REVIEW PAPER

ENGINEERING OF SOLID LIPID NANOPARTICLES FOR ENHANCEMENT OF ANTIDIABETIC EFFECT OF *MORINGA OLEIFERA*: A COMPLETE REVIEW

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Received: 25 June 2026 | Revised: 01 July 2026 | Accepted: 30 July 2026 | Available Online: 03 Aug 2026

Abstract
Diabetes mellitus is a chronic metabolic disorder characterised by progressive dysfunction of pancreatic β-cells, insulin resistance, oxidative stress, chronic inflammation and severe micro and macro-vascular complications. Current anti-diabetic drugs are effective in controlling glycaemia but their long-term use is frequently limited by adverse effects, loss of therapeutic response and poor patient compliance. Therefore, medicinal plants with multi target pharmacological activities have been widely explored as complementary therapeutic options. In this group *Moringa oleifera* Lam. has shown potential as a medicinal and nutritional plant. It is rich in flavonoids, phenolic acids, glucosinolates, isothiocyanates, vitamins and minerals. The experimental evidences indicate that these phytoconstituents modulate various molecular pathways and show antioxidant, anti-inflammatory, antihyperglycaemic and antihyperlipidaemic activities. Review critically summarises current knowledge on phytochemistry, antidiabetic mechanisms and discusses Solid lipid nanoparticle formulation strategies, in-vitro and in-vivo evaluation, pharmacokinetic behaviour and translational considerations. Additional topics cover recent progress in Quality by Design (QbD), regulatory expectations and emerging opportunities for clinical development. The review integrates medicinal plant research and nanotechnology based drug delivery to provide a comprehensive framework for the rational development of *M. oleifera* loaded SLNs as next generation phytopharmaceuticals.

Key words: Diabetes mellitus; Moringa oleifera; Phytochemicals; Phytopharmaceuticals; Quality by Design (QbD); Solid lipid nanoparticles (SLNs).

How to cite this article: Ramanathan M, Janardhanan VS, Anitha G, Ethiraj T. Engineering of solid lipid nanoparticles for enhancement of antidiabetic effect of Moringa oleifera: a complete review. Int J Drug Deliv Technol. 2026;16(74s): 344-359. DOI: 10.25258/ijddt.16.74s.40

1. Introduction

Diabetes mellitus (DM) is one of the major public health challenges of the twenty-first century affecting millions of people worldwide, and constituting a substantial clinical, social and economic burden. Diabetes is a metabolic disorder of multi-factorial aetiology, characterised by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action or both and associated with progressive dysfunction of carbohydrate, lipid and protein metabolism. High blood sugar levels cause oxidative stress, poor blood vessel function, and low-grade inflammation over time. All these leads to the faster development of eye, kidney, nerve, and heart problems (American Diabetes Association, 2024; Saeedi et al., 2021). Management of diabetes has improved greatly with the use of synthetic antidiabetic drugs such as metformin, sulfonylureas, sodium glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. However, factors such as gastrointestinal intolerance, hypoglycaemia, weight gain, treatment costs and waning efficacy, continue to fuel the quest for safer and more efficacious therapeutic alternatives (Davies et al., 2022). A growing scientific interest is focused on medicinal plants with multitarget pharmacology as

potential adjunct or complementary therapies. Moringa oleifera Lam. is one among such medicinal plants commonly known as drumstick tree or miracle tree. It has attracted much interest due to its remarkable nutritional composition and broad spectrum of biological activities. Rich in flavonoids, phenolic acids, glucosinolates, carotenoids, vitamins and essential minerals, the leaves contain many compounds with potent antioxidant and antihyperglycaemic activities. These phytochemicals have been reported to inhibit the activity of carbohydrate-hydrolysing enzymes, improve insulin signalling, reduce oxidative stress, and suppress inflammatory mediators involved in the pathogenesis of diabetes (Anwar et al., 2007; Mbikay, 2012). However, many of the important phytoconstituents of *M. oleifera* have shown promising pharmacological evidence but poor aqueous solubility, limited gastrointestinal absorption and extensive metabolic degradation limiting their clinical utility. Thus, advanced nanocarrier systems have emerged as a promising strategy to overcome these pharmaceutical barriers. Among lipid-based nanocarriers, Solid Lipid Nanoparticles (SLNs) attracted special interest due to their biocompatibility, biodegradability, protection of sensitive phytochemicals and the controlled drug release in a scalable pharmaceutical platform (Müller et al., 2000; Wissing et al., 2004).

The current review critically discusses the available evidence on engineering of SLNs for delivery of *M. oleifera* phytoconstituents in management of diabetes. This review integrates phytochemistry, pharmaceutics, nanotechnology and translational medicine to present the current achievements, limitations and future research priorities, which may facilitate the development of clinically effective herbal nanomedicines.

2. Diabetes mellitus

2.1 Pathophysiology and natural compounds

Diabetes mellitus (DM) is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. The high blood sugar levels result from problems with insulin secretion, insulin action, or both. Progressive damage to various organ systems particularly cardiovascular system, kidneys, eyes and peripheral nerves results from abnormalities in carbohydrate, lipid and protein metabolism caused by chronic hyperglycaemia (American Diabetes Association, 2024). Over the last few decades, diabetes has transformed from a disease mainly associated with lifestyle factors to a major worldwide public health problem affecting people of all socioeconomic and age groups. The prevalence of diabetes has increased rapidly and is strongly associated with sedentary life styles, obesity, poor dietary habits, population ageing and genetic susceptibility (Saeedi et al., 2021). Among the medicinal plants, Moringa oleifera has shown great potential with high phytochemical content and diverse biological activities . Thus, knowledge of the pathophysiology of diabetes is basic to understanding the role that the phytoconstituents of *M. oleifera* and their nanoformulations could play in the management of the disease.

2.2 Epidemiology of Diabetes Mellitus:

In worldwide Type 2 diabetes mellitus (T2DM) is increasing among the younger adults and adolescents on the background of the global obesity epidemic accounts for about 90–95% of the diagnosed cases (American Diabetes Association, 2024)

2.3 Types of Diabetes Mellitus

The different types of diabetes mellitus are classified based on the pathophysiology.

