Design and Development of Solid Lipid Nanoparticles to enhance the oral absorbability of poorly soluble drugs in the special preference of Antihyperlipidemic drugs

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Abstract- **Evidently, oral delivery is recommended as the most practical drug administration method due to its many benefits over other delivery methods, including the absence of pain perception, ease of self-administration, and great patient compliance. The large array of commercially available medications are often given orally all over the world. The effectiveness of these medications depends on their oral absorbability, which in turn depends mostly on the physiological makeup of the gut and pharmacological characteristics. Drugs' ability to cross GI barriers is negatively impacted by several of its unfavourable properties, including poor hydrophobicity, low permeability, chemical instability, and excessive first-pass metabolism. The GI tract has membrane barriers that are biological, chemical, enzymatic, and physical that prevent poorly absorbed medications from being transported and working as intended. As a result, encapsulating the drug in and allowing it to absorb on the surface of the nanocarrier systems is one of the most promising methods for improving the absorption of these medications. These nanosystems serve as an intelligent means of transferring insoluble and poorly permeable compounds over obstacles. They could alter the way that medications loaded on nanoparticles move across membranes, thereby enhancing their ability to diffuse over obstacles in the intestinal mucosa. As an efficient replacement carrier to the conventional colloidal techniques, such as liposomes and polymeric particles, solid lipid nanoparticles (SLNs), a novel nanosized drug delivery technology, have been attracting increased interest. Solid lipid nanoparticles gaining interest in delivery of drugs which finds hurdles in absorption due to low solubility and poor oral absorption. The current investigations' goal was to use a novel lipid-based formulation called solid lipid nanoparticles to increase the oral bioavailability of a model medication from the antihyperlipidemic therapeutic category. The solid lipid nanoparticle may improve medicine oral bioavailability by bypassing the hepatic metabolism of the drug, increasing permeability through the lymphatic pathway.**

Keywords: **Solid lipid nanoparticles, hyperlipidemia, simvastatin, NDDS.**

1. INTRODUCTION

Hyperlipidemia is the medical term for high blood lipid and fat levels. Large lipoproteins are used to carry the lipids in the blood. According to their densities, the lipoproteins can be categorised into five main groups: chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). These fats include triglycerides, phospholipids, cholesterol, and its esters. These are crucial for our bodies to function, but high levels can lead to heart disease and stroke.[1, 2]

Drugs used to treat hyperlipidemia reduce cholesterol by blocking the biosynthesis process. The medications known as statins competitively block HMG-CoA reductase, lowering serum cholesterol levels. The enzyme that catalyses the conversion of 3-hydroxyl-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate during cholesterol production is known as 3-Hydroxyl-3-methyl glutaryl coenzyme reductase. These include fluvastatin, atorvastatin, rosuvastatin, pitavastatin, simvastatin, and pravastatin.[3]

Traditional colloidal carriers such emulsions, liposomes, and polymeric micro- and nanoparticles are inferior to solid lipid nanoparticles (SLNS) as a carrier system. For medications in BCS Classes II and IV, SLNs are made up of lipid and surfactant coatings. Surfactant coats the lipid solid core of the colloidal carrier, which has a range in size from 50 to 1000 nm. Solid lipid is used to replace the emulsions' liquid lipids. Surfactant must be in aqueous form, and the lipid matrix must be solid at body and room temperatures.[4, 5]

Because of their wide surface area and high drug loading, SLNs work better pharmaceutically. Because they are biodegradable and biocompatible, SLNs allow precise targeting and controlled drug delivery. SLNS can improve the oral bioavailability of a lipophilic medication. These SLNs exhibit a high lipophilic drug encapsulation efficiency.

Through the lymphatic system, the SLNS specifically targets M-cells, which are more vulnerable to hepatic metabolism. A possible alternative medication delivery technology that avoids hepatic metabolism is the SLN.[6]

2. EXPERIMENT

2.1 Materials

Selection of the excipients and process was done by pre-optimization studies and for the final batch and formulation optimization studies were performed. In pre-optimization studies selection of phospholipid, selection of solvent, selection of surfactant was done.

