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BIOAVAILABILITY ENHANCEMENT AND CHARACTERIZATION OF POORLY WATER-SOLUBLE DRUG

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ABSTRACT: Objectives: Lovastatin is an antilipidemic medication categorised as a statin, which exhibits limited absorption when taken orally owing to its low solubility and inconsistent dissolution rate. The primary objective of this research was to improve the drug's solubility and dissolving rate, as well as gain insight into its oral bioavailability. **Materials and Methods:** A precipitation-ultrasonication process was used to formulate Lovastatin nanosuspensions, with PVP k30, PEG 6000, and Tween 80 serving as stabilisers. The nanosuspensions that were created were analysed to determine their polydispersity index (PDI), particle size, surface shape, zeta potential, and *in-vitro* release rate. **Results:** The optimised formulation exhibited a particle size of 185±0.56 nm, a zeta potential of -27.8 mV, and a PDI of 0.042±0.32, indicating excellent stability. The morphological analysis revealed that the particles had nanoscale dimensions. The drug content was determined to be within the range of 73-94%. The in vitro analysis demonstrated a significantly accelerated drug release within a one-hour timeframe. Stability investigations revealed that the optimised formulation P2 exhibited greater stability when stored at a temperature of 4°C. **Conclusion:** The formulated lovastatin nanosuspension exhibited enhancements in solubility, dissolving rate, and oral bioavailability when compared to both the pure drug and its commercially available version. Therefore, the use of lovastatin nanosuspension has the potential to enhance the absorption of lovastatin when taken orally.

INTRODUCTION: Approximately one-third of the molecules now under development in the pharmaceutical sector are characterised by low water solubility. Solubility, particularly in aqueous systems, is a crucial characteristic of a medicinal ingredient [1].

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The solubility and dissolving characteristics of a medicine play a crucial role in determining its oral bioavailability. The low solubility rates of these medicines restrict their bioavailability.

Enhancing the capacity of poorly soluble medications to be absorbed by the mouth is still a very difficult objective in the field of drug research. Various strategies have been investigated to address the issue of low solubility. Reducing the size of particles from microns to nanometers leads to a substantial augmentation in surface area and the corresponding rate of dissolution [2].

Nanosuspensions are colloidal dispersions of drug particles, with a particle size below one micron, suspended in a liquid phase. Nanoparticle engineering facilitates the formulation of nanosuspensions containing poorly soluble medicines, either on their own or in combination with pharmaceutical excipients [3].

A nanosuspension refers to a liquid phase containing solid drug particles that are dispersed in a colloidal manner, with a particle size less than 1 µm and an average particle size ranging from 200 to 600 nm [4]. The composition comprises only of the active pharmaceutical ingredient and stabilising agents, such as surfactants or polymers. Their diminutive particle size enables efficient delivery of medication molecules to cells, resulting in an optimal therapeutic impact and minimised negative consequences [5]. Nanosuspension technology offers many advantages for delivering poorly soluble medications, including enhanced drug dissolving rate, higher absorption rate and extent, and therefore improved therapeutic bioavailability.

Although there have been advancements in understanding this subject, nanosuspensions are still hindered by the issue of instability resulting from nucleation and particle development. Ostwald ripening is a phenomenon where the high surface energy of nano-sized particles causes them to aggregate when there is no stabiliser present [6]. Stabilisers must become moist, meaning they gather at the boundary between the drug particles to create ionic or steric obstacles. The choice and quantity of stabiliser significantly impact the physical stability and behaviour of nanosuspensions in living organisms. The stabilisers that have been investigated so far include poloxamers, cellulose derivatives, lecithins, polysorbates, and povidone [7].

Considering these principles, the medication lovastatin (LA), which has low solubility, was prepared as a nanosuspension. The chemical structure of LA, as seen in **Fig. 1**, indicates that it is a medication with low solubility in water. It is classed as class II according to the Biopharmaceutics Classification System (BCS). LA is a member of the statin class of pharmaceuticals and is well recognised as one of the most potent medications for reducing cholesterol levels[8]. Lactic acid blocks the production of cholesterol by inhibiting the enzyme "3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase" [9, 10]. Furthermore, LA demonstrated the capacity to reduce the concentration of low-density lipoprotein (LDL), while leaving the level of high-density lipoprotein unchanged. Multiple studies have shown that LA has decreased the death rate associated with coronary heart disease [11-13]. While the oral administration of LA is often used, it typically exhibits low oral bioavailability as a result of its limited solubility [14].