2.3.1 Diabetes mellitus Type I

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterised by immune-mediated destruction of pancreatic beta cells resulting in an absolute deficiency of insulin. (American Diabetes Association. 2024)

2.3.2 Type II Diabetes Mellitus

Type 2 diabetes mellitus is characterised by progressive insulin resistance and beta-cell dysfunction. Major contributing factors include obesity, physical inactivity, dietary factors and genetic susceptibility (DeFronzo et al., 2015).

2.3.3 Pregnancy and diabetes

Pregnancy hormones produced by the placenta cause insulin resistance and can lead to gestational diabetes. Glucose metabolism usually returns to normal after delivery, but women with this condition are at increased risk of developing T2DM later in life. (Bellamy et al., 2009; American Diabetes Association, 2024)

2.3.4 Other special varieties

Less common forms include monogenic diabetes syndromes, pancreatic disease, endocrinopathies, and drug-induced diabetes. They are not common but need an individualised therapeutic approach. (Holt *et al*., 2021)

2.4. Oxidative stress and chronic inflammation

In diabetic complications, oxidative stress pathogenesis is well known to be a key mechanism. Excessive production of reactive oxygen species (ROS) causes damage to lipids, proteins and nucleic acids, leading to endothelial dysfunction and progressive tissue injury. Chronic activation of inflammatory pathways like nuclear factor-kappa B (NF-κB) leads to the release of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and other pro-

inflammatory cytokines. Oxidative stress and inflammation are closely interrelated, therefore there is an interest for medicinal plants with high content of antioxidants. (Forbes & Cooper, 2013; Leone, et al., 2015).

2.5 Current drug management

Today Diabetes management is based on lifestyle modification and pharmacological therapy to achieve and maintain glycaemic control and to preventcomplications.The main groups of antidiabetic drugs include: Biguanides Metformin Sulfonylureas Meglitinides Thiazolidinediones DPP-4 inhibitors Alpha-glucosidase inhibitors Agonistas do receptor de GLP-1 Inibidores do SGLT2 Insulin preparations These agents have dramatically improved patient outcomes but their use is limited by gastrointestinal adverse effects, hypoglycaemia, weight gain, fluid retention, high cost of therapy and variable long-term efficacy. Such limitations have stimulated the search for adjunctive therapies based on medicinal plants and sophisticated drug delivery systems. (Davies et al., 2022. American Diabetes Association. 2024).

2.6 Need of Herbal Nanomedicine

Diabetes is a multifactorial disease and therapeutic agents that modulate multiple biochemical pathways may be superior to single-target interventions. Medicinal plants are complex mixtures of phyto-chemicals. Phytochemicals are often reported to possess synergistic pharmacological activities such as antioxidant, anti-inflammatory, antihyperglycaemic and lipid lowering activities . But many plant compounds are not very soluble in water, are poorly absorbed by the gastrointestinal tract and are rapidly degraded by metabolism. Nanotechnology based delivery systems, especially Solid Lipid Nanoparticles, offers a way to overcome these pharmaceutical limitations and at the same time to preserve the biological activity of herbal phytoconstituents. This integration of perspectives provides the conceptual background for the present review. (Mukherjee, Ray & Thakur, 2009; Mehnert & Mäder, 2012)

3. Phytoconstituents of *M. oleifera* and Molecular Mechanism in Diabetes management

M. oleifera contains a complex mixture of flavonoids, phenolic acids, glucosinolates, isothiocyanates, alkaloids, carotenoids, sterols, vitamins and essential minerals that regulate synergistically multiple biochemical pathways related to diabetes mellitus (Leone et al., 2015; Vergara-Jimenez et al., 2017). Current evidence suggests that these phytochemicals improve glucose homeostasis through reduction of oxidative stress, suppression of chronic inflammation, enhancement of insulin sensitivity, protection of pancreatic β-cells, and modulation of carbohydrate metabolism. (DeFronzo et al., 2015).

4. Classification of Phytochemicals

The compounds are classified by their chemical structures and biological activities (Table 4.1).

Table 4.1 Groups of phytochemicals of Moringa oleifera

Phytochemicals	Major Compounds	Principal Biological Activity
Flavonoids	Quercetin, Kaempferol, Rutin, Myricetin	Antioxidant, antihyperglycaemic, anti-inflammatory
Phenolic acids	Chlorogenic acid, Gallic acid, Caffeic acid, Ferulic acid	Free radical scavenging, enzyme inhibition
Glucosinolates	Glucomoringin	Precursor of bioactive isothiocyanates
Isothiocyanates	Moringin, Benzyl isothiocyanate	Anti-inflammatory, insulin sensitizing
Sterols	β-Sitosterol, Stigmasterol	Lipid-lowering activity
Carotenoids	β-Carotene, Lutein	Antioxidant protection
Vitamins	Vitamin C, Vitamin E	Oxidative stress reduction
Minerals	Calcium, Magnesium, Potassium, Zinc	Enzyme activation and metabolic regulation

The pharmacological activity of *M. oleifera* is not attributed to a single constituent but to the interaction of multiple phytochemicals. (Leone et al., 2015; Gopalakrishnan, Doriya & Kumar, 2016).

4.1 Flavonoids:

Flavonoids are the most researched class of phytochemicals in *M. oleifera.* These polyphenolic compounds are potent antioxidants due to the presence of hydroxyl groups that readily donate hydrogen atoms to neutralise reactive oxygen species. In addition to scavenging free radicals, flavonoids modulate several intracellular signalling pathways related to insulin action, glucose transport, and

inflammation (Dabeek & Marra, 2019). As many flavonoids are poorly soluble in water, encapsulation in SLNs is proposed to increase their intestinal absorption and systemic bioavailability. (Vergara-Jiménez et al.,2017).

