivery systems since it enhances the drug loading capacity of the lipids and also improves the overall drug encapsulation efficiency. Figure 2 shows the WAXD diffractograms of SRMS 142 consisting softisan 142 and 60% P90G (Friedrich and Müller-Goymann,

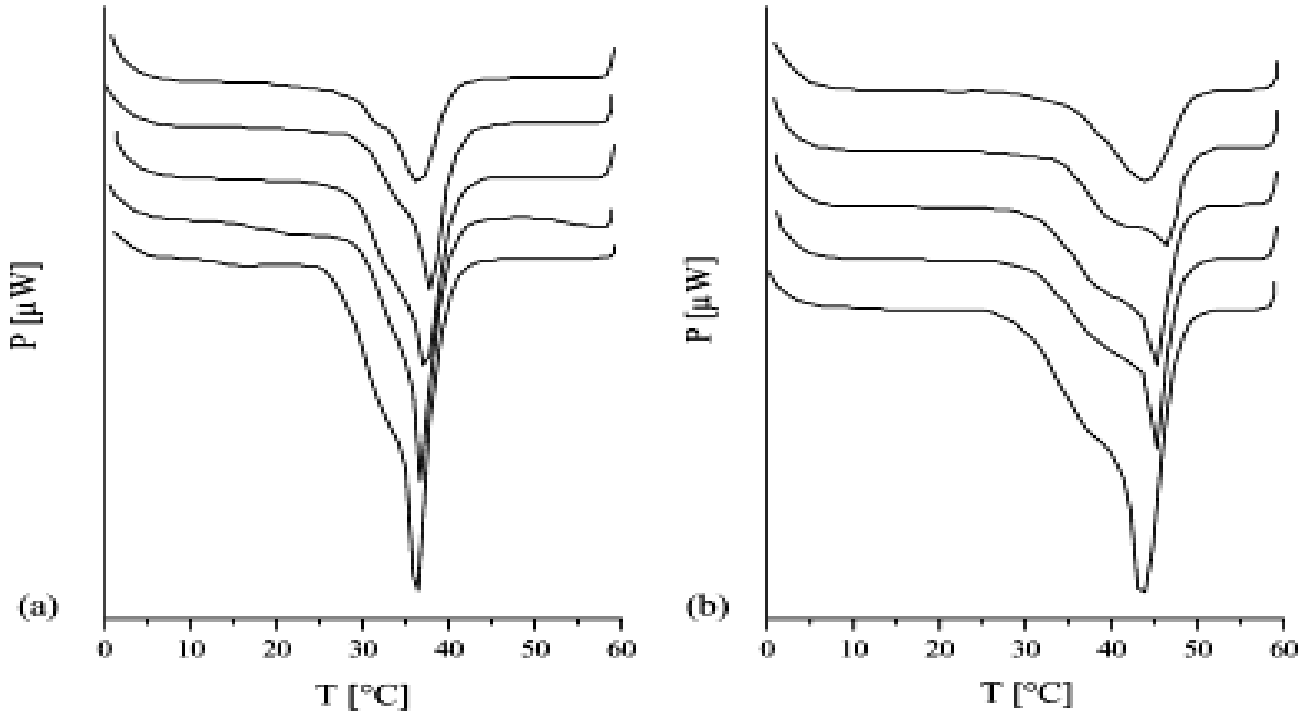



**Figure 1.** DCS thermograms of (a) SRMS 100 (lecithin S100 mixtures) and (b) SRMS 142 (lecithin S142 mixtures, with 0, 30, 40, 50 and 60% (w/w) bottom to top), S: softisan® (Friedrich and Müller-Goymann, 2003).