2.2 Method

2.2.1 Selection of lipid

Based on the particle size and PDI of the generated nanoparticles as well as the solubility of drag in different lipids, the lipid for the solid lipid nanoparticle formulation was selected. A number of lipids, including glyceryl monostearate, compritol 888 ATO, and stearic acid, were used to make the SLNs. The particle morphology was examined under the Leica microscope at 100 X with immersion oil while the particle size and PDI were measured using the Microtrac.[7, 8]

2.2.2 Selection of solvent

When selecting a solvent, factors including boiling point, solvent toxicity, and lipid and pharmaceutical solubility should all be taken into account. The fact that chloroform is soluble in lipids and drugs led to its selection as the standard solvent.[9]

2.2.3 Selection of surfactant

The surfactant for the solid lipid nanoparticles formulation was chosen based on the particle size and PDI of the generated nanoparticles. For this, three surfactants were selected.[10]

Table 1: Various surfactants used in formulation of solid lipid nanoparticles

S.No.	Surfactant	Particle size (nm)	PDI
1.	Polyvinyl alcohol	180	1.079
2.	Polaxamer-188	225	1.294
3.	Tween 80	258	2.946

Result: The smallest particle size and PDI of solid lipid nanoparticles were generated by polyvinyl alcohol. This surfactant was therefore chosen to produce the solid lipid nanoparticles.

2.3.4 Optimization of process parameters

Numerous processing elements that were optimised before the production technique was decided upon influence the way of making solid lipid nanoparticles.[11]

2.3.4.1 Optimization of sonication time

Particles are stirred up using ultrasonic sound energy frequencies. By boosting cavitational force, which causes lipid droplets to condense to nano size and increase surface area, sample sonication reduces particle size. The sonication's amplitude was maintained at 50%.

To calculate the sonication time, the particle size and PDI were employed. Table 2 makes mention of this.[12]

2.3.4.2 Optimization of high speed and high-pressure homogenization

When high shear homogenization is optimised, the rotating speed (rpm) and time are also taken into account. Based on the PDI and particle size of newly created solid lipid nanoparticles, this is done. It was initially used for high shear mixing to create pre-emulsions. The optimisation of pressure (in bars) and cycles (in repetitions) is necessary for high pressure homogenization. This process is necessary to convert the coarse emulsion into nanoscale particles while making SLNs. This is mentioned in Table 2.[13]

Table 2: Optimization of process parameter used in formulation of SLNs

S. No.	Sonication time (min.)	High speed homogenization (min)	High press. homogenization		Particle size (nm)	PDI
			Bar	Cycle		
1.	0	10	1000	3	434	4.831
2.	5	10	1000	5	357	2.734
3.	5	0	500	5	200	0.478

4.	3	10	1000	1	255	0.554
5.	7	10	500	3	600	1.338
6.	5	5	1000	3	434	1.729
7.	5	15	1000	5	385	1.653
8.	5	10	500	3	680	0.978
9.	3	10	1000	2	490	0.653
10.	3	10	1500	4	300	0.778
11.	5	10	1000	3	571	0.346
12.	5	10	1000	5	486	1.329
13.	5	10	500	1	256	1.076
14.	5	10	1000	5	396	2.963

Result: The lowest particle size and PDI of solid lipid nanoparticles were produced by the following process variables. A high shear homogenization time of 10 minutes at a speed of 5000 rpm, a sonication time of 15 minutes at 50% amplitude, a high-pressure homogenization bar (pressure) of 1000, and a cycle (repetition) of 5 were optimized for the preparation of solid lipid nanoparticles.