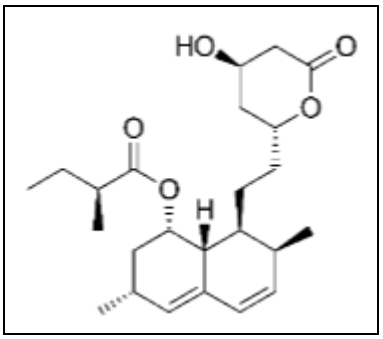

FIG. 1: LOVASTATIN

Various strategies have been used in the scientific literature to enhance the solubility and absorption of lovastatin in water. These include the development of nanostructured drug delivery systems. For example, Jun and Daxin [15], Sunil *et al.*[16], and Gande *et al.*[17] developed stabilised self-emulsifying drug delivery systems using NLC, hydrogel, and solid lipid nanoparticles (SLN) respectively, to improve the bioavailability and solubility of lovastatin. However, there is no comparative data available to demonstrate how their formulations enhance the bioavailability of the drug compared to the already existing marketed product. In this work, lovastatin nanosuspensions were made utilising the ultrasonication technique and several stabilisers including PVP k30, PEG 6000, and Tween 80. The characterization of nano-sized lovastatin included particle size measurement, scanning electron microscopy (SEM) imaging, dissolution test, FTIR, and differential scanning calorimetry (DSC).

MATERIAL AND METHODS:

Materials: A free sample of lovastatin was obtained from Lupin Pharmaceuticals in Goa. PVP k-30, PEG 6000 and Tween 80 were provided by Rankem, Mumbai. Chloroform, Acetone, Ethanol,

and Methanol were purchased from Molychem, Mumbai.

Formulation of Lovastatin Nanosuspension: A nanosuspension was generated using the precipitation-ultrasonication technique. The medication was solubilized in methanol using sonication for 5 minutes at ambient temperature. A variety of stabilisers were dissolved in water to produce a range of antisolvent solutions. Both solutions were filtered using a 0.45µm filter. The antisolvent was chilled to a temperature of 3°C using an ice-water bath. Next, a medication solution was rapidly administered using a syringe, with the needle inserted immediately into a stabiliser solution inside 50 ml of the pre-chilled antisolvent. This was done at various stirring speeds using an overhead stirrer, allowing the volatile solvent to evaporate naturally at room temperature for a duration of 4-5 hours. Following the precipitation of the antisolvent, the sample was promptly transferred to a test tube and subjected to ultrasonic treatment for varying durations (in minutes). The 6 mm diameter probe was submerged in the liquid, causing the wave to propagate downwards and then bounce back upwards. The nanosuspension preparation used a batch size of 50 ml.

Characterization of Formulated Nanosuspensions:
Particle Size, Zeta Potential, and Polydispersity Index: The particle size analyzer used to determine these characteristics was the Delsa Nano C, manufactured by Beckman Coulter Counter in the USA. The analysis was conducted at a 90° angle relative to the incoming beam, using the N4 Plus software. The nanosuspensions underwent analysis to determine their particle size and polydispersity index. The zeta potential was calculated by measuring the electrophoretic mobility of particles in an electrical field using the same device. The analysis of all samples was conducted three times.

Drug Entrapment Efficiency: A volume of 10 millilitres of nanosuspension was subjected to centrifugation at a speed of 5000 rpm for 20 minutes. The liquid portion of the solution was passed through a filter to separate it from any solid particles. A volume of one millilitre of these filtrates was mixed with water and the absorbance at the maximum wavelength (λ max) was measured using a UV spectrophotometer, using water as the reference [18]. The quantity of unbound medicines in the formulations was quantified, and subsequently, the entrapment efficiency was computed.

%EE = Total drug content – Free dissolve drug / Drug amount used × 100

Fourier Transform Infrared Spectroscopy (FT-IR): The FT-IR study was performed to examine potential chemical bond interactions between the medication and excipients. The FT-IR spectra was obtained using a "Shimadzu 8400 spectrophotometer". The materials were analysed within the spectral range of 4000 to 400 cm-1. The solid powder sample was dehydrated in an oven at around 300^{o}C, pulverised, combined with potassium bromide at a weight ratio of 1:10, and compressed at a pressure of 15000 psig. The resulting disc was then subjected to scanning.

Differential Scanning Calorimetry (DSC): The thermal properties of LA and optimized formulation were analysed using DSC using a Mettler Toledo instrument from Switzerland. For the analysis of aluminium pans, 5 mg samples were subjected to heating at a scanning rate of 10°C per minute throughout the temperature range of 40–200°C. This process was carried out under a nitrogen flow rate of 50 mL per minute.