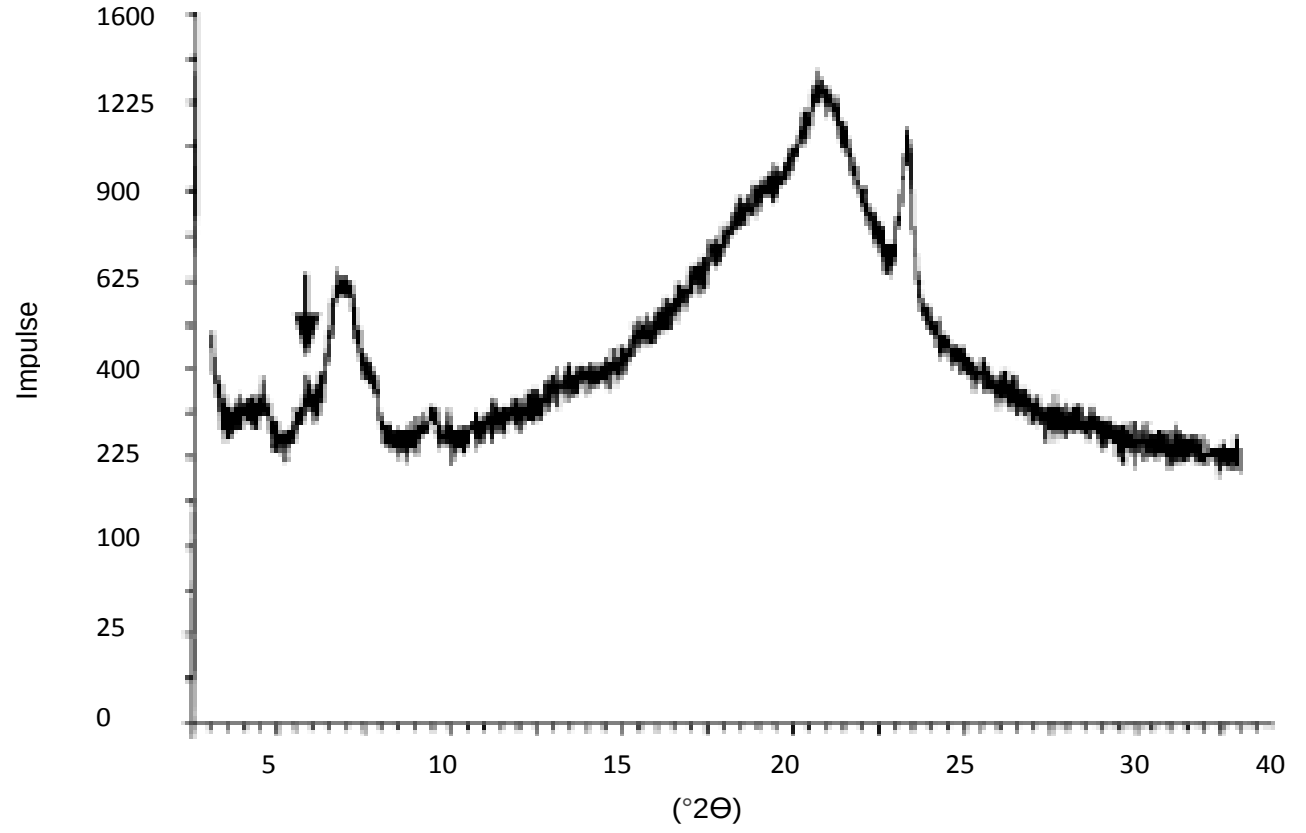



**Figure 2.** WAXD diffractograms of SRMS 142 consisting softisan 142 and 60% P90G (Friedrich and Müller-Goymann, 2003).

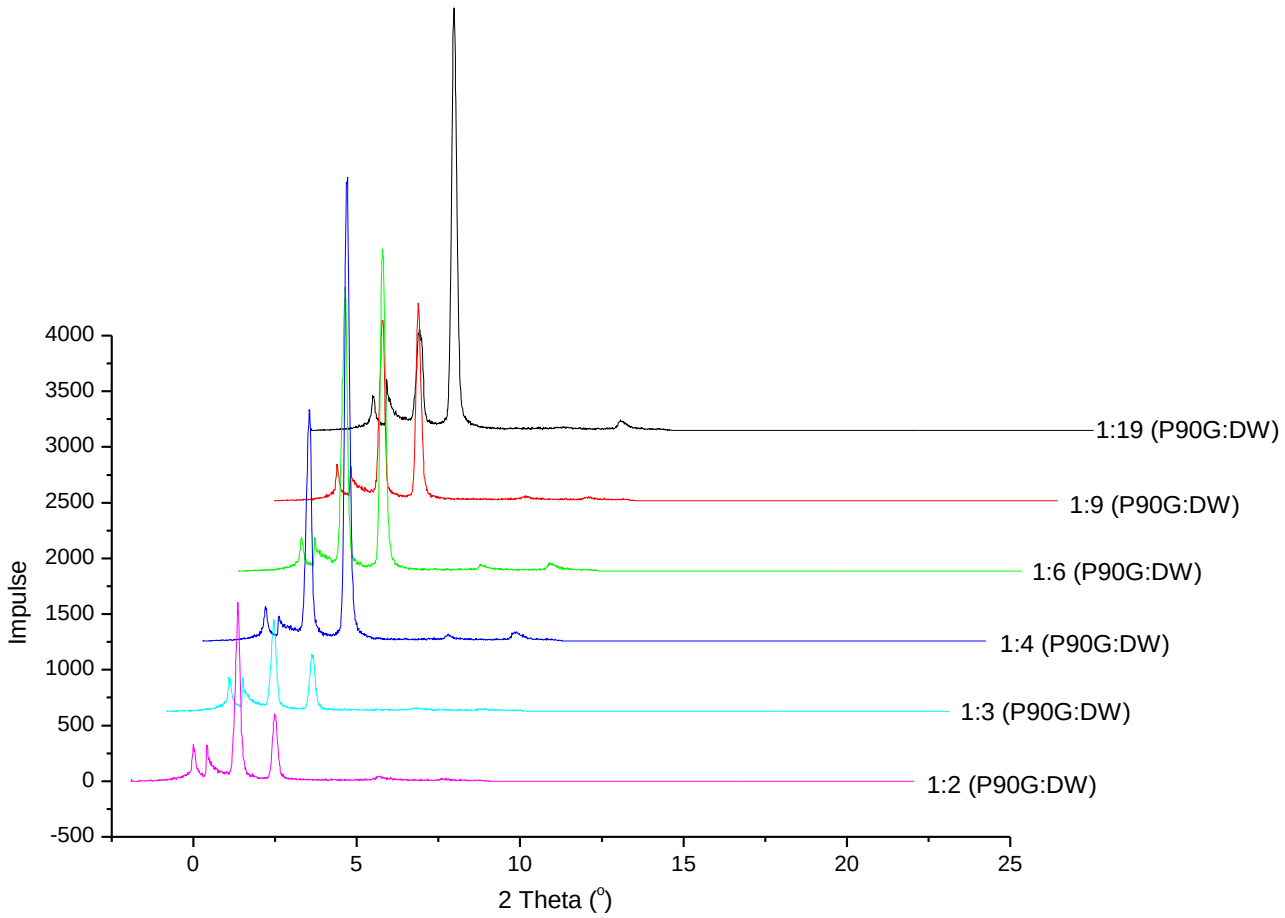



**Figure 3.** SAXD differactograms of different batches of lipid matrices formulated with different ratios of P90G and dika fats; DW - Dika wax (Chinaeke et al., 2013).

