Journal of Multidisciplinary Engineering Science and Technology (JMEST)
ISSN: 2458-9403
Vol. 6 Issue 12, December - 2019, Special Issue

Strategies for the Development of Mitragyna speciosa (Kratom) Leaves Extract Loaded with Solid Lipid Nanoparticles

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***Abstract*—Currently, the use of medicinal plants as an alternative medicine for various treatment has increased tremendously due to their positive effects. This include a potential plant-based source, Mitragyna speciosa (MS) leaves (kratom leaves). Besides, previous study has reported the other pharmacological properties of MS which includes anaesthetic, antinociceptive, analgesic and stimulant effects. In general, the pharmacological effects of MS leaves are mainly attributed to its principal alkaloid called Mitragynine. The Mitragynine dose employed in recent studies showed that the dose for analgesic (30–200 mg/kg), pharmacokinetics (20–50 mg/kg) and toxicity (200–477 mg/kg) which varied largely across rodent species. Research has been reported that Mitragynine has been studied at the preclinical stage and progressively gaining more attention as a potential substitute or adjunct drug therapy for addiction and pain. These properties are claim to be beneficial in wound healing thus, proper vehicle mechanism should be applied so that the MS leaves could benefits fully in the treatment of wound healing.**

Hence, an advanced carrier system technology such as solid lipid nanoparticles (SLNPs) are suitable transportation due to their good biocompatibility, small particle size and low toxicity which enables for better penetration into skin. SLNPs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers such as nanoemulsions, liposomes and polymeric nanoparticles. SLNPs also possesses good stability and is able to control the release of the incorporated drug. When compared with polymeric nanoparticles, the physiological lipids-made SLNPs is definitely better tolerated by the human body and its lipophilic nature helps it to penetrate deeper into skin.

Keywords: Mitragyna speciosa, Mitragynine, Antimicrobial Activity, Solid Lipid Nanoparticle, Transdermal Drug Delivery

I. INTRODUCTION

Mitragyna speciosa (MS) leaves has been traditionally consumed as a leaves decoction for its stimulant effects to counter fatigue, to treat fever, diarrhea and also wound healing. Besides, Takayama, 2004 and Shellard, 1989 reported the other pharmacological properties of MS which include anesthetic, antinociceptive, analgesic and stimulant effects. In general, the pharmacological effects of MS leaves are mainly attributed to its principal alkaloid called mitragynine (Fig. 1) [1,2].

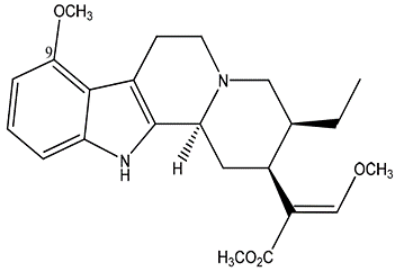

Fig. 1. *The chemical structure of Mitragynine, $C_{23}H_{30}N_2O_4$ in Mitragyna speciosa leaves*

Since then several pharmacological studies have been undertaken to evaluate this assertion objectively. However, the mitragynine dose employed in recent studies showed that the dose for analgesic (30–200 mg/kg) [3,4,5], pharmacokinetics (20–50 mg/kg) [6,7,8] and toxicity (200–477 mg/kg) [4,5] which varied largely across rodent species. Currently, research studies reported that mitragynine has been studied at the preclinical stage and progressively gaining more attention as a potential substitute or adjunct drug therapy for addiction and pain [9,10]. In addition, the higher antioxidant properties and antimicrobial of the leaves make it potentially suitable for wound therapy. Studies from Parthasarathy et al., 2009, reported that the MS leaves has shown to have antioxidant properties with DPPH IC_{50} values of the aqueous, alkaloid and methanolic MS extracts were 213.4, 104.81 and 37.08 µg/mL, respectively, total phenolic content were 66.0 mg, 88.4, 105.6 mg GAE/g, respectively and total flavonoids were 28.2, 20.0 and 91.1 mg CAE/g respectively. In addition, the MS leaves extracts showed antimicrobial activity against *Salmonella typhi* and *Bacillus subtilis*. The minimum inhibitory concentrations (MICs) of MS extracts was determined by the broth dilution method ranged from

3.12 to 6.25 mg/mL. The alkaloid extract was found to be most effective against all of the tested organism [11].