2.5 Preparation of simvastatin-loaded solid lipid nanoparticles

Simvastatin-loaded solid lipid nanoparticles were prepared by using the solvent emulsification-evaporation method. The phospholipid and drug (simvastatin) were dissolved in chloroform (organic solvent) and vortexed for 5 minutes to dissolve the drug and solid lipid completely in the solvent to get a homogenous transparent lipid solution that is immiscible with the aqueous phase. With the help of high speed-homogenizer, the prepared organic solution was emulsified with an aqueous phase. The oil in water emulsion was converted in to a coarse emulsion. To evaporate the organic solvent from the solution it was operated on rotatory evaporator (Buchi) at room temperature and decreased pressure on 100 RPM ± 10. The dry product was collected ina petridish to evaporate the remaining moisture at room temperature. Then it is filled in a vial and packed with rubber stopper and aluminium seal.[14, 15]

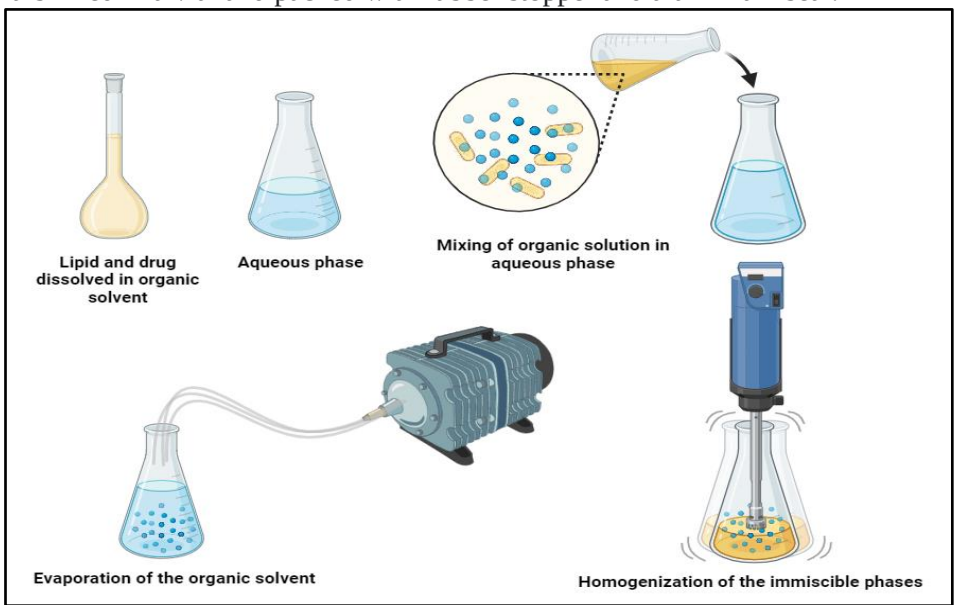

Fig. 1: Solvent emulsification and evaporation method for the preparation of SLN

2.6 Characterization of simvastatin loaded solid lipid nanoparticles

To guarantee the quality of the SLNs, it is necessary to characterise them appropriately and correctly. Characterization of SLN is a key issue due to the dynamic nature of the delivery system, however this is due to the complexity and colloidal structure of the particles. Some of the critical parameters examined for SLNs include particle size, size distribution kinetics (zeta potential), degree of lipid modification and crystallinity (polymorphism), coexistence of

additional colloidal structures (miscelles, liposomes, super-cooled melts, drug nanoparticles), time scale of distribution processes, amount of drug present, in-vitro drug release, and surface morphology.[16]

2.6.1 Particle size distribution

Mean particle size and PDI were determined using nanotrac wave (Microtrac (SA) using water as a dispersion medium.