4.1.1. Quercetine

Quercetin is among the most important pharmacological flavonoids in *M. oleifera* leaves. Structurally it belongs to the subclass of flavonols, and possesses five hydroxyl groups which account for its high antioxidant activity. Experimental studies have shown that quercetin: α-amylase & α-glucosidase activates. Inhibits AMP-activated protein kinase (AMPK) ↑ GLUT4 translocation, Insulin receptor signalling increases, Inhibits NF-κB-dependent inflammation Decreases reactive oxygen species Protection of pancreatic β-cells against apoptosis. However, poor aqueous solubility and extensive intestinal metabolism of quercetin impede its clinical translation, leading to low oral bioavailability. Lipid-based nanocarriers such as SLNs have shown promise to enhance the stability and systemic exposure of quercetin. (Dabeek & Marra,2019; Boots, Haenen & Bast, 2008).

4.1.2 Kaempferol

Kaempferol is another important flavonol found in the leaves of *M. oleifera*. It has antioxidant, anti-inflammatory and anti-hyperglycaemic activities via modulation of several signalling pathways involved in glucose metabolism. Mechanisms reported PI3K/Akt signalling activation Reduced insulin resistance Inhibition of inflammatory cytokines production Enhanced β-cell viability Inhibition of oxidative stress Increase of peripheral glucose uptake (Calderón-Montaño et al., 2011; Leone et al., 2015).

4.1.3 Rutin

Rutin is a glycosylated derivative of quercetin, which plays a significant role in the antioxidant profile of *M. oleifera*. Rutin is chemically more stable than quercetin, but still exhibits low absorption by mouth . The following effects of Rutin have been reported: Lower lipid peroxidation Enhance the activity of endogenous antioxidant enzymes Protection of Vascular Endothelial Cells Inhibit advanced glycation end-product (AGE) formation Increase insulin sensitivity. These effects can contribute to the prevention of diabetic microvascular complications such as nephropathy and retinopathy. (Ganeshpurkar and Saluja, 2017

4.2 Phenolic acids:

The main phenolic acids present in *M. oleifera* are chlorogenic acid, gallic acid, caffeic acid and ferulic acid (Vergara-Jimenez et al., 2017).

4.2.1 Chlorogenic Acid Chlorogenic Acid

It is a Major Hydroxycinnamic Acid, and Its Impact on Glucose Homeostasis It has been shown to inhibit the activity of α-glucosidase and to decrease the glucose transport across the intestinal epithelium, thus delaying the absorption of glucose from the intestine. In addition, chlorogenic acid has been shown to inhibit hepatic glucose production through inhibition of glucose-6-phosphatase and modulation of AMP-activated protein kinase (AMPK) activity, thus reducing fasting blood glucose levels (Meng et al., 2013).

4.2.2 Gallic acid

Gallic acid is a naturally occurring trihydroxybenzoic acid with strong antioxidant, anti-inflammatory and antidiabetic activity. (Al Zahrani *et al*., 2020; Variya *et al*., 2020).

4.2.3. Caffeic acid

The antioxidant activity of caffeic acid is attributed to the presence of two hydroxyl groups on the aromatic ring. Caffeic acid directly scavenges free radicals and modulates glucose metabolism by activating insulin signalling pathways and inhibiting inflammatory transcription factors. (Espíndola *et al*., 2019)

4.2.4 Ferulic Acid

The other hydroxycinnamic acid found in *M. oleifera* is ferulic acid. It has antioxidant, antihyperglycaemic and cardioprotective effects by a number of complementary mechanisms. (Zhao and Moghadasian, 2008).

5. Active Phytoconstituents and chellanges to formulate as dosage

5.1 Solubilities of the Phytoconstituents

The major antidiabetic components of *M. oleifera*, viz. quercetin, kaempferol and some phenolic compounds are less soluble in water. Oral absorption requires dissolution in gastrointestinal fluids as the first step. Poor solubility results in decreased dissolution. So, only a small part of the administered dose is available for permeation across the intestinal epithelium. Low solubility means: Slow dissolution rate ↓ intestinal absorption. (Leone et al, 2015; Dabeek & Marra, 2019).

5.2 Chemical instability in GI passage

The degradation of polyphenolic compounds is due to the exposure to the acidic conditions of the stomach, digestive enzymes and oxidative reactions during the gastrointestinal transit. Bioactivity can be greatly reduced by hydrolysis, oxidation and structural modification before absorption . Several phytoconstituents of Moringa are also liable to affect Light, Heat, Oxygen, Moisture, Variable pH conditions. Hence, protection of these compounds during their passage through the gastrointestinal tract

is crucial for maintaining pharmacological activity. The phytochemicals are physically isolated from the adverse environmental conditions, thus improving the chemical stability and prolonging the shelf life through lipid-based encapsulation. (Gopalakrishnan et al., 2016; Mehnert & Mäder, 2012).

5.3 First-pass metabolism

Many phytochemicals after absorption from the intestine undergo extensive first-pass metabolism in the intestinal wall and liver. Conjugation reactions (glucuronidation, sulfation and methylation) greatly diminish the amount of pharmacologically active compounds reaching the systemic circulation. This extensive metabolism of flavonoids e.g. quercetin and kaempferol results in: Low concentrations in plasma Biological half-life: Poor clinical effect Interindividual variability is high. (Porter, Trevaskis & Charman, 2007; Di & Kerns, 2016)

5.4 Pharmaceutical Limitations

The limitations are tabulated in Table 4.1

Table 5.1 Limitations of *Moringa oleifera* Phytoconstituents

Phytoconstituent	Major Limitation	Pharmaceutical Consequence	Potential Benefit of SLNs
Quercetin	Poor aqueous solubility	Low oral bioavailability	Improved dissolution and absorption
Kaempferol	Extensive first-pass metabolism	Reduced systemic exposure	Sustained release and enhanced bioavailability
Chlorogenic acid	Chemical instability	Reduced biological activity	Protection within lipid matrix
Gallic acid	Rapid metabolism	Short duration of action	Prolonged circulation
Moringin	Stability concerns	Variable therapeutic response	Improved protection and controlled release

(Müller, Mäder and Gohla, 2000; Mehnert and Mäder, 2001; Porter, Trevaskis and Charman, 2007; Leone *et al*., 2015).