Saturation Solubility: The saturation solubility of the nanosuspension was evaluated by putting it in a vial and subjecting it to continuous stirring for 48 hours using a magnetic stirrer set at 100 RPM, with the aim of achieving saturation. Afterward, a 2-milliliter quantity of nanosuspension was transferred into an eppendorf tube and centrifuged at a rate of 10,000 revolutions per minute for 30 minutes. The liquid portion was passed through a 0.2µm syringe filter and examined using a "UV-visible spectrophotometer [UV-1800, Shimadzu, Japan]" at the wavelength where the medication absorbs the lightest. The liquid was appropriately diluted with the same liquid used as a reference. Each sample was analysed three times. The saturation solubility was determined by using the calibration curve [19].

***In-vitro* Drug Release Study:** The *in-vitro* drug release of formulations was conducted utilising the dialysis bag diffusion method. A precisely

measured amount of nanosuspension (approx. 10 mg of the drug) was put into a dialysis bag, which was then securely sealed. Subsequently, the bag was hung for a duration of 1 hour in a container holding 900 mL of phosphate buffer with a pH of 6.8. At predetermined intervals, 5 mL portions of the material were extracted from the compartment, and an equal volume was replenished with new buffer. The material was analysed using spectrophotometry by measuring the absorbance at 238 nm after appropriate dilution [20].

Short Term Stability Studies: The optimised formulation underwent stability testing following the rules set by the International Council on Harmonisation (ICH). The formulation underwent exposure to different temperature and relative humidity settings, namely 4°C/65% RH and 25°C/65% RH, for a duration of three months in a humidity-controlled oven. The samples were collected and assessed for particle dimensions and the percentage of medication released throughout time, namely at intervals of 0, 1, 2, and 3 months.

RESULTS: Nanosuspension technology is a promising method for formulating medications with low water solubility, such as lovastatin. The precipitation-ultrasonication method is a widely used technique for producing nanosuspensions in laboratory settings. Due to the need of minimum equipment and fewer chemicals, the manufacturing of nanoparticles using this approach is considered more inexpensive. Six formulations were produced using PVP k30, PEG 6000, and Tween 80 as stabilisers.

Particle size Analysis: The evaluation of particle size of the formulations was done using SEM. The particle size in a nanosuspension is a crucial factor as reduced particle size increases the surface area, leading to an enhanced rate of dissolution [21]. When the size of particles reduces to the nano scale, the solubility of medications which are water insoluble improves significantly. The outcomes of the experiment are shown in **Table 1.**

Polydispersity Index (PDI): The PDI quantifies the range of particle sizes, spanning from 0 to 1. A sample is considered monodisperse when the PDI value approaches zero. A PDI score below 0.2 is considered indicative of a limited size distribution. The table 1 displays the PDI values for all the formulations. However, a polydisperse distribution is regarded to occur when the PDI value exceeds 0.2[22]. Within the generated nanosuspension formulation, P1 and P2 exhibited a uniform size distribution with PDI values of 0.29 and 0.042, respectively. P3, P4, P5, and P6 had distributions of particle sizes with varying degrees of heterogeneity, as indicated by their respective PDI values of 0.66, 0.53, 0.81, and 0.48.

Zeta Potential: The zeta potential significantly influenced the storage stability of the colloid dispersion system by creating electrostatic barriers that prevented the nanoparticles from aggregating and agglomerating [23]. In order to ensure the physical stability of a nanosuspension, it is typically recommended to have a zeta potential of at least -30 mV for systems that are stabilised by electrostatic forces, or -20 mV for systems that are stabilised through steric forces. The current investigation determined that the lovastatin nanosuspension exhibited negative zeta potential values ranging from -1.67 to -26.9 mV (as shown in **Table 1**). The formulation (P2) exhibited a negative side and had a value of -27.8, indicating that the chosen strategy for development and optimisation resulted in a stable nanoformulation.