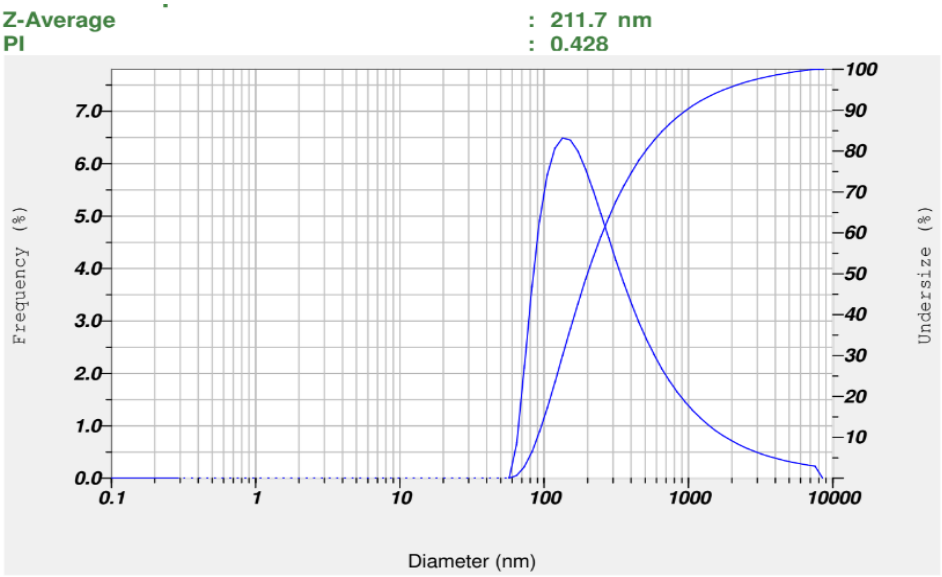

Fig. 2: Particle size distribution of optimized.36 SIM-SLN formulation

Result and conclusion: When evaluated experimentally, the size of the solid lipid nanoparticles was discovered 211.7 nm, with a PDI of 0.428, which was consistent with the expected value.

2.6.2 Microscopic studies

Figure 3 depicts the results of examining samples of the improved solid lipid nanoparticle formulation under a 100 X Leica microscope with an oil immersion lens.

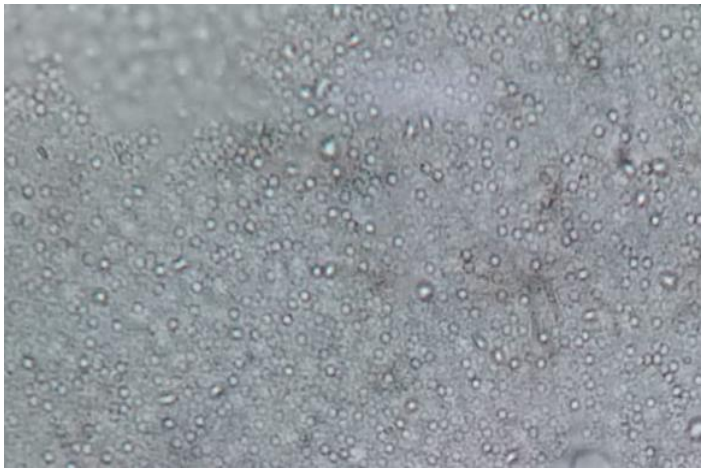

Fig. 3: Optical microscopy of optimized SIM-SLN

2.6.3 Transmission electron microscopy

In a TEM Philiphs CM 200, 20-200 kV)) the SIM-SLN was morphologically investigated. The solid lipid nanoparticle dispersion was 100-fold diluted with filtered water. A 20-ul aliquot was placed on a copper grid that had been carbon-coated and air-dried for ten minutes. Her paper was used to absorb the extra mixture, and phosphotungustic acid (w/v) was employed to colour the sample. After the sample dried for two hours in the air, the excess reagent was removed using the filter paper in fig. 4.

