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Formulation and Evaluation of Solid Lipid Nanoparticle (SLN) of Andrographolide by Solvent Evaporation Method

Chandra Prakash Dwivedi[*1], Dr. Ankur Choubey[1], Dr. Naveen Gupta[1], Dr. Dharmendra Singh Rajput[1], Dr. Dusmanta Kumar Pradhan[2]

[1]Patel College of Pharmacy, Madhyanchal professional University (MPU), Bhopal-462044 (MP), India.

[2]Raigarh College of Pharmacy, Raigarh, C.G.

***Corresponding Author:**

Chandra Prakash Dwivedi

Patel College of Pharmacy, Madhyanchal Professional University, Bhopal, M.P.

Mail id: -Chandraprakash9009@gmail.com

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ABSTRACT

Andrographolide is a potential therapeutic agent that suffers from poor aqueous solubility. Nanoparticles are frequently employed to control the delivery of drugs and various growth factors to tissues/cells. Nanocarriers, in diverse formulations, have the potential to transport both synthetic and natural anticancer therapeutic drugs Therapy applications of AG are, however, seriously constrained because of poor bioavailability, short plasma half-life, and inappropriate tissue localization. Nanoparticulation of AG was therefore envisaged as a possible solution for management of liver dysfunction. Modified solvent evaporation method can be utilized for the development of lecithin nanoparticles. Polymer and crosslinking agent concentrations and sonication time are rate-limiting factors for the development of the optimized formulation. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts to achieve desirable rheological and in vitro release property for in situ forming system.

Keywords: *Solid lipid nanoparticles, Andrographolide, Solvent evaporation method, Lecithin, Phosphatidylcholine, Almond oil*

1. INTRODUCTION

Nanoscience is now a leading science, providing opportunities for fundamental and applied research across the board of cognitive sciences. The emergence of nanoscience and nanotechnology is driving a technological revolution on a worldwide scale. Nanotechnology is usually applied to materials ranging from 1 to 100 nm. Nanomaterials differ from their bulk materials by a wide range of characteristics, including size, physical strength, chemical reactivity, electrical conductance, magnetism, and optical effects.

In recent years, nanotechnology has been widely applied in the field of biomedicine due to its advantages in reducing drug toxicity, improving drug stability, and enabling controlled release of drugs. By formulating drugs into nanoparticles, new characteristics can be imparted to the drugs, leading to enhanced bioavailability, reduced side effects, controlled release, and improved therapeutic efficacy. For many water-insoluble therapeutic drugs, the development of drug-loaded nanoparticles not only improves their solubility, bioavailability, and stability but also reduces drug toxicity and enhances treatment outcomes.

Various factors, including temperature, pH, reaction time, metal salt volume, and plant extract volume influence the green synthesis of nanoparticles. The interaction of these factors is critical in determining the shape and size of synthesized NPs the temperature plays a crucial role in the synthesis of silver nanoparticles. Typically, the reaction takes place at room temperature, which is a prolonged process, but increasing the temperature of the reaction mixture can speed it up. The temperature range for the reaction is mostly set between 30 and 100 °C. Increasing the reaction temperature decreases the rate of Ag^+ ions, leading to the homogeneous nucleation of silver nuclei. The process enables the production of small-sized silver nanoparticles. Studies have shown that higher temperatures in the reaction mixture lead to a decrease in the rate of nanoparticle synthesis but an increase in stability. Furthermore, it has been observed that silver nanoparticles produced at higher temperatures tend to have smaller sizes.

The reaction time is crucial in synthesizing nanoparticles, as it allows for proper interaction between the salt and the reducing complex components found in the testing extract. The reaction time begins when the reactant is added to the beaker and continues until the reaction occurs. Plants with higher concentrations of secondary metabolites or phytochemicals reduce salt more efficiently. Conversely, plants with fewer reduced compounds take longer to reduce salt. However, plants with fewer secondary metabolites still quickly produce nanoparticles. The reaction time is influenced by factors such as the acidity or basicity of the reaction mixture, temperature, the reducing power of the plant extract, light intensity, enzymes, and secondary metabolites present in the extract.

The pH level significantly impacts biomolecules, altering their electrical charges and potentially hindering their ability to cap and stabilize. It, in turn, can impact the growth of nanoparticles. When synthesizing nanoparticles, the pH level determines their properties and reaction kinetics. Different plant extracts contain various bioactive components, such as polyphenols, flavonoids, and proteins, which can act as reducing agents but exhibit different reactivity at different pH levels. Optimizing the pH conditions during the synthesis is crucial to maximize the reduction efficiency and control the size and shape of the resulting nanoparticles.