5.4. Transfer to lipid-based nanocarriers

For above reason, conventional powders, capsules and extracts do not often reach the optimal therapeutic efficacy, despite their promising pharmacological activity. Advanced nanocarriers based on lipids can bypass many of these barriers simultaneously, by increasing solubility, protecting phytochemicals from degradation, increasing absorption and providing controlled drug release. Among the various lipid based delivery systems, solid lipid nanoparticles have been of great interest due to their biocompatibility, scalability and ability to encapsulate a wide range of lipophilic and moderately hydrophilic phytoconstituents. This chapter reviews the design principles, composition and pharmaceutical benefits of SLNs as a delivery platform for *Moringa oleifera* in the management of diabetes. (Mukherjee, Ray and Thakur, 2009)

6. Solid Lipid Nanoparticles:
Basic Principles, Composition, Drug Loading Models and Therapeutic Benefits

The successful therapeutic application of phytoconstituents from medicinal plants depends on their inherent pharmacological activity and their capability to reach the target tissue at therapeutically effective concentrations. As discussed in the previous chapter, the majority of the key bioactive compounds in *Moringa oleifera*, including quercetin, kaempferol, chlorogenic acid and moringin, have poor water solubility and limited intestinal permeability, as well as extensive first-pass metabolism. These limitations significantly reduce oral bioavailability and limit clinical translation, despite promising preclinical evidence (Leone et al., 2015; Vergara-Jimenez et al., 2017).

Lipid-based nanocarriers have emerged as an effective strategy to overcome these pharmaceutical barriers. Among these, Solid Lipid Nanoparticles (SLNs) have been of particular interest since they combine the advantages of polymeric nanoparticles, emulsions and liposomes while minimising many of their limitations. SLNs are composed of physiologically compatible lipids that are solid at room and body temperature and are stabilised by surfactants in an aqueous phase. This particular architecture offers a better protection to the encapsulated bioactive compounds and at the same time allows the controlled release of the drug and its improved oral absorption (Müller, Mäder & Gohla, 2000).

6. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are submicron colloidal carriers having a variety of shapes and crystalline structures with a size range of 50-1000 nm, but of most interest from the pharmaceutical point of view is the size range of 100-

300 nm. A typical SLN consists of three domains: ((Fig.6.1)

1. A solid lipid core, in which the hydrophobic drug or phytoconstituent is entrapped.
2. A surfactant layer to stabilise SLN dispersion
3. Aqueous phase, colloidal dispersion medium

SLNs have a solid hydrophobic lipid core at physiological temperature which allows controlled release of the loaded drug or phytoconstituent. Unlike classical emulsions having a liquid dispersed phase, SLNs consist of a solid lipid matrix, (Müller, Mäder & Gohla (2000); Mehnert & Mäder (2012)).

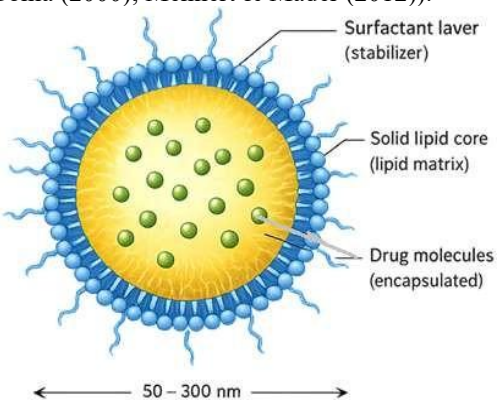

Fig. 6.1 Solid lipid nanoparticle structure

6.1 Composition of Solid Lipid Nanoparticles

Solid Lipid Nanoparticles consist of three main components such as solid lipids, surfactants and co-surfactants. The selection of component is based on the physicochemical properties of the drug or phytoconstituent to be delivered and the desired rate of release.

6.1.1 Solid Lipids

The properties of the solid lipid are of special interest because it is the main component of SLN and influences directly the physicochemical properties of the nanoparticles. The most common solid lipids in pharmaceutical formulations are:

Glyceryl monostearate (GMS), Compritol® 888 ATO, Stearic acid, Cetyl palmitate, Tripalmitin, Tristearin, Precirol® ATO 5. (Table 6.1)

Table 6.1 Common solid lipids used in SLN formulation

Lipid	Characteristics	Pharmaceutical Advantages
Glyceryl monostearate	Monoglyceride	Excellent drug entrapment; oral compatibility
Compritol® 888 ATO	Glycerol behenate	Sustained drug release
Stearic acid	Fatty acid	Economical and biodegradable
Cetyl palmitate	Wax ester	High physical stability
Tripalmitin	Triglyceride	Suitable for lipophilic drugs
Tristearin	Triglyceride	High crystallinity

(Müller, Mäder and Gohla, 2000; Mehnert and Mäder, 2001; Wissing, Kayser and Müller, 2004).

6.1.2 Surfactants

Surfactants are an important part of the formulation of SLN, because they greatly reduce the interfacial tension between the melted lipid and the aqueous phase, which leads to the formation of nanoparticles and stabilisation of the dispersion. Commonly used surfactants in SLN formulation include: Poloxamer 188, Poloxamer 407, Tween 80, Tween 20, Lecithin, Sodium cholate. Poloxamer 407 is a suitable choice for oral formulations, because it is non-ionic and has great patient safety profiles and permits the preparation of SLNs with good sterical stabilisation to improve storage stability. (Ekambaram, Sathali and Priyanka, 2012)

6.1.3 Co-surfactant

Co-surfactants are often used together with surfactants to increase the interfacial flexibility and to optimise the particle size distribution during homogenisation. Typical examples of co-surfactants are Capryol® 90, Transcutol® P, Propylene glycol, Polyethylene glycol Generally, the combination of surfactant and co-surfactant was better than surfactant alone in reducing the particle size and increasing the entrapment efficiency. (Nair *et al*., 2022)

6.2 Models of Drug Incorporation

The mechanisms of drug incorporation into SLNs may vary depending on the physicochemical properties of the drug or phytoconstituent to be incorporated into SLNs and the characteristics of the chosen solid lipid. Three major patterns of drug incorporation are following.