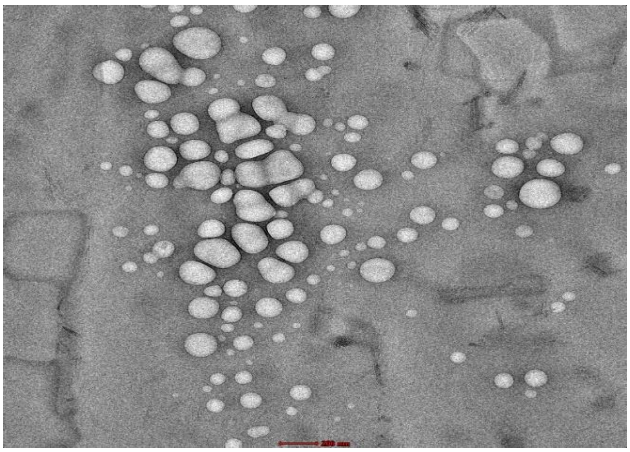

Fig. 4: TEM image of Simvastatin loaded SLN

2.6.4 Differential scanning calorimetry

A differential scanning calorimeter (Perkin Elmer DSC 6000) calibrated with indium was used to conduct differential scanning calorimetry (DSC) testing. Simvastatin, comprito 888 ATO pellets, and simvastatin solid lipid nanoparticle samples were all subjected to DSC analysis. The studies used 3-5 mg samples that were sealed in common aluminium pans. Thermograms were recorded at a scanning rate of 10° C/min. At temperatures ranging from 50 to 200°C, each sample was scanned. The temperature with the highest excess heat capacity was determined to be the phase transition temperature.

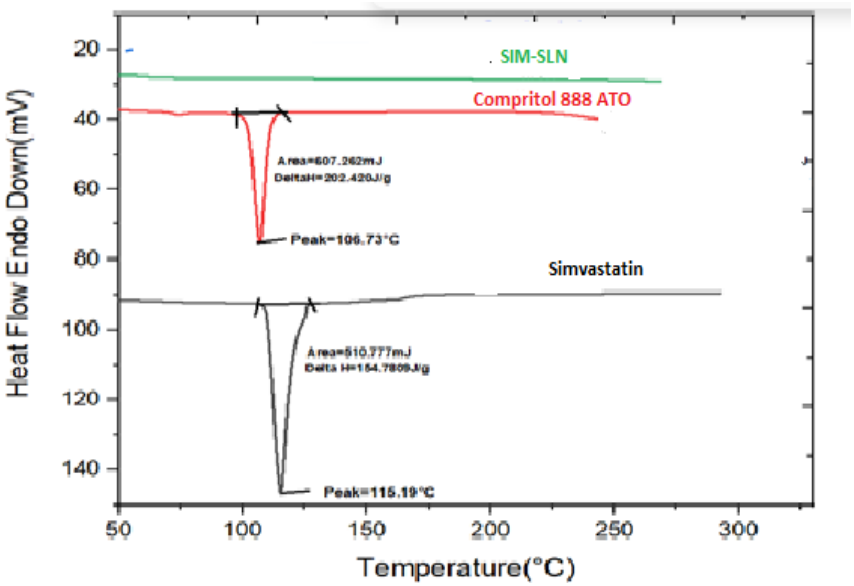

Fig. 5: DSC overlay of Simvastatin, compritol 888 ATO pellets and Simvastatin loaded solid lipid nanoparticles

Result and conclusion: Simvastatin, compritol 888 ATO pellets, and SIM-solid lipid nanoparticles DSC thermograms are shown in Figure 19. The DSC melting thermogram's endotherm is 117.18°C. The transformation of the medicine into an amorphous form and the uniform distribution of the medication in solid lipid nanoparticles were both confirmed by the lack of a crystalline peak in the formulation of the particles.

2.6.5 Entrapment efficiency

SIM-SLN suspension centrifuged for 15 minutes at 5,000 rpm. A UV- Visible Spectrophotometer (Shimadzu 1700) set at 238 nm was used to measure the medication content in the supernatant. By deducting the amount of untrapped drug from the total amount of drug added, the amount of drug that was entrapped was determined. In order to calculate the % entrapment efficiency, the formula shown below was used:[17]

Entrapment efficiency was determined by the formula:

$$\%\textbf{Entrapment efficiency} = \frac{\textbf{Actual drug content}}{\textbf{Theoritical drug content}} \times \mathbf{100}$$

Result and conclusion: At 15 mg simvastatin concentration, the encapsulation efficiency of the prepared Simvastatin SLN was 67.42 %, which was close to the predicted value.