Liver disease causes about 2 million deaths annually and accounts for 4% of total deaths. Most deaths are associated with the progression of liver cirrhosis and hepatocellular carcinoma (HCC). HCC is the fourth tumour-associated death worldwide. Many factors such as the hepatitis B and C virus, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD) will induce chronic cirrhosis and ultimately develop into HCC. Furthermore, with the obesity pandemic, there is increasing concern about the serious challenge of NAFLD-related HCC.

More than 80% of primary liver tumours are defined by HCC. As a result of the lack of effective therapeutics, the 5-year survival of HCC is only 20%. Liver transplantation will greatly prolong HCC survival, but the lack of donor organs and recrudescence after transplantation also limit this therapy. Patients who cannot tolerate surgery or chemotherapeutics generally receive systemic therapies, targeted therapy, and immune therapy.

Solvent-emulsification diffusion method technique, solvent and water are mutually saturated to maintain initial thermodynamic equilibrium. Afterwards, the lipids and drug are dissolved in the water-saturated solvent. Solvent containing drug and lipids are emulsified in a solvent-saturated aqueous emulsifier solution by a homogenizer to form an o/w emulsion. The lipid nanoparticles precipitate after dilution with excess water (ratio: 1:5–1:10) due to diffusion of the organic solvent from the emulsion droplets to the continuous phase. The solvent can be removed by ultrafiltration or lyophilisation. Solvent diffusion is more innovative and most of the solvent employed show a better safety profile compared to volatile solvents. The objectives of proposed work are to formulate nanoparticles to control and continue release rate of drug at the site of localization. Nanoparticles show better medication as contrast with other dosage form and focus to a specific cell type or receptor. Nanoparticle can be used to target the herbal medicines to individual organ which improves the selectivity, solubility, drug delivery, safety, effectiveness and reduces the frequent dose.

2. MATERIAL AND METHODS

Solvent emulsification-evaporation technique

In this method the lipid was first melted above its melting point and drug was dissolved into the melted lipid. The drug-lipid mixture was dissolved completely in an organic solvent by using sonication technique. The surfactant was dissolved in purified water to make an aqueous phase and the water phase was heated to the same temperature as that of lipid phase. The lipid phase was added slowly into hot aqueous phase using high speed mechanical stirring. As the high-speed stirring takes pale, the temperature was increased due to the heat generated. Because of increased temperature, the volatile organic solvent gets evaporated and lipid nanoparticles start to precipitate due to low concentration of dispersion medium. These lipid nanoparticles were solidified through cooling at room temperature and filtered through membrane filter. Washed nanoparticles were lyophilized for stable formulation.

Table 1: Response surface regression in different batches prepared for andrographolide SLNs using 33 factorial designs by solvent evaporation technique

Formulation Code	Lipid content (X_1)			Amount of surfactant (X_2) (%) (Tween 20)	Addition of sonication time (X_3) (Min.)
	Lecithin (LC) (mg) X_a	Phosphatidylcholine (PC) (mg) X_b	Almond oil (AO) (mg) X_c		
SE-SLN1	150	0	150	10	10
SE-SLN2	0	150	150	10	10
SE-SLN3	150	50	100	10	10

SE-SLN4	50	150	100	10	10
SE-SLN5	150	100	50	10	10
SE-SLN6	50	100	150	10	10
SE-SLN7	100	150	50	10	10
SE-SLN8	100	50	150	10	10

Characterization of nanoparticles: Organoleptic properties of the nanoparticles like colour, odour and physical appearance were observed visually and recorded. Practical yield was calculated using the Eqn., PY (%) = amount of product obtained/ amount of total solid used (polymer+ drug) ×100.

Percent drug loading and entrapment efficiency (EE): Weighed samples of drug-loaded nanoparticles (10 mg) were dissolved in 10 ml of dichloromethane under sonication for 1 h. The samples were filtered through a membrane filter and analysed spectrophotometrically at 248 nm using a UV/Vis spectrophotometer (Shimadzu 1800). The percent drug loading and EE were determined using the below Eqns. All analyses were carried out in triplicate [9]. % drug loading = mass of drug in nanoparticles/mass of nanoparticles recovered × 100; % EE = mass of drug in nanoparticles/ mass of drug used in preparation×100.

