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Research Article:

Optimization of a Low-Energy Method for Preparation of Solid Lipid Nanoparticle

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Abstract

Background/Objectives: Low-energy methods have gained interest for the preparation of Solid lipid nanoparticles (SLNs) due to their simplicity efficiency, reduced mechanical stress, and lack of need for high energy equipment. This study aimed to compare various low-energy preparation techniques for SLNs, optimize formulation variables, and evaluate their potential for delivering a lipophilic model drug, Vitamin D3. **Methods:** Multiple individual and combined low-energy methods were employed for SLN preparation, Vitamin D3 was used as a model drug. Key formulation parameters were assessed, and the resulting SLNs were evaluated for particle size, entrapment efficiency and zeta potential. Results: While individual low-energy methods showed limitations such as particle instability and suboptimal size distribution, a novel combined approach overcame these challenges. The optimized formulation exhibited high entrapment efficiency and a favorable zeta potential, indicating good colloidal stability. **Conclusions:** Comparing low-energy preparation techniques presents a scalable and efficient strategy to improve SLN formulations. The optimized SLNs could be useful in the future for enhanced Vitamin D3 bioavailability and controlled release, supporting their application in drug delivery systems.

1. Introduction

Solid lipid nano particles (SLNs), are sought out to be novel, promising carriers for the delivery of lipophilic, poorly water soluble drugs. They have the ability to increase the stability and the bioavailability of drugs due to their unique structure and composition. The structure enhances stability by protecting from degradation, reducing drug leakage and improves overall physical stability by preventing particles aggregation and maintaining structural integrity. The bioavailability is improved due to the increased drug loading efficiency i.e. having a larger surface area due to their small nano size ranging between 50 to 1000 nm leading to increased solubility and absorption (1–5). Their composition is mainly made up of a solid lipid at room temperature, a surfactant for stabilization, the active pharmaceutical compound and an organic.
solvent depending on the method of preparation.. There are numerous methods in which they can be prepared depending upon the availability of the instruments in lab, the heat lability of the compound(s) compared to the melting point of the lipid and also the extent to the amount of SLNs to be prepared whether in small or large scale. These methods were initially introduced by Gasco (6) but have been widely modified according to the needs of individual researchers. Preparation methods are classified using various systems, which include high-energy, microemulsion based and solvent required approaches.
Solid lipid nanoparticles (SLNs) demonstrate significant advantages in drug delivery across various routes including; oral, ocular and transdermal applications. Overall, there use has led to improved bioavailability, modulated drug release, enhanced permeation and reduced toxicity when compared to conventional formulations (7–13)
In studies related to high pressure homogenization, to increase the antiproliferative effect of Zataria multiflora (ZM) against breast cancer and melanoma cells, the use of stearic acid and span 60 as lipid phase and tween 80 as surfactant in aqueous phase for the formation of SLNs found a particle size of 176 ± 8nm, a PDI of 0.22 ± 0.1 and an entrapment efficiency of 67 ± 5%. In addition, the viability of cancer cells was found to be reduced to under 13% (14). In another study, curcumin SLNs were prepared using tween 80 and phospholipon90G in water as aqueous phase and Compritol 888 ATO with glycerol monostearate (GMS) as lipid phase. Characterization studies on optimum

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formula found the average particle size 540.2 ± 45.1 nm, an EE of 79.74 ± 0.88% and PDI of 0.2921 ± 0.0062. According to a separate study, using stearic acid, Compritol and Tween 80 for the formulation of combined paclitaxel and curcumin into SLNs, results found a particle size of optimum formula to be 193.21 ± 4.7nm, PDI of 0.168 ± 0.003 and EE of paclitaxel and curcumin; 96.11 ± 3.49% and 94.57 ± 3.11% respectively (15).