6.2.1 Homogeneous Matrix Model

The model assumes that the drug is uniformly distributed in the lipid matrix. Drug release follows a pattern that is determined by both diffusion and matrix erosion. This model is especially useful when a long and constant release of a drug is desired. (Wissing, Kayser and Müller, 2004)

6.2.2 Drug enriches the shell model

This model represents a drug distribution pattern with the majority of the drug in the upper part of the nanoparticle. SLNs with drug-enriched shell present an initial burst release of the entrapped material, followed by a slow release. (Mehnert and Mäder, 2001)

6.2.3 Drug-Loaded Core Model

This model leads to a core-type drug distribution with the majority of drug located in the core of the nanoparticle. This type of distribution pattern results in lower drug release rates as the drug has to escape from the particle core . The choice of a drug incorporation model depends on the properties of the solid lipid and the physicochemical properties of the drug or phytoconstituent (Mehnert & Mäder (2012); Jenning, Gysler & Schäfer-Korting (2000).

6.3 Benefits of Solid Lipid Nanoparticles for Moringa oleifera

1. Protection of flavonoids and phenolic acid against oxidative degradation
2. Improved dissolution properties of poorly soluble phytochemicals
3. Enhanced gastrointestinal absorption of the encapsulated compounds
4. Bypass extensive hepatic first-pass metabolism via the lymphatic route
5. Control of the drug release rate of the nanoparticles.
6. Improved patient compliance due to less frequent dosing
7. SLN components being biodegradable and biocompatible

6.4 Limitations of Solid Lipid Nanoparticles

However, despite the many advantages mentioned above, in some cases the use of SLNs may have a few disadvantages. The majority of them are related to the physico-chemical properties of solid lipids, which may not allow the application of this nanoparticle design.

These are:

1. Some phytoconstituents have limited drug-loading capacity; but this limitation can be overcome to some extent by using Nanostructured Lipid Carriers (NLCs)
2. Drug release from SLNs may be affected by lipid polymorphism.
3. Lipid re-crystallization might cause drug desorption from the lipid core.
4. Requirement of optimisation of lipid/solid surfactant ratio in most cases for SLN formulation •
5. Low stability of SLNs produced under inappropriate storage conditions

7. *Moringa oleifera* Loaded SLN: Formulation Development Strategies

Formulation and preparation variables influence the physicochemical properties of SLNs, including particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency, drug loading, drug release profile and stability, for example. Formulation development is a very challenging task in case of herbal formulations due to complexity of plant extracts and presence of numerous phyto-constituents with dissimilar molecular weights and partition coefficients. The properties of the individual components will determine the choice of the formulation method and, in the end, the characteristics of the final nanoconstruct. For Moringa oleifera, the possibility to prepare SLNs from ethyl acetate and ethanolic extracts has been investigated, since these extracts are shown to contain considerable amounts of flavonoids, phenolic acids and isothiocyanates. However, these extracts contain many other phytochemicals with different physicochemical properties that have to be considered.

7.1 Preformulation studies

Pre-formulation studies may be carried out to determine the physicochemical properties of the extract and its compatibility with different excipients to design an optimum formulation. Such studies would include such key elements as:

1. Determine solubility in chosen lipids
2. Partition coefficient.
3. Thermal characteristics of the extract.
4. Compatibility of excipients. (FTIR and DSC)
5. Melting point of the lipid chosen
6. Oxidative stability of extract.

In particular, compatibility studies of the Moringa oleifera extract and excipients are important to determine any potentially adverse interactions prior to the initiation of large scale formulation development. Several published studies on the encapsulation of herbal drugs in SLNs lack comprehensive pre-formulation studies resulting in formulation failures in the subsequent phases. (Aulton and Taylor, 2018)

7.2 Choice of Lipid Matrices

The lipid matrix is the most abundant component of SLNs and thus influences drug incorporation, crystallinity and release. Ideal characteristics of a lipid matrix an ideal lipid matrix should have all of the characters are:

1. Stable at room and body temperature
2. Biodegradable and biocompatible.
3. Good affinity for plant constituents.
4. Be pharmacologically safe.
5. Enable the formation of stable nanoparticles after homogenization. (Pardeike, Hommoss and Müller, 2009)

Table 7.1 Comparison of Common Lipids for Herbal SLNs

Lipid	Advantages	Potential

		Limitations
Glyceryl monostearate	Good entrapment, controlled release, oral compatibility	Moderate crystallinity
Compritol® 888 ATO	Sustained release, excellent stability	Higher melting point
Stearic acid	Economical, biodegradable	Lower drug-loading for some compounds
Cetyl palmitate	Good physical stability	Slower release profile
Tristearin	High crystallinity	Drug expulsion during storage

7.3 Surfactant selection

Surfactants are important in lowering interfacial tensions and preventing SLN dispersions from aggregating. The following surfactants are widely used in the preparation of SLNs: Poloxamer 188, poloxamer 407, tween 80, tween 20, soy lecithin Poloxamer 407.

7.4 Co-surfactants

Co-surfactants are employed to improve the flexibility of the interfacial layer and to facilitate the creation of the emulsion with nanosize droplets. Examples: Capryol® 90, transcutol® P, propylene glycol, polyethylene glycol

7.5 Critical variables in formulation

Many formulation variables may affect SLNs with respect to their physicochemical properties.

1. **Lipid concentration:** The increase in lipid concentration generally leads to the increase in the EE and size of the particles, due to the increased viscosity of the system.
2. **Surfactant concentration**: Surfactant reduces the particle size and increases the stability of suspension. However, excessive surfactant enhances drug release and reduces EE.
3. **Homogenisation pressure** Higher homogenisation pressure leads to the production of smaller particles due to the higher shear forces. Too high pressure can create undesired heat that can destroy thermolabile phytochemicals.
4. **Number of Homogenisation** Cycles More cycles generally reduce particle size but increase the time of the manufacturing process.
5. **Sonication time** Sonication after high pressure homogenisation or probe sonication decreases the particle size. Excessive sonication can cause heat generation and undesired damage to the active compounds.
6. **Cooling rate** The cooling rate strongly influences the formation of lipid crystals and hence the localisation of phytoconstituents within the SLN matrix. Rapid cooling facilitates uniform distribution of drugs while slow cooling may result in formation of the shell of crystalline lipid.