TABLE 1: PARTICLE SIZE, PDI, ZETA POTENTIAL AND DRUG ENTRAPMENT EFFICIENCY OF ALL FORMULATIONS

S. no.	Formulation Code	Particle size (nm)	PDI (Mv)	Zeta potential (mV)	Drug entrapment efficiency (%)
1	P1	310 ± 0.23	0.29 ± 0.02	-22.9 ± 0.02	80.45±0.01
2	P2	185 ± 0.56	0.042 ± 0.32	-27.8 ± 0.12	94.75 ± 0.62
3	P3	389 ± 0.66	0.66 ± 0.23	-19.5 ± 0.32	78.56±0.72
4	P4	195 ± 0.42	0.53 ± 0.42	-9.5 ± 0.15	88.26± 0.86
5	P5	285 ± 0.12	0.81 ± 0.63	-23.2 ± 0.15	93.48±0.10
6	P6	210 ± 0.02	0.48 ± 0.35	-19.8 ± 0.05	73.69±0.73

Drug Entrapment Efficiency: Table 1 shows the computed % drug entrapment efficiency for each formulation. P2 exhibited a high lovastatin entrapment effectiveness (94.75 ± 0.62%) in

comparison to other nano formulations. The reason for this might be because the surfactant lessens the tension that exists between the aqueous phase and the polymer. The most important aspect affecting entrapment efficiency is the stabiliser concentrations utilised.

Saturation Solubility Studies: Determining the solubility of a medication in different pH medium is essential for drug development since it provides a comprehensive understanding of the drug's behaviour in different pH media. The solubility of lovastatin nanosuspension (P2) was improved, measuring 152.32 ± 0.11 mg/L. The produced nanosuspension's solubility is shown in **Table 2.**

TABLE 2: SATURATION SOLUBILITY OF FORMULATED NANOSUSPENSIONS

S. no.	Formulation code	Absorbance at 290 mg/L
1	P1	132.65 ± 0.12
2	P2	152.32±0.11
3	P3	124.30±0.02
4	P4	101.36± 0.86
5	P5	93.48±0.10
6	P6	75.65±0.73

SEM Images: The SEM image of the optimised formulation P2 **Fig. 2** indicated that the particles had a spherical morphology and were uniformly dispersed.

The particle size was determined to be 185 ± 0.56 nm, which closely matched the value obtained from the particle size analyzer.

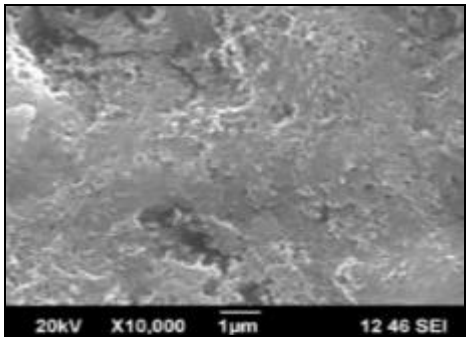

FIG. 2: SEM IMAGE OF P2 NANOSUSPENSION

***In-vitro* Drug Release Studies: Fig. 3** illustrates the results of a drug release study conducted in a phosphate buffer (pH 6.8) for a duration of 1 hour. The findings showed that formulation P2had the highest release rate owing to its smallest particle size. The percentage of medication released after 1 hour for the optimised formulation was 92.83%, whereas for the pure drug formulation it was 39.73%. This is due to the inverse relationship between particle size and surface area, where smaller particles have a higher surface area. Therefore, the medicine that is located at or in close proximity to the surface may be readily released.

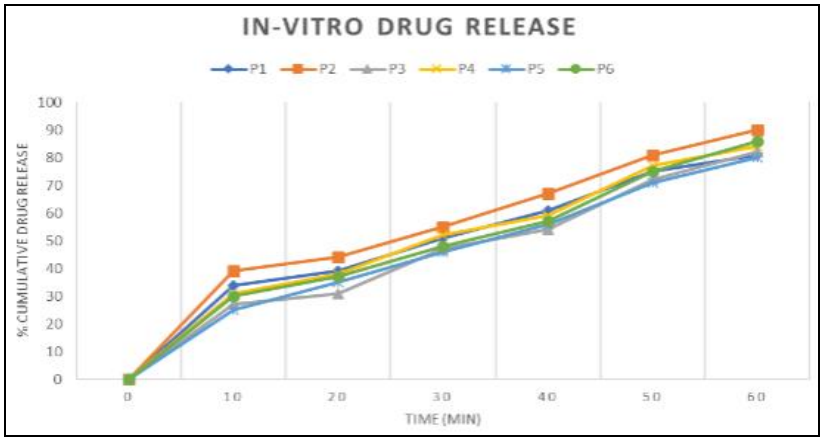

FIG. 3: *IN-VITRO* DRUG RELEASE PROFILE FOR LOVASTATIN NANOSUSPENSIONS

FTIR: Fig. 4 displays the FTIR spectrum of pure LA, as well as the excipients and optimised formulations mentioned earlier. The spectrum of LA exhibited prominent peaks at 1050 cm^{-1} and 1275 cm^{-1}, attributed to the ester C-O-C and lactone bending vibrations. Additionally, another peak was seen at 2930 cm^{-1}, representing the existence of methyl and methylene C-H stretching. Additional peaks were seen while using an optimised formulation, perhaps attributed to the presence of polymers. Spectroscopic analysis showed that the addition of LA to the nanoparticles did not modify the characteristics of their functional groups. Therefore, it verifies the composition of the medication.