2.6.6 Determination of drug content

The SLN particle carrying 10 mg of Simvastatin equivalent was weighed and dissolved in 100 ml of 10% methanol. The drug content was determined using a UV/Visible spectrophotometer (Shimadzu 1700) at 229 nm in comparison to a blank.

The drug content was determined by the following formula:

$$\%\textbf{Drug content} = \frac{\textbf{Actual amount of drug}}{\textbf{Theoritical amount of drug}} \times \textbf{100}$$

Result and conclusion: Drug content of the optimized SIM-SLN formulation was found to be 112 %

2.6.7 In-vitro drug release studies

Utilising the dialysis B method, an in-vitro release investigation of the produced solid lipid nanoparticle was conducted in 200 ml of pH 6.8 phosphate buffers at 37+0.5 °C and 300 rpm. For the investigation, MWCO-12000-14000 kDa (Himedia) dialysis membrane was used. SIM-SLN, equivalent to five mg of calcium atorvastatin, was introduced to the dialysis bag along with phosphate buffer, pH 6.8, and both end membranes were cut. At various time intervals, 5 ml samples were removed and replaced with an equivalent volume of new buffer. The samples were examined using a blank pH buffer solution and a Shimadzu 1700 UV-Visible spectrophotometer at 238 nm. The studies were all completed in duplicate.[18]

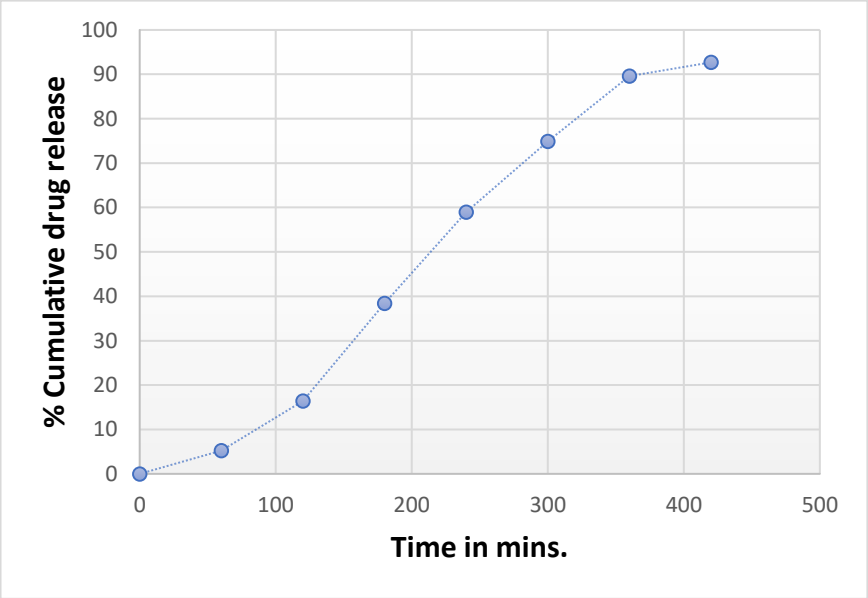

Fig. 6: In-vitro drug release of optimized SIM-SLN formulation in phosphate buffer (pH 6.8)