Low energy methods of preparation exhibit limitations as instability (poor monodisperse systems aggregate over time), larger nanoparticle size with a broader PDI, lower drug loading and EE when compared to high energy methods. However, literature has found some successful outcomes using low energy methods by optimization and tweaking proven methods. Improvement of antiseizure activity of cryptolepine was achieved by reducing the particle size to ensure permeability across the blood brain barrier. Formulation into SLNs composed of poloxamer 188 (surfactant), propylene glycol (co-solvent) and stearic acid. Solvent evaporation technique required the use of ethanol. In addition, sonication was employed to achieve a particle size of 152.4 ± 16.3, PDI of 0.21 and an EE of 83.4 ± 1.3% (16). In another study investigating dermal drug delivery systems, incorporation of vitamin A SLNs into a gel. Ultrasonication technique was applied and the SLNs were composed of; tween 80, beeswax and span 80. Studies found a reduction of particle size of 64.85 ± 4.259nm, an EE of 66.01 ± 8.67% and a PDI of 0.292 ± 0.035 (17)

The above studies revealed that preparation of a SLNs with the desired PS, EE, PDI and ZP depend not only upon the method of preparation, whether high or low energy techniques, but careful optimization of the variables including the type and concentration of lipid(s) and surfactant(s) used will highly impact the formulation quality.

In this research we aim to explore the impact of several low energy preparation methods on the quality of vitamin d3 (as a model drug) loaded SLNs by measuring key factors associated with reliable nanoparticles including EE, Particle size, PDI and Zeta potential in addition to the short-term stability study for the resulted nanoparticle.

2. Materials and Methods

2.1. Materials

Pure vitamin D_3 (cholecalciferol) was purchased from Meryer China; purity 98%, CAS no. 67-97-0. Glyceryl mono stearate (GMS) and Polysorbate 80 (Tween 80) were purchased from HiMedia India. While Span 60, stearic acid, cetyl alcohol, methanol and ethanol were purchased from Scharlau, Spain.

2.2. Methods

2.2.1 Preparation of SLNs

2.2.1.1 Microemulsion Technique

Micro emulsion method was used according to Gasco (18) with some modifications. An aqueous solution of water and Tween 80 were heated to the same temperature of the lipid phase containing lipid, drug, span 60 and ethanol (60 °C). The hot aqueous solution was then slowly added to the melted lipid solution producing a hot o/w emulsion. A SLN dispersion was obtained by adding the hot o/w emulsion to cold water at a 1:20 ratio (microemulsion: water v/v) on a magnetic stirrer with continuous stirring for 30 minutes (19,20)

2.2.1.2 Ultrasonication

Bath sonicator was used for sonication method. Method described by Madan which formulated halbetasol loaded SLNs (21) with modifications was used. Two separate solutions; lipid phase (lipid, drug and span 60) and aqueous phase (water and Tween 80) were prepared at the same temperature (60 □C). The aqueous phase was then slowly added to the lipid phase under continuous stirring on magnetic stirrer for various periods of time at 1200 RPM. This was immediately followed by intermittent sonication for 15 minutes at 60 □C.

2.2.1.3 Solvent injection/evaporation

Solvent injection/evaporation method, in which the lipid phase consisting of; drug, lipid, organic solvent and span 60 was heated to 60 □C. The lipid phase was slowly added drop by drop to the aqueous phase (water and tween 80) heated to same temperature with continuous stirring on magnetic stirrer with syringe. The emulsion was left on magnetic stirrer for 30 minutes at 600 RPM (22–24).

2.2.1.4 Combination of Emulsification, Solvent injection/evaporation and ultrasonication

The Vitamin D_3 loaded SLN dispersions, as described in **Table 1**, were prepared using a combination of the solvent injection/solvent evaporation method and ultrasonication method (25–27). The lipid phase was prepared by heating the solid lipid; stearic acid and lipophilic surfactant; span 60 with vitamin D_3 to temperature of 5C above the melting point of the lipid with the addition of 1 ml solvent; ethanol. An aqueous phase of hydrophilic surfactant; tween 80 and distilled water were heated to the same temperature as the lipid phase. The lipid phase was slowly added, drop by drop to the aqueous phase which was under constant magnetic stirring. This was followed by intermittent sonication for 15 minutes. The dispersion was allowed to then cool under continuous stirring to form the SLN dispersion.

2.2.2 Characterization of SLN dispersions

2.2.2.1 Particle size and Polydispersity index (PDI)

Particle size and polydispersity index (PDI) of vitamin D_3 were determined by dynamic light scattering (DLS) using a particle size/zeta potential analyzer (Lite sizer DLS 500, Anton Par instruments Ltd., Austria). Measurements were performed in an aqueous medium of distilled water at 25 °C and at an angle of 90 °. Average size of each sample was calculated accordingly.