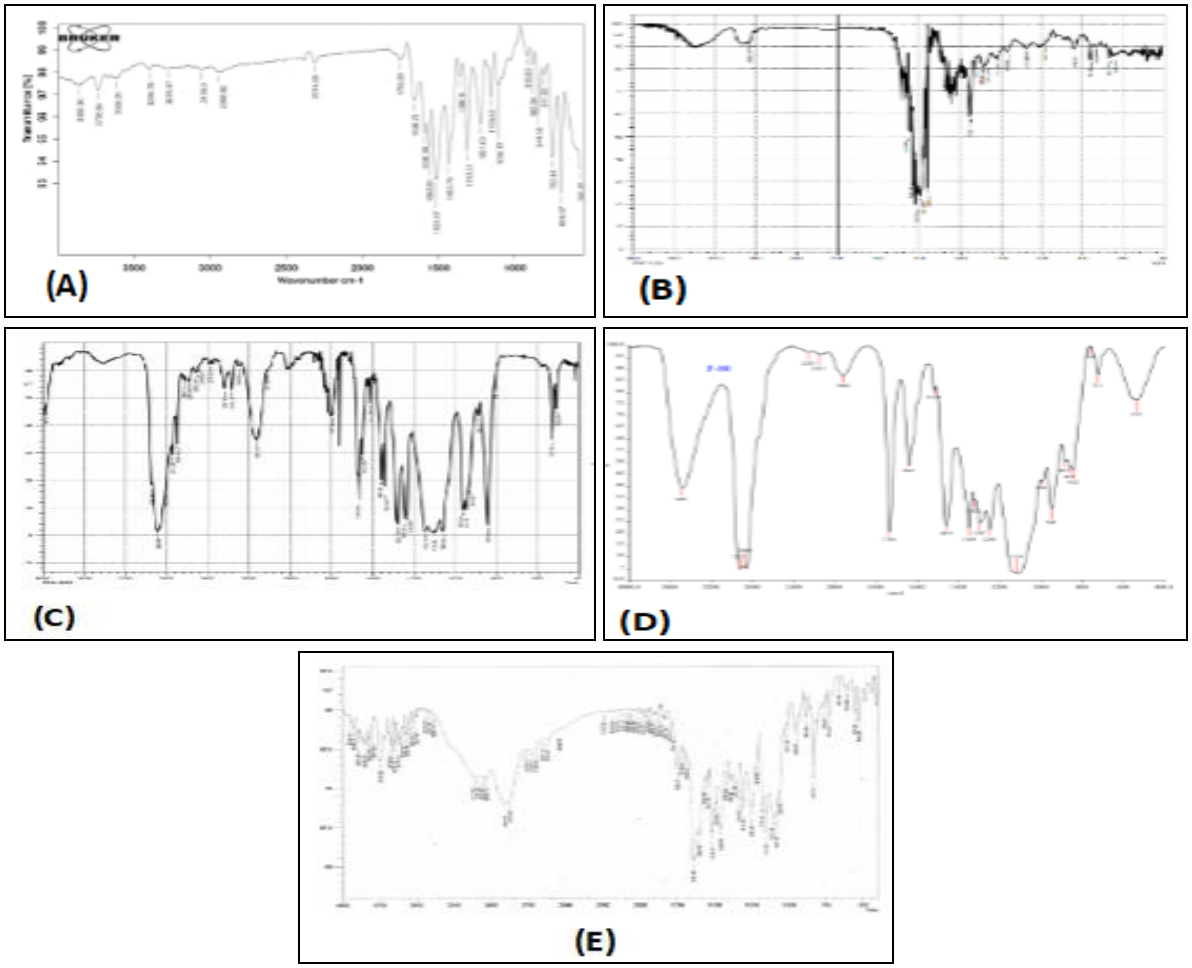

FIG. 4: IR SPECTRA OF A) PURE LOVASTATIN, B) PVP- K30, C) PEG 6000, D) TWEEN 80, E) OPTIMIZED FORMULATION P2

Thermal Analysis: DSC was used to examine the impact of a surfactant on the internal composition of lovastatin nanosuspension. **Fig. 5** displays the DSC thermograph of both the pure lovastatin powder and the optimised nanosuspension formulation. The lovastatin powder exhibited a melting exotherm at a temperature of 174.31°C, which aligns with its melting point. In the formulation, the exotherm was seen at a somewhat lower temperature of 166.95°C. The thermograms indicated that there was no interaction between the medication and the surfactant [24].