2003). The interlayer spacing in the SRMS may be calculated from the reflections using Bragg's equation (Equation 2):

$$n\lambda = 2d \sin\theta \quad (2)$$

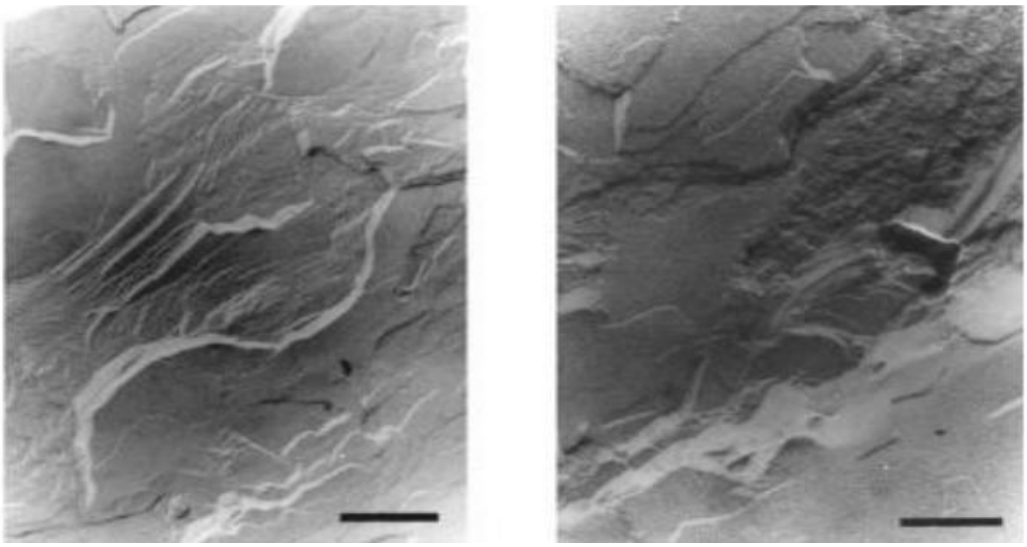
Where, $\lambda$ is the wavelength of the incident X-ray beam, n is a positive integer which describes the order of the interference and θ is the scattering angle. The parameter *d*, otherwise called the interlayer spacing, is the separation between a particular set of planes of the crystal lattice structure (Attama et al., 2006).

## Small angle X-ray diffraction analysis (SAXD)

SAXD is used to analyze the long range order of the crystalline structure of the lipid matrices. Interlayer spacing is the separation between a particular set of planes of the crystal lattice structure (Attama and Müller-Goymann, 2006). Many lipids are known to arrange themselves in layered structures with a repeat distance of few nanometers, thus giving rise to Bragg reflections in the small angle region. The repeat distances correspond to the thickness of the lipid layers (Attama et al., 2006). If the diffractograms produced by the SRMS are lamellar, it shows that the crystal arrangements of the individual lipids were disorganized. Lipid matrices with a certain degree of disorder are considered to be ideal for formulation of microparticulate lipid carriers due to their high active ingredient payload capacity (Attama et al., 2006; Attama and Muller-Goymann, 2007). Figure 3 shows the SAXD diffractograms of SRMS formulated with Phospholipon 90G and dika wax (Chinaeke et al., 2013).

## Transmission electron microscopy (TEM) and Photon correlation spectroscopy

TEM could reveal typical features of the triglyceride lattice such as planar layers in the SRMS. Photon correlation spectroscopy (PCS) measurements may be performed with a Zetasizer. Figure 4 shows the TEM



(a) (b)

**Figure 4.** TEM micrographs of: (a) softisan 100 (bar= 303 nm), (b): SRMS 100 consisting of softisan 100 and 50% of P90G (bar = 182 nm) (Friedrich and Müller-Goymann, 2003).

micrographs of (a): softisan 100 (bar= 303 nm), (b): SRMS 100 consisting of softisan 100 and 50% of P90G (Friedrich and Müller-Goymann, 2003).

### Determination of drug solubility in the SRMS

For investigations on drug solubilization in the SRMS, the drug is added to the melt of the SRMS and then solubilized under stirring at a temperature used in formulating the SRMS and the solubility limit of the drugs in the SRMS melt determined both macroscopically and microscopically. Also, solubility may correspond to the highest drug concentration at which a transparent melt is be obtained (Friedrich and Müller-Goymann, 2003; Galal et al., 2004).