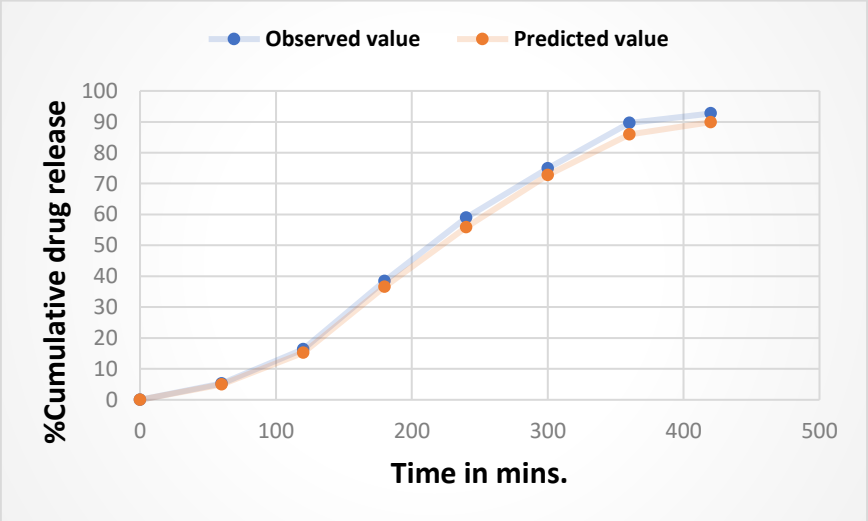

Fig. 7: Comparative release profile of predicted and observed formulation of SIM-SLN

Result and conclusion: When it was tested experimentally, the percentage cumulative drug release was determined to be 91.66 % in 8 hours, which was close to the projected number.

3. CONCLUSION

The solid lipid nanoparticle drug delivery technology can be employed as a solution to improve drug oral bioavailability and address the problems brought on by low drug oral bioavailability. One of the most extensively utilised techniques for improving oral bioavailability is the use of solid lipid nanoparticles. For the selection of process parameters optimization studies were done in which optimization of sonication time, optimization of high speed and high-pressure homogenization were performed. The lowest particle size and PDI of solid lipid nanoparticles were produced by the following process variables. A high shear homogenization time of 10 minutes at a speed (rpm) of 5000, a sonication time of 5 minutes at 50% amplitude, a high pressure homogenization bar (pressure) of 1000, and a cycle (repetition) of 5 were optimised for the creation of solid lipid nanoparticles. The simvastatin loaded solid lipid nanoparticles loaded were prepared by emulsification-ultrasonication method by selected quantity of excipient and drug from the optimization studies. Characterization studies were conducted to evaluate the solid lipid nanoparticles properties included particle size, entrapment efficiency, drug loading, and in-vitro drug release. Particle size was found to be 211.7 nm with PDI 0.428, Microscopic image confirmed that simvastatin loaded solid lipid nanoparticles were formed when it was observed under the microscope. The shape and vesicles were confirmed by the TEM and results confirmed the preparation of SIM loaded SLN. In the DSC evaluation the DSC melting thermogram's endotherm is 117.18°C. The transformation of the medicine into an amorphous form and the uniform distribution of the medication in solid lipid nanoparticles were both confirmed by the lack of a crystalline peak in the formulation of the particles. Entrapment efficiency was determined by ultracentrifuged method. At 15 mg simvastatin concentration, the encapsulation efficiency of the prepared Simvastatin SLN was 67.42 %, which was close to the predicted value. Drug content of the optimized SIM-SLN formulation was found to be 112 %. In-vitro drug release studies were done by dialysis bag method, when it was tested experimentally, the percentage cumulative drug release was determined to be 91.66 % in 8 hours, which was close to the projected number. As a result, the findings suggest that a solid lipid nanoparticle drug delivery method for simvastatin can be created to improve its oral bioavailability.

4. SOURCE OF SUPPORT

Nil

5. CONFLICT OF INTEREST

I hereby declared that there is no conflict of interest, financially and otherwise. All the work done is original.