Particle size analysis: Determination of mean average particle size of fenofibrate nanoparticles was carried out by using Malvern instrument ver. 6.12. The analysis was performed by adding 0.3 ml sample into the viewing unit dynamic light scattering is used to measure particle size and molecule size. The particle size analysis was performed at a scattering angle of 90° at room temperature. The diameter was averaged from three parallel measurements and expressed as mean ± standard deviation. This technique measures the diffusion of particles moving under Brownian motion, and converts it to size and a size distribution [10].

Zeta potential measurement: The analysis was performed by using the Malvern Zetasizer ver. 6.12 (Malvern instrument, UK) the electrophoretic mobility was converted to the zeta potential. To determine the zeta potential, nanoparticle samples were diluted with KCl (0.1 mM) and placed in electrophoretic cell where an electrical field of 15.2 V/cm was applied. All measurement was performed in triplicate [11].

In vitro drug release studies: The in-vitro release of drug from griseofulvin loaded SLNs was performed using treated dialysis membrane. The SLNs suspension in 1 mL quantity was poured to dialysis tube and sealed. The tube was transferred to a vial having 10 mL of phosphate buffer solution pH 6.4 mixed with 2% tween 80. The sample was subjected to a shaker apparatus maintained at 37±1°C. The speed of strokes was fixed at 5o min-1. The samples in 2 mL quantity from the vial were taken out at time hour of 0, 0.5, 1, 2, 4, 8, 12, 16, 20 &24h. The sink conditions were maintained by replacing the amount of sample with fresh media. The samples were analysed by UV spectroscopy method at 236 nm. The release of drug from SLNs was compared with the release of drug from pure drug suspension [12-13].

Table 2: Physicochemical evaluation of prepared nanoparticles

Formulation Code	Particle size (nm)	Layers	PDI	Zeta potential (mV)	Drug Entrapment (%)
SE-SLN1	155.13±1.11	Single	0.229±0.94	-20.01±0.91	61.25±0.6
SE-SLN2	154.21±1.07	Single	0.229±0.09	-20.11±0.89	63.05±0.8
SE-SLN3	152.11±1.05	Single	0.228±0.99	-20.09±1.01	65.12±1.2
SE-SLN4	130.12±1.06	Single	0.228±0.11	-20.03±0.91	62.75±0.2
SE-SLN5	152.99±1.08	Single	0.227±0.98	-20.18±0.91	64.15±0.3
SE-SLN6	150.18±1.15	Single	0.227±0.05	-21.08±1.01	68.32±1.2
SE-SLN7	130.21±1.12	Single	0.224±0.07	-22.12±1.08	71.81±0.9
SE-SLN8	130.88±0.95	Single	0.228±0.97	-21.98±1.15	79.03±0.9

Results and Discussion: After visual observation, the sample of fenofibrate was found to be a white and crystalline powder. The reported melting point of fenofibrate is in the range of 80 to 82° and the observed melting point was 81°, which confirmed purity of the drug. Practical yield, drug loading and EE were given in Table 2. Practical yield of the prepared nanoparticles was in the range of 49.00 ± 0.70 to 68.57 ± 1.00 %. The yield of nanoparticles decreased with increasing the concentration of drug and polymer ratio, which might be due to generation of stickiness by polymer lecithin. It was found that with increasing the amount of polymer, the actual drug loading and EE increased. The EE was found to be in the range from 61.25 ± 0.6 to 79.03 ± 0.3 %. It was observed that the drug content and encapsulation efficiency depend on the concentration of polymer, solvent ratio and stirring rate. On the basis of high yield, actual drug content and encapsulation efficiency batch F6 was observed as optimized batch for the preparation of nanoparticles.

The average particle size of nanoparticles was found to be 130.12±1.06 to 155.13±1.11 nm. The zeta potential is defined as the electrical potential between the medium and the layer of the fluid attached to the dispersed particles [16]. Zeta potential is a measure of the magnitude of the electrostatic or charge repulsion or attraction between particles and is one of the fundamental parameters known to affect stability. Zeta potential of prepared nanoparticles was found in range between -20.01±0.91 to -22.12±1.08 mV. It was found that higher the zeta potential less will be the particle aggregation, due to electric repulsion and hence more will be the stability of nanoparticles. The release of drug from SLNs was compared with the release of drug from pure drug suspension. The concentration of drug was calculated by extrapolating of curve and by making a graph between times versus % cumulative release.