2.2.2.2 Zeta potential

Zeta potential of the optimum sample (S4) was determined using (Lite sizer DLS 500, Anton Par instruments LTD., Austria).

2.2.2.3 Entrapment Efficiency (EE) and Drug loading (DL)

The entrapment efficiency (EE) of the optimum batch number was determined in triplicate (n=3). A volume of 1 ml SLN dispersion was centrifuged at 12,000 RPM at a time of 1 hour. The volume of supernatant layer was determined and the absorbance of the sample was measured (28,29). VitD3 levels were determined against a standard calibration curve prepared in the same solvent and analyzed by spectrophotometric analysis using double

beam UV–Visible Spectrophotometer at 265 nm. The concentration was detected and EE was calculated using equation 1 (27). Similarly, drug loading capacity was calculated using equation 2 (30).

$$\% \text{ EE} = \frac{\text{Initial amount of drug} - \text{Free amount of Drug}}{\text{Initial amount of drug}} \times 100 \quad \text{(Equation 1)}$$

$$\% \text{ DL} = \frac{\text{Initial amount of drug} - \text{Free amount of Drug}}{\text{Weight of lipid(s)}} \times 100 \quad \text{(Equation 2)}$$

Table 1. Composition of batches of Vitamin D3 loaded SLN and method(s) in which were conducted

No.	ME	US	S/E	E/US/S	Drug (mg)	Stearic acid (%)	Ethanol (ml)	Span 60: Tween 80 Ratio	Total % of Surfactant
S1				✓	1	1	1	1:3	0.5
S2				✓	1	1	1	1:1	0.5
S3				✓	1	1	1	3:1	0.5
S4	✓	✓	✓	✓	1	1	1	1:3	1
S5				✓	1	1	1	1:1	1
S6				✓	1	1	1	3:1	1
S7	✓	✓	✓	✓	1	1	1	1:3	2
S8				✓	1	1	1	1:1	2
S9				✓	1	1	1	3:1	2
S10	✓	✓	✓	✓	1	2	1	1:3	1
S11				✓	1	2	1	1:1	1
S12				✓	1	2	1	3:1	1
S13	✓	✓	✓	✓	1	2	1	1:3	2
S14				✓	1	2	1	1:1	2
S15				✓	1	2	1	3:1	2

Abbreviations: ME; microemulsion, US;ultrasonication, S/E; solvent injection/ evaporation, E; emulsification

2.2.3 Short term stability studies

The evaluation of the optimum formula S4 was conducted by determining the effect of the simple storage of SLN dispersion in a sealed glass vial at refrigerated (4 °C) condition for a period of 4 weeks. The short-term stability was assessed to any change to the particle size and/or particle size distribution and zeta potential.

3. Results and Discussion

3.1 Selection of suitable method of preparation

The selection of suitable method of preparation was dependent on the stability and particle aggregation/coalescence within 24 hours after formulation. Initial studies on individual methods found no positive results indicating nanoparticle formation using formulas S4, S7, S10 and S13 as the preliminary formulas for method testing. Although prior research has demonstrated the effectiveness of individual preparation methods, the current study did not replicate these findings. Instead, successful outcomes were only achieved through a combined methodological approach. This led to more extensive studies to determine the optimization of the variables. This may be because individual low energy techniques could not independently ensure the optimal particle size, stability, and encapsulation efficiency, whereas the combined approach allowed for better control over critical formulation parameters. Low energy methods can produce SLNs that are physically unstable. Slight changes in formulation conditions significantly affect the particle size and stability. This sensitivity leads to aggregation or particle growth, impairing the desirable nanoscale properties. In addition, low energy methods depend heavily on surfactant and co-surfactant systems to lower interfacial tension for emulsion formation. Minor variations can lead to premature drug expulsion or particle aggregation (31–34).