## TYPES OF SRMS-BASED DRUG DELIVERY SYSTEMS

### Solid lipid nanoparticles (SLN)

Friedrich and Müller-Goymann (2003) studied the effect of lipid matrix composition, homogenization speed, surfactant composition on the properties of nanosuspensions. They found out that for production of SRMS-based nanosuspensions, a polysorbate 80/SRMS ratio of 1:5 is sufficient for particle size reduction. Homogenization on cold with resulting product temperatures far below the melting points (m.p.) of the systems causes broad particle size distributions. They also found that to achieve small nanoparticles with a narrow particle size distribution, homogenization on hot is not required. Instead, the suspension temperature has to be just near the m.p. for more flexibility of the solid lipids or for a partial melting. This could be controlled by varying the homogenization pressure at room temperature. A pressure of 1000 bar results in a temperature near the m.p. of SRMS100 (formed with lecithin and softisan 100), that of 1500 bar in a temperature near the SRMS142 (formed with lecithin and Softisn 154) m.p. They also concluded that an increase in transition temperature after production caused an increase in particle size because of particle agglomeration or growth (Friedrich and Müller-Goymann, 2003).

### Solid lipid microparticles (SLM)

SLM based on SRMS have been developed recently in order to control the release of drugs. Nnamani et al. (2010) formulated SRMS142-based solid lipid microparticles of glibenclamide and the findings showed that SRMS142 generated an imperfect matrix 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. The results also showed that P90Gylated-softisan® 142 conjugate, otherwise referred to as SRMS142, have numerous advantages: wetting, solubilization, drug stabilization, emulsification, and modified release. Umeyor et al. (2012) also formulated SRMS-based SLM for intramuscular administration of gentamicin. SRMS formulated with Phospholipon® 90G and softisan® 154 were used to prepare gentamicin-loaded SLMs and results revealed high encapsulation efficiency of about 92%

and sustained release of drug for once daily administration were obtained. Momoh et al. (2012) also produced ibuprofen-loaded SLMs based on SRMS and reported sustained release properties in addition to good *in vivo* anti-inflammatory properties. Uronnachi et al. (2013) also worked on the pharmacokinetics and biodistribution of zidovudine loaded in a solidified reverse micellar delivery system and also reported good *in vivo* bioavailability of zidovudine in addition to controlled release properties. Chime et al. (2012 and 2013 a) worked on indomethacin-loaded SLMs-based on SRMS 154 and diclofenac potassium-loaded SLMs based on SRMS 154. The results showed high encapsulation efficiency of up to 90%, good loading capacity of SRMS, gastro protective potentials, enhanced *in vivo* bioavailability and good sustained release properties for once daily administration (Chime et al., 2012; 2013 a).

## SRMS-based tablets

Solid lipid tablets based on SRMS have recently been produced by molding (Umeyor et al., 2012 b; Chime et al., 2013 b). In this method, softisan® 154 and lecithin were utilized. The drug was dissolved or dispersed in the lipid matrix and tablets were produced by molding using tablet mold. Gentamicin oral tablets were been produced by this method using lipid matrix based on solidified reverse micellar solutions consisting of phospholipid and triglycerides (Umeyor et al., 2012b) and the results show that SRMS-based tablets containing gentamicin were successfully prepared by fusion melt-solidification method which is simple, reproducible, scalable and cheap (Umeyor et al., 2012b) and tablets exhibited sustained release properties. SRMS-based tablets could be an alternative to the conventional parenteral dosage form of gentamicin. Some non-steroidal anti-inflammatory drugs (NSAIDs) based on SRMS have also been produced (Chime et al., 2013b). Diclofenac potassium and indomethacin solid lipid tablets have been produced and results showed that the tablets had sustained release properties for once daily administration in addition to ulcer inhibition potentials. Diclofenac potassium tablets based on SRMS showed good hardness and friability profiles, sustained release properties and possessed good anti-inflammatory and anti-nociceptive/analgesic effects. The formulations also exhibited good gastro-protective properties, as it inhibited the ulcerogenic potentials of diclofenac potassium by about 85% (Chime et al., 2013b). The *in vitro* release profile of diclofenac potassium tablet based on SRMS was comparable to the release profile of a market brand, coated diclofenac potassium. However, formulations showed higher sustained drug release. Advantages of lipid based tablets include: low cost of ingredients, low cost of technologies (equipment and labour requirement for the production of lipid dosage forms are minimal, unlike the conventional tablets) and improved oral bioavailability and reduced side effects of drugs (Chime et al., 2013b).