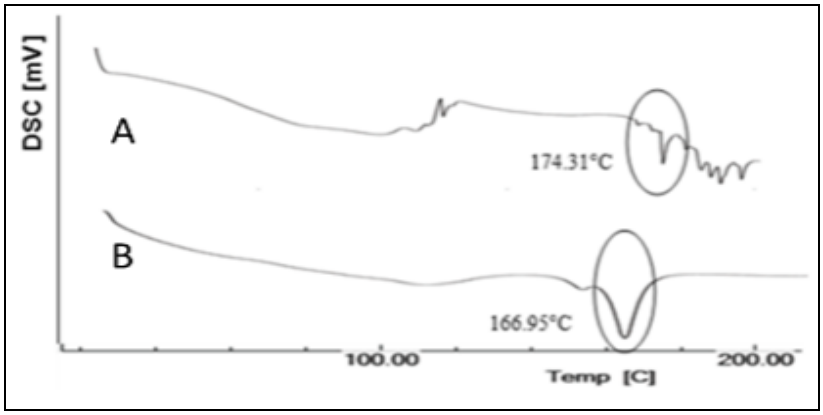

FIG. 5: DSC THERMOGRAMS OF [A] PURE LOVASTATIN [B] OPTIMIZED NANOSUSPENSION OF LOVASTATIN (P2)

Stability Studies: Utilising physiochemical analyses, including assessments of PDI, particle size, *in-vitro* release experiments, and drug content %, the lovastatin formulation (P2) was chosen for

expedited stability investigations. The sample held at a temperature of 4°C demonstrated excellent stability due to the very low temperature. At this particular temperature, the lovastatin's ability to dissolve decreased, resulting in a higher amount of super saturation and quick formation of nuclei.

As the number of nuclei rose, the concentration of solute on each nucleus decreased, resulting in a reduced potential for the formation of smaller crystals. In addition, low temperature reduces the rate of diffusion and growth kinetics at the specific boundary layer contact [25]. The particle size exhibited a small increase in both the formulation at ambient temperature and the formulation at 40°C.

The *in-vitro* dissolution profile data of the nanoformulation demonstrates that the solubility rates of lovastatin were adequate in both 0.1N HCl. The medication content surviving after three months was exceptional. The aforementioned statistics were documented in **Table 3.**

TABLE 3: STABILITY STUDY OF OPTIMIZED LOVASTATIN NANOSUSPENSION

Formulation	Temperature condition at storage	Initial particle size (nm)	Particle size after 3 months (nm)
P2	4°C	81.34 ± 89.96	185.64 ± 5.34
	Room temperature		187.78 ± 20.40
	40°C		191.15 ± 19.06

CONCLUSION: This research aimed to create a novel nanosuspension formulation to enhance the oral absorption and bioavailability of lovastatin. The precipitation-ultrasonication approach was used to enhance the therapeutic effectiveness of LA. The production of stabilised nanoparticles of LA was carried out using precipitation-ultrasonication technique, with various processing conditions being used. The FTIR and DSC investigations indicated that there was no interaction between the excipients and lovastatin included in the nanosuspension. Formulation P2 was chosen as the optimised formulation based on its particle size, drug content, and drug release profile.

The dissolution investigation conducted in a phosphate buffer reveals that the nanosuspension formulation exhibits a greater drug release rate in comparison to both the pure drug and the commercially available formulation. Stability experiments were performed for the optimised formulation P2. The results indicated that the formulation was more stable when stored at a temperature of 4°C. Hence, nanosuspensions provide a potential alternative to existing delivery strategies with the goal of enhancing the biopharmaceutical properties of medications that have limited solubility in water. Therefore, the lovastatin nanosuspension formulation created using the precipitation-ultrasonication technique could possess more therapeutic efficacy compared to traditional formulations.

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CONFLICT OF INTEREST: The authors declare that they do not have any conflict of interest.

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