3.2 Optimization of different variables

Once the low energy method was determined this led to optimization of the various factors within the formulation. The different variables involved in the fabrication of vitamin D3 loaded SLN included; lipid concentration, surfactant ratios (tween 80/span 60) and concentration, and sonication time. Lipid concentration found that by increasing the lipid from 1% to 2 % there was an increase in particle size from 279.1 nm to 404 nm. This may be due to the formation of liposomal and other structures indicating 1% lipid concentration was found ideal choice for formulating SLN (35). The use of a combination of surfactants (lipophilic; hydrophilic and lipophilic; span 60) enhance the stability of the prepared SLN leading to a more

desirable polydispersity index (PDI). In this study the vitamin D3 loaded SLNs were fabricated using a combination of solvent injection/solvent evaporation and sonication techniques. As can be seen in **Table 2** the best results can be seen in formula S4 with 1% stearic acid lipid, and a ratio of 1:3; span 60: tween 80 surfactant of total percentage of 1 %. The average particle size of formula S4 was 279 nm and a PDI of 0.252. The small PDI indicates uniform particle size of homogenous distribution (36). The 1% surfactant concentration was sought to be optimum, as 0.5% probably was insufficient to stabilize SLN, whereas to high of a concentration as 2% may adsorb on the surface of the SLN leading to an increase in particle diameter. These results were found to be similar to those of SLN production using various concentrations of surfactants by Chirio in 2019 who formulated curcumin loaded SLNs (37).

The lower PDI is thought to be a result of the optimum ratio of the surfactants that impart the stability of the particles dispersed. This is especially useful when considering the HLB (hydrophilic lipophilic balance). As the HLB of tween 80 and span 60 are 15 and 4.7 respectively (38,39) and in order to form a stable dispersion with stearic acid as lipid it requires HLB of the system to be more hydrophilic, i.e have a higher tween 80 to span 60 ratio (40). This corresponds with results when comparing the particle size and PDI of formulas S1 and S3 which are similar except for difference in surfactant ratios and comparing formulas of S4 and S6. Particle size values for formulas S7, S11 and S12 are unavailable and unnecessary as particles were seen through visual observation. Ultrasonication is frequently used during the fabrication of SLNs to reduce both particle size and the PDI. It is effective in breaking up aggregate formation. Intermittent sonication is important in order to prevent over-heating and prevent degradation of compound (41,42).

Table 2. Particle size and PDI of batches prepared for Vitamin D_3 loaded SLNs

Formula No.	Particle size (nm)	PDI
S1	739	0.79
S2	708	1.2
S3	732.3	1.16
S4	279.1	0.252
S5	299	0.288
S6	407.6	0.271
S7	-	-
S8	767.8	0.22
S9	527	
S10	404.8	0.258
S11	-	-
S12	-	-
S13	888	0.703
S14	452.1	0.258
S15	1268	0.249

3.3. Zeta Potential

The zeta potential also known as particle charge is of significant importance for nanoparticle development and helps detect the physical stability of the overall nano-formulation. Prevention of aggregation and establishing redistribution of particles is met with high surface charges; independent on whether they are positive or negative. A zeta potential of ≥ ±20mV is thought to produce a stable nanoparticle dispersion but for short periods of time. However, a zeta potential of ≥±30mV predicts optimum physical stability of the nanoparticle's dispersion (19,43,44). The zeta potential/surface charge of the optimum formula S4 was determined and a value of -33.9±1.7mV was observed (see **Figure 1**).