## Suppositories

Controlled release of SRMS-based suppositories containing metoclopramide-HCl was formulated by Schneeweis and Müller-Goymann (2000). The SRMS consisted of 70% Witepsol W35 and 30% (w:w) lecithin. A 1% (w/w) metoclopramide-HCl (MCP) was solubilizied in the SRMS. After melting and on contact with water or any physicological aqueous media the SRMS exihibits an application induced transformation into a semisolid system of liquid crystalline microstructure. Due to a low coefficient of diffusion in this mesophase a controlled release of the drug may be possible. The release profiles of the *in vitro* experiments showed zero order kinetics and a sustained release of the SRMS-suppositories (SRMS-supp.) in comparison with commercial suppositories (Schneeweis and Müller-Goymann, 2000).

## Advantages of SRMS based carriers

The advantages of SRMS include:

1) Generally, SRMS offers controlled release of drug, thereby enhancing patients' compliance and leading to better disease management and reduced toxicity.
2) The formulations can be tailored to meet a wide range of product development.
3) Feasibility of various administration routes.
4) Enhanced *in vivo* bioavailability.
5) Enhanced physical stability.
6) High carrier capacity.
7) Ease of formulation and scale up.
8) Protects loaded liable drugs against drug degradation.

## Drug release from reverse micelles

When the reverse micellar delivery system comes into contact with an external fluid of the environment such as water or other biological fluid, a burst or gradual release of the ionic amphiphiles may occur. A concurrent release of the additional ionic amphiphiles and the agent of interest follow. The ionic amphiphiles released dissolve in the aqueous fluid media forming ionic monomers. Upon release of agent(s) of interest, depending on the prevailing pH of the fluid environment and the pKa of the chemical compound, ionised molecules are formed. These ions carry permanent charges opposite to that of the polar region of the ionic amphiphiles. The oppositely charged polar groups of the ionised agents of interest and amphiphiles attract each other. At some point when sufficient ionic monomers of the amphiphile are attracted

to the charged species in the aqueous fluid, aggregation and reverse micelle formation occurs. This point is believed to be the critical reverse micelle concentration (CMC) (Mac-Gregor and Markham, 2010). These reverse micelles, in the aqueous fluid environment, eventually form colloidal microemulsions. In the human gastro-intesyinal tract (GIT), such reverse micelles are in direct contact with the lipophilic membranes of the absorbing mucosal cells. Due to the inherent lipophilicity of the outer surface of the reverse-micelles, they partition rapidly into these membranes, thereby facilitating absorption. Once the reverse micelles partition into the lipophilic membrane, the concentration of the amphiphilic molecule component of the reverse micelles diminish below the CMC. The reverse micelles undergo disaggregation and release the polar agent within their core. The kinetics of transport and transmembrane release of these agents may be essentially zero order or near about zero order (Mac-Gregor and Markham, 2010).

## CONCLUSION

SRMS could safely deliver and sustain the release of drugs and has advantages over polymeric delivery systems. It is easy to formulate and scale up and is produced using completely biodegradable lipids. The materials required for the production of SRMS are relatively cheap and available and could enhance patients' compliance by reducing side effects and preventing repeated dosing. SRMS could also be used in formulating liquid as well as semisolid and solid dosage forms.

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