To improve the transportation of the active matter in MS leaves, solid lipid nanoparticles (SLNPs) will be chosen as a carrier system for better penetration into skin. SLNPs are colloidal particles ranging in size between 10 to 1000 nm. SLNPs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers such as nanoemulsions, liposomes and polymeric nanoparticles. They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. Examples of solid lipid materials are triglycerides, complex glyceride mixture and wax. SLNPs also possesses excellent stability and able to control the incorporated drug release. When compared with polymeric nanoparticles, the physiological lipids-made SLNPs is better tolerated by the human body and its lipophilic nature helps it to penetrate deeper into the skin [12,13].

Recent research claimed that SLNPs are desirable in transdermal drug delivery. This is due to its various sizes and its availability in modifying surface polarity to boost skin penetration. It is believed that the SLNPs exhibit mechanical flexion where they can reach deeper into upper skin regions [14]. The usage of SLNPs for drug delivery system offered low toxicity because of the solvent less system used during the preparation and amenability to large scale production and sterilization. Moreover, this nanoparticle system able to facilitate the contact of the active substances with stratum corneum for its small particle size and high surface area. Thus, this allow high permeation of carried substances through the viable skin [15].

II. DESIGN OF ACTIVE INGREDIENTS INCORPORATED INTO SLNPS

The structure of SLNPs depends on formulation composition such as lipid, surfactants and active compounds. Table 1. shows the examples of ingredients used in solid lipid nanoparticles.

TABLE 1. INGREDIENTS USED IN FORMULATION OF SOLID LIPID NANOPARTICLES

Ingredients	Concentration (% w/w)	Reference
Lipid	3.33	[16]
Phospholipids	0.6- 1.5	[17]
Tristearin glyceride	95	[17]
Ploxomer188	1.2- 5	[18]
Cetyl palmitate	10	[19]
Tween 85	0.5	[20]
Tween 80	50	[20]
Ethanol/butanol	2	[21]

There are three design model of active ingredients incorporated into SLNPs [22]:

a) Homogeneous matrix model

A homogeneous matrix with molecularily dispersed drug or drug being present in amorphous clusters is thought to be mainly obtained when applying the cold homogenization method and when incorporating very lipophilic drugs in SLN with the hot homogenization method. In the cold homogenization method, the bulk lipid contains the dissolved drug in molecularily dispersed form, mechanical breaking by high pressure homogenization leads to nanoparticles having the homogeneous matrix structure. The same will happen when the oil droplet produced by the hot homogenization method is being cooled, crystallizes and no phase separation between lipid and drug occurs during this cooling process. This model is assumed to be valid for incorporation of drug prednisolone, which can show release from 1 day up to weeks [23].

b) Drug-enriched shell model

An outer shell enriched with active ingredient can be obtained when phase separation occurs during the cooling process from the liquid oil droplet to the formation of a solid lipid nanoparticle. A fast release can be highly desired when application of SLNPs to the skin should increase the drug penetration especially when using the occlusive effect of SLNPs at the same time [24].

c) Drug-enriched core model

A core enriched with active compound can be formed when the opposite occurs, which means the active compound starts precipitating first and the shell will have distinctly less drug [24].

III. PREPARATION OF SOLID LIPID NANOPARTICLES

A. High pressure homogenization

A powerful technique that pushes a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally, 5-10% lipid content is used but up to 40% lipid content has also been investigated. Hot and cold homogenization are used in these technique.

