Int. J. Sci. R. Tech., 2024 1(12)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Development And Assessment Of A Bcs Class II - SGLT2 (Sodium Glucose Cotransporter 2) Inhibitor Drug In The Form Of Solid Lipid Nanoparticles By Selecting Different Lipids, Co-Surfactants, And Manufacturing Techniques

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ABSTRACT

Solid lipid nanoparticles (SLNs) represent a promising drug delivery system capable of delivering a wide variety of drugs, including both hydrophobic and hydrophilic compounds. They can be customized for specific therapeutic applications, such as targeted drug delivery, sustained release, and reduced toxicity. The research focused on developing SLN formulations using emulsification-solvent evaporation and hot homogenization. This involved optimizing the concentrations of surfactants and co-surfactants/stabilizers to achieve stable formulations. Preliminary results indicated that the lipids and surfactants with the highest miscibility with the active pharmaceutical ingredient (API) were selected. The lipid, surfactant, and co-surfactant concentrations were optimized to create a stable formulation. The study found that the API exhibited poor thermal stability up to the melting points of the shortlisted excipients, retained its BCS (Biopharmaceutical Classification System) class II classification, and showed low solubility and permeability. However, the selected API was determined to have a dose of approximately 2.5 mg, demonstrating improved thermal stability and degradation behavior. The minimum concentrations of lipids required to achieve a stable formulation were also established. With appropriate formulation and process optimization, SLNs are promising for future therapeutic applications, particularly in chemotherapy, vaccine delivery, and gene therapy.

Keywords: Solid lipid nanoparticles (SLNs), Drug delivery system, emulsification-solvent evaporation, hot homogenization, co-surfactants/stabilizers.

INTRODUCTION

Drug Delivery System (DDS) has been used successfully in the past few decades to cure illnesses and enhance health because of its improved systemic circulation and ability to regulate the drug's pharmacological action. As pharmacology and pharmacokinetics advanced, the idea of controlled release emerged, demonstrating the significance of drug release in assessing therapeutic efficacy [1]. Since it was initially authorized in the 1950s, the controlled-release formulation of a medication has garnered a lot of interest because of its many benefits over traditional medications. It delivers medications for a set amount of time and at a set rate. Furthermore, controlled drug delivery systems can endure for days or even years because they are not impacted by physiological variables. With constant or variable release rates, it also offers spatial control over drug delivery [2]. Additionally, it decreases medication toxicity and enhances patient acceptance, compliance, pharmacological activity, efficacy, target site accumulation, and solubility [3]. Extensive efforts have been made to explore the drug delivery systems by which each with its own advantages and limitations, however, the vital goals of all of the systems are to enhance safety and efficacy by means of improving bioavailability, reduce drug toxicity, targeting to specific organ, and improve the stability of the drug. Past decade has witnessed solid lipid nanoparticles (SLN) as competitive drug delivery system to liposome, emulsions, and polymeric nanoparticles and it is ascribed to their potential of

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

delivering proteins and peptides, along with small molecules [4]. Various nano drug delivery systems are depicted in Figure 1[25].

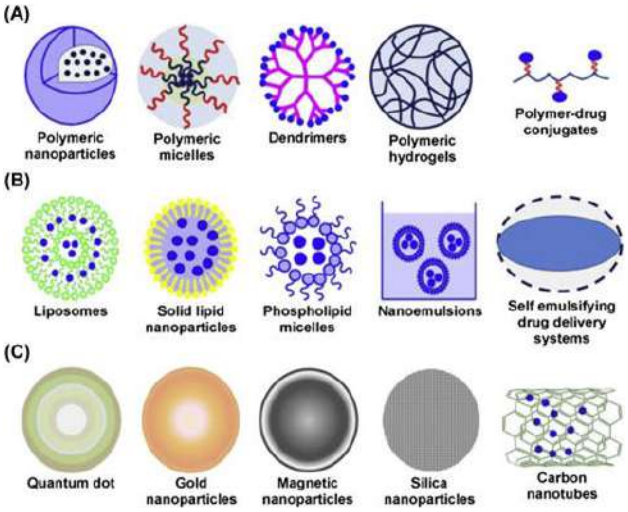

Figure 1: Various nano drug delivery systems.