7.6 Quality by Design (QbD) Optimisation of Formulation

Quality by Design (QbD) in the pharmaceutical field provide a better understanding of the relationship between formulation variables and critical quality attributes (CQA). Good design usually takes place in the following steps:

1. Quality target product profile (QTPP)
2. Critical Quality Attributes (CQA)
3. Critical material attributes (CMA)
4. Critical process parameters (CPPs).
5. Design of experiments (DoE);

Critical quality attributes of SLNs generally include particle size, polydispersity index, Zeta potential, EE, drug loading, drug release characteristics, physical stability. The QbD approach enables the development of robust formulations with the best composition and manufacturing process. Furthermore, implementation of the principles of QbD helps in achieving regulatory approvals as the formulation development is done according to the ICH guidelines. Worth to mention, despite the overwhelming support of the QbD concept, so far it has not been widely applied for herbal nanoformulations. Future studies should focus on the integration of phytochemical standardisation and the application of QbD for optimisation of herbal SLNs. (Yu, 2008; Bonaccorso *et al*., 2021)

7.8 Scaling Up Considerations

The laboratory preparation methods have been optimised extensively but the ultimate goal of SLN fabrication is often industrial production . Therefore, the development of the most optimal and scalable preparation strategy is required. The primary challenge in SLN scale-up is to maintain the particle size uniformity after transition from lab scale manufacturing to industrial production. Also essential are prevention of lipid polymorphism, aggregation, achieving batch consistency, minimising production costs, applicability of the manufacturing process for pilot-scale and industrial manufacturing, continuous manufacturing. In our view, continuous high pressure homogenisation combined with PAT is the most promising approach for large-scale production of herbal SLNs.

8. Preparation methods of Moringa oleifera loaded solid lipid nanoparticles:

The effect of manufacturing process has been studied on the size distribution, polydispersity index (PDI), zeta potential, entrapment efficiency (EE), drug loading, lipid crystallinity, release profile and long term stability of SLNs. For herbal formulations such as Moringa oleifera extracts, the preparation process is more challenging as multiple phytochemicals should be incorporated within the lipid core in order to deliver the desired therapeutic efficacy (Mehnert & Mäder, 2012). The choice of an optimal method of preparation depends largely on the stability of the extract, the physicochemical properties of the lipid fraction, the desired properties of SLNs, industrial applicability and regulatory acceptance. So, there is no common approach for the fabrication of the SLN. Instead, scientists should choose the method best suited to provide the required product quality while considering the practical and economic aspects of GMP manufacturing.

8.1 Hot high pressure homogenisation (HHPH)

This method includes melting the lipid and mixing the herbal extract into the liquid lipid to make a suspension. An aqueous solution of surfactant is then added by shear forces and elevated temperatures to form a coarse emulsion. The coarse emulsion is further treated under high pressures. The particle sizes are drastically reduced by increasing the shear forces. After homogenisation the suspension is cooled, which results in solidification of lipid crystals.

(Müller, Radtke and Wissing (2002); Mehnert and Mäder (2012)

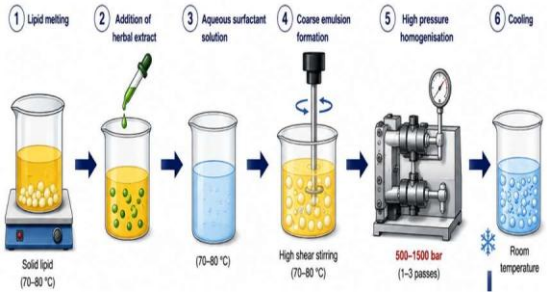

Fig.8.1 HHPH process

8.3 Ultrasonication Method

Ultrasonication is one of the most commonly used laboratory scale methods to produce SLNs with a narrow particle size distribution. It is a very convenient technique requiring minimal equipment. Basically, the method means preparation of a coarse emulsion of lipid, extract and surfactant which is subsequently subjected to ultrasonic irradiation until a fine emulsion with nanosized lipid particles is obtained. (Chavda *et al*., 2022)

8.4 Microemulsion Technique

The microemulsion method is based on the formation of a thermodynamically stable microemulsion by mixing of the lipid, surfactant, co-surfactant and aqueous phase at temperatures above the melting point of the lipid. The hot microemulsion formed is poured into cold water under stirring. The lipid recrystallises quickly and SLNs are spontaneously formed (Pardeike, Hommoss and Müller, 2009).

8.5 Solvent Emulsification-Evaporatioin Method

In the solvent emulsification-evaporation method the active ingredients and lipid are firstly dissolved in organic solvent. The organic solution is then emulsified in an aqueous surfactant solution and the solvent is then removed by evaporation under vacuum.

8.6 Solvent Injection Technique

In the solvent injection method the lipid is first solubilised in a water-miscible solvent. The organic solution is then injected into an aqueous solution of surfactant and the solvent is removed by evaporation. The injection step leads to a rapid formation of a fine suspension of lipids due to the good miscibility of the organic and aqueous phases.

8.7 Double Emulsion Method

Double emulsion (W/O/W) technique is mainly suitable for hydrophilic compounds. It is based on the formation of a water-in-oil emulsion through the injection of an aqueous solution of the active ingredients into molten lipid followed by emulsification in an aqueous solution of surfactant. (Table 8.1)

Table 8.1 Advantages and disadvantages of various methods of SLN preparation

Method	Major Advantage	Main Limitation	Industrial Suitability	Suitability for *M.oringa* Extract
HHPH	Scalable, solvent-free	Heat exposure	Excellent	High
CHPH	Protects thermolabile compounds	Broad particle distribution	High	High
Ultra-sonication	Simple and economical	Limited scale-up	Moderate	Excellent (research)
Micro-emulsion	Uniform particle size	High surfactant concentration	Moderate	Good
Solvent	Mild	Solvent	Moder	Good

emulsification	processing	residues	ate	
Solvent injection	Simple operation	Solvent removal required	Moderate	Good
Double emulsion	Suitable for hydrophilic compounds	Complex processing	Limited	Moderate

(Müller, Mäder and Gohla, 2000; Mehnert and Mäder, 2001; Muchow, Maincent and Müller, 2008; Mukherjee, Ray and Thakur, 2009; Pardeike, Hommoss and Müller, 2009; Ekambaram, Sathali and Priyanka, 2012)

8.8 New manufacturing approaches and artificial intelligence-supported process optimisation

Modern pharmaceutical engineering practices suggest several approaches to improve reproducibility and scalability of SLN manufacturing. These are High shear homogenisation (continuous) microfluidizer continuous flow manufacturing analyses process technology and artificial intelligence-supported process optimisation The combination of these approaches with Quality by Design paradigm has the potential to reduce formulation variability and speed up regulatory approval.