Hot homogenization is carried out at temperatures above the melting point of the lipid. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. Higher temperatures give smaller particle sizes because the viscosity of inner phase decreased and causes the degradation rate of drug and the carrier to increases.
Moreover, higher homogenization pressure often leads to an increase of particle size due to high kinetic energy of the particles. During cold homogenization technique, the drug containing lipid melt is cooled and the solid lipid ground to lipid microparticles. These lipid microparticles are dispersed in a cold surfactant

solution yielding a pre-suspension and homogenized at or below room temperature. This approach is economical and convenient for lab scale but may give rise to polydisperse distribution and require intensive energy process [25].

B. Solvent evaporation

In solvent evaporation method, lipophilic material is dissolved in a water-immiscible organic solvent such as cyclohexane which emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar). The advantages of using this technique is that it is a continuous process, scalable and commercially demonstrated. However, during the process biomolecule in SLNPs maybe damage due to extremely intensive energy process [25].

C. Microemulsion based method

This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase. They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid like stearic acid, polysorbate 20 as an emulsifier, butanol as co-emulsifiers and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. SLNPs dispersion can be used as granulation fluid for transferring in to solid product such as tablets and pellets by granulation process. The high-temperature gradients in the process facilitate the lipid crystallization and prevent aggregation. Due to the dilution step, the achievable lipid contents are considerably lower compared with the high pressure homogenization method based formulations. This technique consider to be more stable and safe energy [25].

IV. Advantages and Disadvantages of Solid Lipid Nanoparticles as Drug Carrier

The basis to overcome the drawbacks of liquid lipid into solid lipid based system are mainly because of they enhance oral bioavailability and reduce plasma profile variability. Besides, solid lipids suitable for scale-up production and alternative materials to polymers. Typically, SLNPs have low toxicity, good biocompatibility, solvent less and suitable for lipophilic drugs. The submicron size of the nanoparticles gives better control over release kinetics of encapsulated compounds and provide chemical protection of labile incorporated compounds [25].

However, there are some disadvantages of using SLNPs which include low drug loading capacity, unexpected dynamics of polymeric transitions and particle growth [26,27,28]. Therefore, further studies on *in vitro* and *in vivo* are required to understand better on the molecular level on SLNPs.

V. Recent Applications of Medicinal Plants Incorporated into Solid Lipid Nanoparticles

According to research, there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from medicinal plants. The possible pure compounds were easily obtained, structural modifications to produce potentially more active and safer drugs could be easily performed. Today, many pharmaceutical industries use medicinal plants for drugs delivery system [29]. In addition, solid lipid nanoparticles are suitable carriers to transport those medicinal plants due to their submicron-size, able to incorporate hydrophilic and lipophilic drugs, non-bio toxicity and easily available for scale up production [30]. Table 2. depicts recent medicinal plants loaded with solid lipid nanoparticles for various application in drug delivery.

TABLE 2. RECENT MEDICINAL PLANTS LOADED WITH SOLID LIPID NANOPARTICLES FOR VARIOUS APPLICATIONS IN DRUG DELIVERY

Medicinal plant	**Application**	**Reference**
Calendula officinalis extract	Wound healing in ophthalmic formulations	[31]
Tripterygium wilfordii extract	Anti-inflammatory in topical delivery	[32]
Nigella sativa L. seed	Cosmetic	[33]
Curcuma longa Linn.extract	Oral application	[34]
Syzygium aromaticum extract	Antioxidant in oral application	[35]

VI. Conclusion

In summary, SLNPs are very complex systems with clear advantages and disadvantages to other colloidal carriers. SLNPs give better biocompatibility, control drug release, improve stability and easy to scale up. Further study needs to be done to understand the *Mitragyna speciosa* loaded with SLNPs structure and dynamics on molecular level *in vitro* and *in vivo* studies.

Acknowledgment

We would like to thank Integrated Chemical Biophysics Research, Faculty of Science, UPM and Centre of Foundation Studies for Agricultural, UPM for support and assistance throughout this research.

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