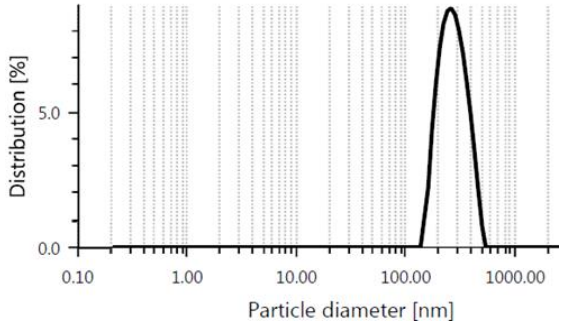

Figure 1. Particle size distribution (intensity) of optimum formula S4

3.4 Entrapment Efficiency (EE) and Drug loading (DL)

Nanoparticles are deemed suitable if a significant amount of the active ingredient they contain have been entrapped. Determining the entrapment efficacy is therefore regarded as a fundamental characteristic of the nanoparticles (15). The optimum formulation of stable SLN dispersion was attained after stirring for 30 minutes to allow complete solvent evaporation and intermittent sonication for 15 minutes with a minimum particle size of 279nm and was further investigated for the EE. A maximum percent of drug entrapment of 90.4 ± 1.55% and a drug loading capacity of 9.03 ± 0.17 % (n=3) was found. The lipophilicity of vitamin D3 which combine to produce amalgam with stearic acid, may be the cause of this enhanced incorporation. It has previously been shown that the drug's solubility in the matrix lipid determines its incorporation ability. In addition, it is influenced by the polymorphic state of lipid material, the chemical and physical structure of the solid lipid matrix, and the miscibility of drug melt and lipid melt (45,46) Stearic acid increases the lipid matrix's flexibility in SLN, which makes it possible to add a certain amount of lipophilic pharmaceutical active drug. Additionally, by incorporating more drug into the lipid layer, higher lipid concentration has led to the solubilization effect on the drug, thus increasing the %EE of the SLNs (47,48).

3.5 Short Term Stability studies

Results of short-term stability studies after 30 days of sample kept at refrigerated temperatures found a slight increase in particle size formation to 452.1 nm with a similar PDI of 0.258 and a decrease of zeta potential to -30.1mV. These results indicate only slight increase and remain in nano particle acceptable range (19).

The impact of many kinetic parameters, including temperature and light, on particle growth has been documented by Freitas and Müller (49), who also shown how sensitive many medicinal products are to these factors. As a result, it is also very typical for pharmaceutical medicines to be stored in a chilly environment, such as a refrigerator.

4. Conclusion

Despite the conceptual advantages of low energy input methods such as simplicity, lower equipment requirements and reduced thermal stress for SLN preparation, practical difficulties such as fragile stability, low drug loading, poor control over particle size, and scale-up challenges have limited their success. These factors contribute to failure or inconsistent outcomes in SLN formulation using low energy methods. This led to the combination of low energy input methods to give more successful SLNs with consistent size and stability. In addition, they produced a significant high entrapment efficiency. Overall, this suggests that combining techniques while optimizing the formulation variables provides better SLN results. Therefore, despite the practicality of low energy methods, the combination approach is recommended to achieve more robust, effective and stable SLN formulations.

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تحسين طريقة منخفضة الطاقة لتحضير جسيمات نانوية دهنية صلبة

الخلاصة/الأهداف: اكتسبت طرق التحضير منخفضة الطاقة اهتمامًا متزايدًا في مجال تحضير الجسيمات النانوية الدهنية الصلبة (SLNs) نظرًا لبساطتها وكفاءتها، وانخفاض الإجهاد الميكانيكي الناتج عنها، وعدم الحاجة إلى معدات عالية الطاقة. هدفت هذه الدراسة إلى مقارنة تقنيات التحضير منخفضة الطاقة المختلفة للجسيمات النانوية الدهنية الصلبة، وتحسين متغيرات التركيبة، وتقييم إمكانية استخدامها في توصيل دواء نموذجي محب للدهون، وهو فيتامين د3. الطرق: استُخدمت عدة طرق فردية ومُدمجة منخفضة الطاقة لتحضير الجسيمات النانوية الدهنية الصلبة، واستُخدم فيتامين د3 كدواء نموذجي. جرى تقييم معايير التركيبة الرئيسية، وقُيّمت الجسيمات النانوية الدهنية الصلبة الناتجة من حيث حجم الجسيمات، وكفاءة الاحتجاز، وجهد زيتا. **النتائج:** على الرغم من أن الطرق الفردية منخفضة الطاقة أظهرت بعض القيود، مثل عدم استقرار الجسيمات وتوزيع الحجم غير الأمثل، إلا أن نهجًا مُدمجًا جديدًا تغلب على هذه التحديات. أظهرت التركيبة المُحسّنة كفاءة احتجاز عالية وجهد زيتا مناسبًا، مما يدل على استقرار غرواني جيد. **الخلاصة:** تُقدّم مقارنة تقنيات التحضير منخفضة الطاقة استراتيجية فعّالة وقابلة للتطوير لتحسين تركيبات الجسيمات النانوية الدهنية الصلبة. قد تكون هذه الجسيمات النانوية المُحسّنة مفيدة في المستقبل لتعزيز التوافر الحيوي لفيتامين د3 وإطلاقه المُتحكّم به، مما يدعم استخدامها في أنظمة توصيل الأدوية.

الكلمات المفتاحية: جسيمات نانوية دهنية صلبة، طرق التحضير، طرق منخفضة الطاقة