9. Characterisation and Quality Evaluation of Solid Lipid Nanoparticles Loaded with Moringa oleifera

Critical quality attributes (CQAs), such as particle size, size distribution, surface charge, morphology, crystallinity, drug loading, entrapment efficiency and release characteristics are now well known to influence the safety and efficacy of lipid-based nanomedicines (Mehnert & Mäder, 2012; ICH Q8(R2), 2009).

9.1 Particle Size Distribution (PSD)

Particle size is one of the most important CQAs, which decides the fate of SLNs in gastrointestinal tract and overall therapeutic efficacy of formulation. Dynamic Light Scattering (DLS), also called Photon Correlation Spectroscopy, is the most common method used to determine the hydrodynamic diameter of nanoparticles in solution. For oral SLNs, the optimum size range is between 100 and 300 nm due to the higher surface area for dissolution, improved cellular uptake and better lymphatic targeting compared to larger particles. Also smaller particles have lower sedimentation rate and better physical stability during storage. Particle size of Moringa oleifera – based SLNs is mainly dependent on the ratio of lipid to surfactant, homogenisation pressure, sonication time, cooling rate and other factors. (Müller, Mäder & Gohla, 2000); Mehnert & Mäder, 2012).

9.2 Polydispersity index (PDI)

The Polydispersity Index is a measure of the width of the particle size distribution of a single sample. Here is a typical PDI interpretation (Table 9.1):

Table 9.1 PDI and interpretations

PDI	Interpretation
<0.20	Highly uniform
0.20–0.30	Acceptable for pharmaceutical formulations
>0.30	Broad distribution; further optimization required

9.4 Zeta Potential

The zeta potential is a measure of colloidal stability of a dispersion and is the electrostatic charge on the surface of nanoparticles. The zeta potential values are discussed below. (Table 9.2)

Table 9.2 Zeta potential and stability

Zeta Potential	Stability
> +30 mV	Excellent
< –30 mV	Excellent
±20–30 mV	Moderate
< ±20 mV	Increased aggregation risk

(Malvern Panalytical, 2020; Honary and Zahir, 2013; Mehnert and Mäder, 2001).

9.5 Morphological Characterisation

9.5.1 Scanning Electron Microscopy (SEM)

SEM is a powerful imaging technique to determine the surface topography of the nanoparticles. Some common observations during SEM analysis of SLNs include the spherical shape, surface roughness and the degree of particle aggregation.

9.5.2 Transmission Electron Microscope (TEM)

TEM is mainly used for the investigation of internal structure of nanoparticles and determination of average particle size. The most common observations during TEM analysis of SLNs are visualisation of the lipid core, estimation of the particle size and detection of particle aggregation. It is worth noting that the particle size obtained by TEM is usually smaller than that obtained by DLS, because of the lack of a hydration layer in the former.

9.5.3 Atomic Force Microscopy (AFM)

AFM is a less common technique to determine the surface roughness and mechanical properties of nanoparticles in 3 dimensions.

9.6 Fourier Transform Infrared Spectroscopy (FTIR)

The major aim of FTIR analysis in SLN characterisation is to determine the physicochemical interactions between drug and excipients. The final formulation for Moringa oleifera based SLNs can be confirmed by FTIR analysis for the presence of the characteristic peaks of pytoconstituents. One important point to be considered when performing FTIR analysis is the fact that small shifts in peak position are quite common and should be not taken as evidence of chemical incompatibility unless other analytical data, such as DSC thermograms, show signs of interactions.

9.7 Differential Scanning Calorimetry (DSC)

The main parameters that can be determined by DSC analysis are melting point of the lipid matrix, crystallinity, polymorphic transitions and drug incorporation. In general, a successful encapsulation of phytoconstituents within the lipid matrix leads to a reduction in the melting enthalpy in comparison to the pure lipid, due to the disruption of the crystal lattice by the encapsulated drug.

9.8 X-ray Diffraction (XRD).

The main aim of XRD analysis is to quantify the degree of crystallinity of the lipid matrix and the extent of transformation of crystalline into amorphous forms during encapsulation. (Table 9.3)

Table 9.3 Summary of characterisation techniques for SLNs

Technique	Purpose	Information Obtained
DLS	Particle size	Mean diameter and size distribution
PDI	Uniformity	Homogeneity of nanoparticle population
Zeta potential	Stability	Surface charge and aggregation tendency
SEM	Surface morphology	Shape and surface characteristics
TEM	Internal morphology	Core structure and particle diameter
FTIR	Compatibility	Drug–excipient interactions
DSC	Thermal analysis	Melting behaviour and crystallinity
XRD	Crystal structure	Polymorphism and amorphous

9.9 Content of drug

The drug content is generally expressed as the total amount of the phytoconstituents present in the SLN formulation. Note that herbal medicines often contain a complex mixture of numerous bioactive constituents. Thus, the drug content can be expressed on the basis of individual constituents such as quercetin, chlorogenic acid or total extractives by an appropriate analytical method. The most widely used analytical techniques for drug content determination include High-performance liquid chromatography (HPLC), High-performance thin-layer chromatography (HPTLC) and UV-Visible spectroscopy. The preferred analytical method is HPLC, as it is fast and accurate for the simultaneous quantification of multiple constituents. For UV analysis, the extract encapsulated in the lipid matrix must be extracted first by dissolving the SLN sample in a suitable solvent, e.g. methanol or ethanol. The solution is then suitably diluted and analysed using a UV spectrophotometer. Then the drug content was determined by comparing the absorbance values with a calibration curve prepared from standard solutions of

9.10 Entrapment Efficiency (EE)

The entrapment efficiency is expressed as the percentage of the total drug incorporated in the lipid matrix. It is one of the most important quality attributes of SLNs as it directly influences the rate of drug release and the overall therapeutic efficacy of the formulation. The EE of SLNs is usually determined by separating the free drug from the nanoparticle suspension using centrifugation or ultrafiltration. The free drug concentration in supernatant is then determined by UV or HPLC analysis.EE is calculated by the standard formula used in pharmaceutical nanotechnology is:

$$EE\% = \frac{\text{Total amount of drug} - \text{Free (unentrapped) drug}}{\text{Total amount of drug}} \times 100$$

9.11 Drug Loading Capacity

Drug loading capacity is defined as the quantity of drug incorporated in a specific amount of SLNs

9.12 Drug Release *In-Vitro* studies

The in vitro drug release study is very important to show the capability of SLNs to deliver the encapsulated phytoconstituents in a sustained manner. The most commonly used method for determination of in vitro drug release is the dialysis bag diffusion method.