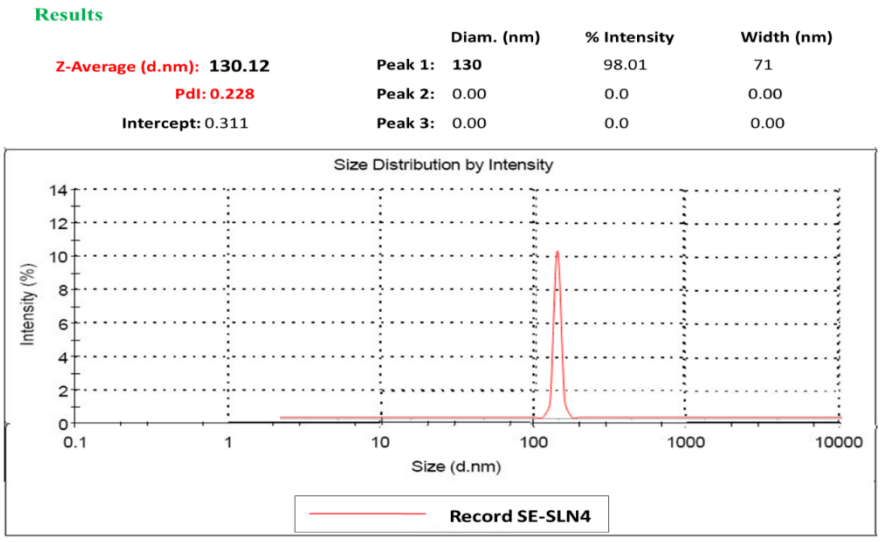

Figure 1: Particle size distribution & Polydispersity Index (PDI) of prepared andrographolide SLNs by solvent evaporation technique (SE-SLN4)

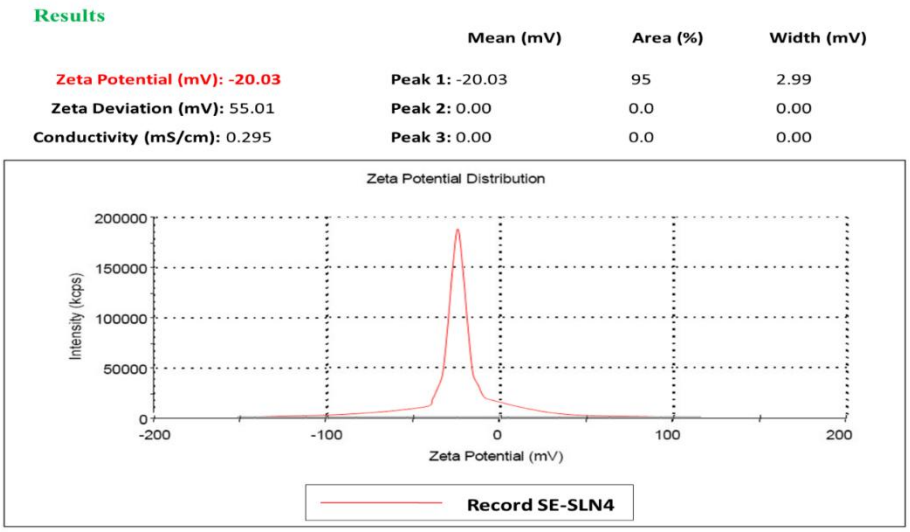

Figure 2: Zeta potential (mV) of prepared andrographolide SLNs by solvent evaporation technique (SE-SLN4)

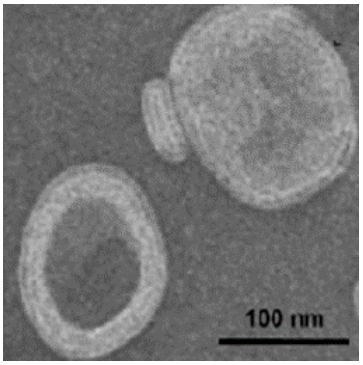

Figure 3: Particle shape of prepared andrographolide SLNs by solvent evaporation technique (SE-SLN4)

Summary and conclusion: It was observed that the solvent evaporation dispersion method was a useful method for the successful incorporation of the poor water-soluble drug Andrographolide with high entrapment efficiency. Furthermore, it could be presumed that if the nanometre range particles were obtained, the bioavailability might be increased. Hence, we can conclude that solid lipid nanoparticles provide controlled release of the drug and these systems are used as drug carriers for lipophilic drugs, to enhance the bioavailability of poorly water-soluble drugs through nanoparticles, as a drug delivery system. The Solid lipid nanoparticles were successfully developed for topical delivery of etoricoxib. SLN dispersions were prepared by melt emulsification and solidification at low temperature method. Physicochemical characterization including particle size, particle size distribution, Zeta potential. In-vitro drug release pattern of SLN showed control release. Immediate releases as well as sustained release both are of interest for topical application.

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