Because of their superior encapsulation capabilities, prolonged drug release, enhanced targeting of disease cells, and increased stability in storage, nanocarriers are becoming increasingly popular as drug delivery methods [5]. Liposomes and polymeric nanoparticles are the most extensively used of the well acknowledged nanoparticles currently employed for medication delivery. The polymeric nanoparticle, a polymer-based nanoparticle, was able to overcome this restriction by demonstrating high encapsulation/drug loading ability as well as stability, whereas liposomes, lipid-based nanoparticles, despite their exceptional biocompatibility, still experienced drug leakage and instability during storage. But it has drawbacks of its own, including less biocompatibility [6, 7]. Researchers explored and created a hybrid system known as polymer-lipid hybrid nanoparticles, which combines the special qualities of the two classes of nanoparticles, in order to get over these drawbacks and produce an efficient nanomaterial. The needs of biocompatibility, high storage stability, sustained drug release, low drug leakage, small particle size, and good encapsulation were all met by this hybrid system [8]. Due to its effectiveness, this technology is currently being employed for both diagnostic and other therapeutic applications. Three separate parts make up polymer-lipid hybrid nanoparticles, and they are as follows: a polymeric core that efficiently contains medications that are hydrophilic or hydrophobic. A lipid shell that offers biocompatibility and high stability, a lipid-polyethylene glycol (PEG) in the outer part that is covered by a lipid layer to provide increased steric stability, prevent immune recognition, and increase time for circulation, and the hydrophilic and hydrophobic nature of the core that produces a high sustained release make this possible [9, 10, 11]. There are numerous uses for polymer-lipid hybrid nanoparticles, including gene transfer and the delivery of different chemotherapeutic drugs in photothermal, photodynamic therapy and ultrasound. Studies have shown that they can be used in the delivery of vaccines and immune activation as well as in imaging and alternative magnetic field (AMF). Hence its wide application in the fast-growing medical environment [12]. Basically, the SLN comprises of the spherical lipid particles which are dispersed in the aqueous solution containing surfactant / co-surfactant solution. Phospholipids forms the hydrophobic core in which hydrophobic drug moiety gets entrapped or / dispersed [13]. Various phospholipids which are used to develop the SLN are enlisted in table 1. SLN combines the advantages offered by other nano drug delivery systems such as liposome, polymeric nanoparticles and nano emulsions without carrying their disadvantages [14]. They are biodegradable, stable, leakproof, hydrolysis, lack of aggregation, particle growth routinely seen with liposome and lipid emulsions. SLN differs from lipid emulsion as they carry solid core instead of liquid which provide extended release of API. Other advantages include the cost-effective raw material, high dispersibility in water, improved drug loading and long-lasting drug release with single injection from few hours to days [15, 16]. In present scope of development of SLN various processing methods were explored aiming to establish the technology which can be readily adapted for future developmental projects by doing required tailoring to achieve the desired product characteristics [16]. Below are the lipids used in fabrication of SLNs.

Table 1: List of lipids

Sr. No.	Lipids
1	Glyceryl behenate
2	Stearic acid
3	Glyceryl monostearate
4	Oleic acid
5	Cetyl alcohol
6	Tristearin
7	Glyceryl caprate

MATERIALS AND METHODS:

Materials:

SGLT2 (sodium-glucose cotransporter 2) inhibitor (model drug) was obtained from Dr. Reddy's Laboratories, India. Glyceryl behenate (Compritol® 888 ATO; COM) was provided by Gattefosse India limited as gift sample. Polysorbate 20 and Polysorbate 80 (Tween 20 and Tween 80), polyethylene glycol 4000 were provided by GANGWAL CHEMICALS PVT.LTD., India. Soya lecithin (Leciva S90) was a kind gift from VAV Lipid private limited, PEARLITOL® PF (Mannitol pyrogen free grade) was a kind gift from ROQUETTE, Sucrose (multi compendial parenteral grade low in endotoxin) was a kind gift from J. T. Baker/Avantar, Purified water was obtained Inhouse (Millipore, MD, USA). All other chemicals were at least of reagent grade and used as received.

Method of preparation:

Multiple methods have been utilized to prepare aqueous dispersions of lipid nanoparticles, each possessing distinct advantages and limitations.