9.13 Mathematical Models for Drug Delivery

Mathematical models are used for the description of the drug release mechanism from different dosage forms, including SLN. (Costa and Lobo, 2001; Dash et al., 2010).

1 **Zero Order Model**: In the zero-order model, the drug release rate is independent of the amount of drug released. In most sustained-release dosage forms, a zero-order

release is desired to achieve a relatively constant rate of drug release. (Costa and Lobo, 2001; Dash *et al*., 2010).
Formula: Qt=Q0+k0t
Qt = Amount (or cumulative %) of drug released at time t
Q0 = Initial amount of drug in solution (usually 0)
0k0 = Zero-order release rate constant
t = Time

2 **First order model:** For drug release, most of the conventional dosage forms can be described by first order model. Qt=Q0e−k1t
Q0 = Initial amount of drug in the dosage form
Qt = Amount of drug remaining at time ttt
k1 = First-order release rate constant
t = Time

3 **Higuchi's Model**: The Higuchi model suggests a diffusion-controlled release mechanism.The linearity between the cumulative percentage of drug released and the square root of time indicates a diffusion-controlled release mechanism. (Higuchi, 1963; Costa and Lobo, 2001)
$Qt=kHt^{1/2}$
Qt = Cumulative amount (or percentage) of drug released at time ttt
kH = Higuchi dissolution (release) constant
t = Time

4 **Model of Korsmeyer–Peppas:** The Korsmeyer–Peppas model has been widely used for the description of drug release from polymeric and lipid matrices. (Korsmeyer *et al*., 1983; Peppas, 1985; Siepmann and Peppas,2011)

$$\log\left(\frac{Mt}{\infty}\right) = \log k + n \log t$$

Mt = Amount of drug released at time t
M∞ = Total amount of drug released at infinite time
Mt/M∞ = Fraction of drug released
k = Kinetic (release) constant
n = Release exponent indicating the drug release mechanism
t = Time
The mechanism of drug release indicated by the release exponent (n) is interpreted as follows.

n value	Mechanism
≤0.45	Fickian diffusion
0.45–0.89	Non-Fickian (anomalous) transport
0.89	Case II transport
>0.89	Super Case II transport

5 **The Hixson–Crowell model**
The Hixson-Crowell model takes into account the change of surface area of the dissolving particle. (Hixson and Crowell, 1931; Costa and Lobo, 2001).
Equation: $(100-Qt)^{1/3} - k_{HC}t$
Qt = Cumulative percentage of drug released at time t
kHC = Hixson–Crowell dissolution rate constant t = Time

9.14 Stability Studies.
Stability testing is an essential part of the pharmaceutical product development and provides information on the physical, chemical and microbiological characteristics of the drug product during the proposed shelf life. Stability studies of herbal SLNs should be carried out according to ICH guidelines. Following parameters should be regularly monitored (Table 9.4):

Table 9.4 Recommended Quality Attributes forSLNs

Parameter	Preferred Outcome	Pharmaceutical Significance
Particle size	100–300 nm	Enhanced oral absorption
Polydispersity Index	≤0.30	Uniform particle distribution
Zeta potential	High physical stability (electrostatic and/or steric)	Reduced aggregation
Drug content	High assay value	Minimal processing loss
Entrapment efficiency	High	Improved sustained release
Drug loading	Optimized without compromising stability	Reduced carrier burden
In vitro release	Controlled, sustained profile	Improved therapeutic performance
Stability	Minimal changes during storage	Commercial feasibility

10. Existing Knowledge Gaps
Many previous studies have demonstrated the improved pharmacological effects of Moringa oleifera –loaded SLNs but pharmacokinetic profiles

have been poorly characterised. The following points need to be explored further:

1 Qualitative and quantitative studies on bioavailability
2 Localisation in tissue Pharmacokinetic - pharmacodynamic (PK-PD) relationship
3 Absence of comparative studies between isolated phytochemicals and standardised extracts.
4 There are few human pharmacokinetic data. Future studies should use validated analytical bioassays in combination with standardised phytochemical fingerprints and population PK modelling to explore the dose exposure response relationship.

11 Artificial Intelligence and Digital Pharma Development

The pharmaceutical field has promising opportunities in Artificial Intelligence (AI) and Machine Learning (ML). The use of AI tools can be of particular use in the area of herbal medicine, where the correlation between the constituents of complex mixture and the biological performance are not well known. Thus, AI algorithms can be applied for predicting the best ratios of lipids and surfactants, predicting the best formulation strategies, modelling drug release and nanoparticle stability, and exploring the relationship between phytochemical composition and biological performance. The combination of AI-driven approaches with experimental research will provide a major boost to the pharmaceutical development of herbal nanomedicines.

12 Outlook

Novel technologies and approaches need to be embraced for the development of future herbal medicines. Some of the emerging concepts that can be utilised in the development of Moringa oleifera-based nanomedicines include application of artificial intelligence for predicting formulation performance, ligand-targeted nanoformulations for enhanced targeting, combination nanoformulations for combining various antidiabetic agents in a single dosage form, and personalised phytomedicine. These opportunities could lead to improved therapeutic efficacy and advances in the field of herbal nanomedicine.

Ethics Statement

This article reviews published studies and does not involve human participants or animals. Therefore, no ethical approval and informed consent were needed.

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