REFERENCES:

1. Stewart, J.; McCallin, T.; Martinez, J.; Chacko, S.; Yusuf, S. J. P. i. r., Hyperlipidemia. **2020,** *41* (8), 393-402.
2. Eaton, C. B. J. P. c. c. i. o. p., Hyperlipidemia. **2005,** *32* (4), 1027-1055.
3. Shelke, S.; Khairnar, A.; Rathod, V.; Kalawane, Y.; Jagtap, A. J. I. J. P. P. S., Reviw on antihyperlipedemia lipophilic drugs and their novel formulation approaches. **2017,** *9*, 1-8.
4. Aungst, B. J. J. J. o. p. s., Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. **1993,** *82* (10), 979-987.
5. Duan, Y.; Dhar, A.; Patel, C.; Khimani, M.; Neogi, S.; Sharma, P.; Kumar, N. S.; Vekariya, R. L. J. R. a., A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. **2020,** *10* (45), 26777-26791.
6. Gustafson, H. H.; Holt-Casper, D.; Grainger, D. W.; Ghandehari, H. J. N. t., Nanoparticle uptake: the phagocyte problem. **2015,** *10* (4), 487-510.
7. Lingayat, V. J.; Zarekar, N. S.; Shendge, R. S. J. N.; Research, N., Solid lipid nanoparticles: a review. **2017,** *4* (2), 67-72.
8. Luo, C.-F.; Yuan, M.; Chen, M.-S.; Liu, S.-M.; Zhu, L.; Huang, B.-Y.; Liu, X.-W.; Xiong, W. J. I. J. o. P., Pharmacokinetics, tissue distribution and relative bioavailability of puerarin solid lipid nanoparticles following oral administration. **2011,** *410* (1-2), 138-144.
9. Mehnert, W.; Mäder, K. J. A. d. d. r., Solid lipid nanoparticles: production, characterization and applications. **2012,** *64*, 83-101.
10. Müller, R. H.; Mäder, K.; Gohla, S. J. E. j. o. p.; biopharmaceutics, Solid lipid nanoparticles (SLN) for controlled drug delivery–a review of the state of the art. **2000,** *50* (1), 161-177.
11. Musielak, E.; Feliczak-Guzik, A.; Nowak, I. J. M., Optimization of the conditions of solid lipid nanoparticles (SLN) synthesis. **2022,** *27* (7), 2202.
12. Naguib, Y. W.; Rodriguez, B. L.; Li, X.; Hursting, S. D.; Williams III, R. O.; Cui, Z. J. M. p., Solid lipid nanoparticle formulations of docetaxel prepared with high melting point triglycerides: in vitro and in vivo evaluation. **2014,** *11* (4), 1239-1249.
13. Raj, S. B.; George, P. S. G.; Kavitha, K.; Reddy, K. B., formulation and in vitro evaluation of convoline (convolvulus pluricaulis) solid lipid nanoparticles.

14. Rohit, B.; Pal, K. I. J. C. N., A method to prepare solid lipid nanoparticles with improved entrapment efficiency of hydrophilic drugs. **2013,** *9* (2), 211-220.
15. Schubert, M.; Müller-Goymann, C. J. E. j. o. p.; biopharmaceutics, Solvent injection as a new approach for manufacturing lipid nanoparticles–evaluation of the method and process parameters. **2003,** *55* (1), 125-131.
16. Trotta, M.; Debernardi, F.; Caputo, O. J. I. j. o. p., Preparation of solid lipid nanoparticles by a solvent emulsification–diffusion technique. **2003,** *257* (1-2), 153-160.
17. Xie, S.; Pan, B.; Wang, M.; Zhu, L.; Wang, F.; Dong, Z.; Wang, X.; Zhou, W. J. N., Formulation, characterization and pharmacokinetics of praziquantel-loaded hydrogenated castor oil solid lipid nanoparticles. **2010,** *5* (5), 693-701.
18. zur Mühlen, A.; Schwarz, C.; Mehnert, W. J. E. j. o. p.; biopharmaceutics, Solid lipid nanoparticles (SLN) for controlled drug delivery–drug release and release mechanism. **1998,** *45* (2), 149-155.