Emulsification-Solvent Evaporation (ESE):

In this method (see Figure 2), lipids are added in a solution state to the aqueous phase in a dispersed form while mechanically stirring. Size reduction is then achieved using a probe sonicator or probe homogenizer. These microemulsions are thermodynamically stable and microheterogeneous, consisting of the active pharmaceutical ingredient (API), oil, water, surfactant, and co-surfactant. The process variables for emulsification include but are not limited to, stirring rate, temperature, and revolutions per minute (rpm) used during homogenization.

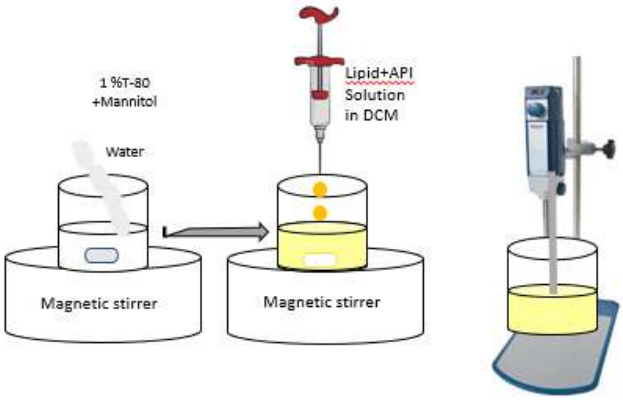

Figure 2: Emulsion method for SLN preparation.

Hot homogenization / high pressure homogenization:

Lipids are melted on a hot plate at a temperature above their melting point, maintained at 10 ºC higher for 5-10 minutes to ensure complete melting. After this, the melted lipid active pharmaceutical ingredient (API) should be added and dispersed into the aqueous phase while stirring or using sonication. The resulting microemulsion undergoes a hot homogenization process with the help of a homogenizer (PANDA PLUS 2000). This homogenization process employs combined shear force, collision, turbulence, cavitation force, and vigorous mixing to achieve the desired reduction in particle size. It is essential to optimize pressure and temperature during this process. A visual representation of high-pressure homogenization is provided in Figure 3.

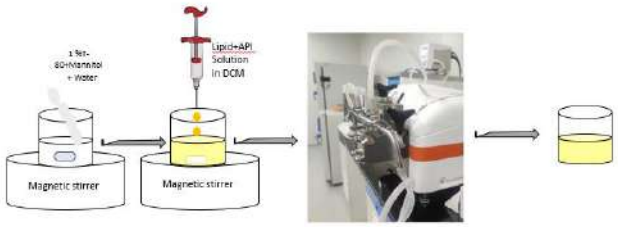

Figure 3: High pressure homogenization: Hot homogenization.

Characterization And Evaluation Of SLN:

For high-quality solid lipid nanoparticle (SLN) development, precise physicochemical characterization is crucial. Key parameters that indicate high-quality SLN include size, morphology, zeta potential, surface charge, drug loading, and drug release.

Particle Size, Shape, Particle Size Distribution And Zetapotential:

The size, shape, and distribution of particles can be measured using electron microscopy techniques such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Additionally, scattering techniques can provide information on particle size, shape, distribution, and zeta potential. Atomic Force Microscopy (AFM) and Photon Correlation Spectroscopy (PCS) are utilized to determine the surface charge of particles.

Solid State Transformation And Integration With Api:

DSC and FT-IR are powerful techniques for examining the crystallinity and interactions between lipids and active pharmaceutical ingredients (APIs). Additionally, PXRD serves as a crucial method to validate the findings from DSC, ensuring robust and reliable results.

Drug Loading, Drug Release And Rheology:

The in-vitro diffusion or dissolution process can gauge drug loading and drug release. The dialysis

tubing/bag and its equivalent formulation can be explored on a dose basis. The rheology can be determined by using a rheometer (Brookfield viscometer).

EXPERIMENT

Preformulation Study

The preformulation study of solid lipid nanoparticles (SLN) involves several key components:

1. Characterization of the active pharmaceutical ingredient (API).
2. Determination of the API's solubility in various aqueous solutions that contain surfactants, as well as in different solvents, co-solvents, and hydroalcoholic solutions.
3. Assessment of the API's solubility in various lipids and co-surfactants.
4. Evaluation of any chemical interactions or physical incompatibilities that may occur.

This study is essential for understanding how the API interacts with other components in the formulation.

Characterization API:

The active pharmaceutical ingredient (API) was first characterized by its melting point and compared with the melting point listed on the Certificate of Analysis (COA). After confirming the polymorphic form of the API, we re-evaluated its suitability for solid lipid nanoparticle (SLN) formulation in terms of thermal stability and degradation behavior. An ideal drug candidate for SLN should have several key characteristics: it should require a low dose, be thermodynamically stable, allow for frequent dosing (twice or thrice a day), have a shorter half-life, undergo first-pass metabolism, and degrade in highly acidic and alkaline conditions. Additionally, it should belong to the Biopharmaceutics Classification System (BCS) class II or IV. The selected API was found to have a dose of approximately 2.5 mg, demonstrated thermal stability up to the melting points of the shortlisted lipids, retained its BCS class II classification, and exhibited poor solubility and permeability. Therefore, it was deemed suitable for formulation into SLN using emulsification and high-pressure homogenization for process development.

Qualitative Solubility Determination:

Kinetic solubility of API and various excipients was determined in aqueous solution containing surfactant, co-surfactant and lipids (qualitative). Observation of the qualitative study is provided in table 2.

Table 2: Qualitative solubility

Sr. No	Aq. Stock solution of excipients (0.5%)	Added stock solution of drug (1mg/mL) in DCM	Observation
1.	Kolliphor EL	160 µL	Range of Precipitation 120-140 µL
2.	Tween -20	280 µL	Range of Precipitation 200-280 µL
3.	Tween -80	300 µL	Range of Precipitation 220-300 µL
4.	PEG 400	140 µL	Range of Precipitation 120-140 µL
5.	Corn oil	100 µL	Range of Precipitation 80-100 µL
6.	PEG 200	100 µL	Range of Precipitation 80-100 µL
7.	Soyabin oil	100 µL	Range of Precipitation 80-100 µL
8.	Miglyol 812	100 µL	Range of Precipitation 80-100 µL
9.	Lecithin	5 mg / mL in DCM	No precipitation

Formulation & Process Development:

Formulation and process development was initiated based on the results from the pre-formulation study (Table 2). This process involved selecting and optimizing the manufacturing processes composition, followed by the optimization of the lyophilization cycle.

Selection And Optimization Of Composition:

Lipids, surfactants, and co-surfactants/stabilizers that demonstrated the highest miscibility with the active pharmaceutical ingredient (API) were selected. Additionally, the minimum concentrations of these lipids, surfactants, and co-surfactants/stabilizers required to achieve a stable solid lipid nanoparticle (SLN) formulation were determined. The details for the same are provided in Table 3.

Table 3: Trails for selection and optimization of composition

Sr. No	Batch number	Objective	Observation / results
1	F1	Solubility study (qualitative)	Kolliphor EL, PEG 400, Tween 80/20 for further optimization.
2	F2	1% T-80	Stable colloidal dispersion

		(Surfactant screening)	
3	F3	1% Kolliphor EL (Surfactant screening)	Unstable colloidal dispersion
4	F4	1% T-80 without co-surfactant	Unstable colloidal dispersion
5	F5	1% Kolliphor EL without co-surfactant	Unstable colloidal dispersion
6	F6	0.5 % T-80 (Concentration of surfactant)	Unstable colloidal dispersion
7	F7	0.5 % K-EL (Concentration of surfactant)	Unstable colloidal dispersion
8	F8	1% T-80 (Concentration of lipid to API)	Stable colloidal dispersion

Screening Of Surfactant:

Non-ionic surfactants mainly Tween and Kolliphor with different concentration were explored aiming to achieve uniform microemulsion / dispersion.

Levels Of Surfactant Studied:

During development, two surfactant concentration levels, 0.5% and 1%, were tested. Among these, 1% was found to be suitable for creating a stable formulation with the desired characteristics. However, over time, aggregation occurred with this concentration. In contrast, at 0.5%, immediate agglomeration was observed.

Effect Of Co-Surfactant:

To improve the stability and prevent the agglomeration, lecithin was added as co-surfactant.

With lecithin addition the microemulsion was found to stable till 2 days.

Selection and optimization of manufacturing process

Single emulsification process:

Manufacturing procedure used to formulate the SLN by using this method are provided below:

Weigh all the ingredients in required quantity, prepare 1% tween 80 solution by using water. Dissolve drug and lipids in Dichloro methane (DCM) and add sucrose under stirring, maintain temperature at 60 ºC for 1 hour then add 1% tween 80 solution drop wise into drug lipid phase and continue stirring for 15 minutes. Employ sonication for 15 minutes (Amplitute 40%, pulse 25, time 5 minutes and temp 40 ºC: One cycle) and Employ Stirring for 4 hr at 50 ºC with 500 rpm, Employ Freeze drying of final solution.

Hot Homogenization:

Manufacturing procedure used to formulate the SLN by using this method are provided below:

Weigh all the ingredients in required quantity, prepare 1% tween 80 solution by using water. Dissolve drug and lipids in Dichloro methane (DCM) and add mannitol under stirring, maintain temperature at 60 ºC for 1 hour then add 1% tween 80 solution drop wise into drug lipid phase and continue stirring for 15 minutes. Employ sonication for 15 minutes (Amplitute 40%, pulse 25, time 5 minutes and temp 40 ºC: One cycle) and Employ Stirring for 4 hr at 50 ºC with 500 rpm,

Pour solution into vials and perform Lyophilization with below recipe.

Lyophilization:

Lyophilization cycle was employed on the probe sonicated and high pressure homogenized microemulsions by using Advantage Pro Lyophilized. Reported glass transition temperature for Drug was 24 ºC while for mannitol and sucralose were -35 ºC and 13 ºC respectively. Using this information lyophilization cycles was designed. As on need basis parameters were changed to obtain intact cake in vial. Detailed observation for studied bulking agents and their impact on cake was summarized in Table 4.

Table 4: Detailed observation for studied bulking agents and their impact on cake.

Sr. No	Batch number	Objective	Observation / results
1	F8	1% T-80 (concentration of lipid to API)	Stable colloidal dispersion
2	F9	Lyo protectant screening	Mannitol was superior to sucrose
3	F9a	Lyo protectant screening-mannitol 10 mg/ml	Elegant cake
4	F9b	Lyo protectant screening-mannitol 15 mg/ml	Elegant cake

CONCLUSION:

The research explored the formulation development of Solid Lipid Nanoparticles (SLNs) as a promising

drug delivery system, particularly for improving the therapeutic efficacy of drugs through controlled release and enhanced stability. SLNs offer significant advantages over traditional drug delivery methods, including better biocompatibility, stability, and controlled drug release. The study demonstrated that SLNs could be prepared using various methods like emulsification-solvent evaporation and hot homogenization by optimizing surfactant concentrations and co-surfactants for stable formulations. Additionally, lyophilization was employed to stabilize the formulations for long-term storage. The results indicated that SLNs are ideal for delivering a wide range of drugs, including hydrophobic and hydrophilic compounds, and can be tailored for specific therapeutic applications such as targeted drug delivery, sustained release, and reduced toxicity. With proper formulation and process optimization, SLNs hold great promise for future therapeutic and diagnostic applications, especially in areas like chemotherapy, vaccine delivery, and gene therapy. By understanding the interactions between the drug, lipids, and excipients, and refining the preparation techniques, SLNs can be further optimized for clinical use, offering a cost-effective, efficient, and patient-friendly drug delivery system. Future work will focus on improving scalability, stability, and the broad application of SLNs in various medical fields.

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HOW TO CITE: Dileep J Babu Bikkina, Rajesh Vooturi, Subhash Zade, Narendra Reddy Tharigoppala, Suresh Kumar Joshi, Development And Assessment Of A Bcs Class II - SGLT2 (Sodium Glucose Cotransporter 2) Inhibitor Drug In The Form Of Solid Lipid Nanoparticles By Selecting Different Lipids, Co-Surfactants, And Manufacturing Techniques, Int. J. Sci. R. Tech., 2024, 1 (12), 277-283. https://doi.org/10.5281/zenodo.14558598