



## Formulation and Evaluation of Fluvastatin Loaded Solid Lipid Nanoparticles

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### ABSTRACT

In the present work Fluvastatin was taken which is anti-hyper lipidemic drug used for chronic treatment. It belongs to BCS class-II which means low soluble & high permeable drug. The current dosage regimen is 20-80mg for 2-3 times a day. The present work aims at reducing the dose of the drug by converting it into nanocarrier systems. For this purpose, SLN's were prepared by employing Compritol as lipid, Soyalecithin as lipophilic surfactant, Tween-80/PEG-400 as hydrophilic surfactant systems. The prepared formulations were named as T1 to T4 with Tween-80 and P1 to P4 with PEG-400. All the prepared formulations are evaluated for drug content, entrapment efficiency and drug release studies. Among all the preparations best formulation was found to be P3 in terms of Drug content of 96.2%, Entrapment efficiency of 90.87% , Drug release of 61.0%, Particle size of 578nm with Zeta potential of -26mV. The present study conclusively demonstrated that the solubility of drug was improved by entrapment of drug into solid lipid carrier which led to prolongation of drug release.

**Keywords:** Solid lipid nanoparticles, anti-hyperlipidemic, compritol, nanocarrier system, nano technology, soyalecithin.

### QUICK RESPONSE CODE →

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### INTRODUCTION

The aim of this study to formulate and evaluate Fluvastatin loaded solid-lipid nanoparticles. Fluvastatin is the drug used in cardiovascular diseases. It is an anti-hyperlipidemic agent that competitively inhibits Hydroxy methyl glutaryl co-enzyme A (HMG CO-A). It is used in patients with cardiovascular problems by reducing cholesterol in plasma for a chronic period. It is available commercially in 20mg, 40mg and 80mg strength as dose with bioavailability of 20-30% following oral administration. Frequent administration and less bioavailability leads to fluctuations in plasma concentration and may also has less patient compliance. These problems can be solved by formulating nanoparticles drug delivery system of these drug which maintains concentration of drug in blood for longer time period with controlled and sustained drug delivery systems. Fluvastatin can be used as a drug candidate for nanotechnology as it improves bioavailability<sup>7</sup>.

Oral drug delivery system is one of the most useful and preferred route of drug delivery for the successful treatment of number of diseases. Owing to its potential advantages includes painless administration, patient compliance, cost effective and noninvasive when compared to other routes like intramuscular, intravenous and pulmonary<sup>12</sup>. It has some drawbacks by which it may

not suitable to some specific populations like paediatrics, geriatrics and mentally ill patients. The poorly oral bioavailability drugs are unable to reach the minimum effective concentration to exhibit therapeutic action. In recent years, nanocarriers were gaining tremendous interest towards researchers due to their remarkable advantages over conventional dosage forms in oral drug delivery of hydrophobic drugs. The best used approach for the enhancement of poorly water-soluble drugs was solid lipid nanoparticles. Repeated administration of drugs may result in certain toxicity to avoid this oral sustained release formulation developed to promote the slow and prolonged release of the drug<sup>1</sup>.

Solid lipid nanoparticles(SLNs) are the lipid based colloidal carriers which was introduced in early nineties. SLNs are submicron colloidal carriers whose dimensions ranges from (50-1000nm) that are composed of physiologically lipid components which are in solid state at room temperature. This is one of the most used approach for the increasing of poorly water-soluble drugs and low oral bioavailability of drugs. Anti-hyperlipidemic agents are used for the treatment of increased levels of fats (lipids) such as cholesterol, in the blood (hyperlipidemia). They are called as lipid-lowering drugs that lowers the level of lipids and lipoproteins in blood<sup>2</sup>. Class II drugs has high absorption number and low dissolution number. The rate limiting step for this is drug dissolution for absorption except at a very high dose number<sup>3</sup>.

### MATERIALS AND METHODOLOGY

#### Materials

Fluvastatin (gift sample from Hetero), Soya Lecithin(SDFL supplier), Compritol was from HIMEDIA, Tween-80 and PEG-400 has taken from SDFL supplier, Distilled water.



## Experimental Methodology

### Hot Homogenization Technique for the Preparation of Nanoparticles

Hot homogenization method is best suitable method for the preparation of solid lipid nanoparticles as it can be performed at elevated temperatures to that of lipids melting point. The reduction in the particle size is due to cavitations and turbulences during homogenization process<sup>11</sup>. In hot homogenization technique the drug was dispersed in the lipid and soya lecithin (surfactant) by melting them above their melting point. This is considered

as oil phase. The aqueous phase was prepared by adding other surfactant Tween 80 or PEG 400 in the distilled water and heated to the temperature of oil phase. Finally the prepared oil phase was added to aqueous phase drop by drop under continuous stirring of 3 hrs at 2700 rpm on homogeniser (Remi motors). The produced O/W emulsion is sonicated (Labotech, Mumbai) for half an hour and cooled to room temperature. At the room temperature the lipid recrystallizes and leads to formation of SLNs<sup>4</sup>.

### Formulation of Nanoparticles by Hot Homogenization Method by Using Different Surfactants

**Table 1:** List of formulations prepared by employing Compritol as a lipid and Tween-80 as Hydrophilic surfactant

S. No	Ingredients	T1	T2	T3	T4
1.	Compritol	1gm	1gm	1gm	1gm
2.	Fluvastatin	10mg	10mg	10mg	10mg
3.	Tween-80	50mg	100mg	200mg	300mg
4.	Soyalecithin	100mg	100mg	100mg	100mg
5.	Water	20ml	20ml	20ml	20ml

**Table 2:** List of formulations prepared by employing Compritol as a lipid and PEG-400 as Hydrophilic surfactant

S. No	INGREDIENTS	P1	P2	P3	P4
1.	Compritol	1gm	1gm	1gm	1gm
2.	Fluvastatin	10mg	10mg	10mg	10mg
3.	PEG-400	50mg	100mg	200mg	300mg
4.	Soyalecithin	100mg	100mg	100mg	100mg
5.	Water	20ml	20ml	20ml	20ml

## Evaluation of Nanoparticles

### Drug content

5ml of prepared nanoparticle suspension was taken to this 10 ml of methanol was added. The dispersion was stirred thoroughly. Then the dispersion was filtered through whattman filter paper, the clear filtrate is further diluted and concentration of drug was measured U.V spectrophotometrically at 302nm<sup>5</sup>.

### Entrapment Efficiency

Prepared nanoparticles were centrifuged at 17000rpm for 40min in high-speed research centrifuge to collect supernatant liquid. The liquid was filtered to measure amount of free drug concentration after suitable dilution with the fresh phosphate buffer of pH 7.2. The absorbance was measured at 302 nm in a UV spectrophotometer to calculate the entrapment efficiency using the formula<sup>10</sup>.

$$E.E = \frac{\text{Amount of total drug} - \text{Amount of drug in aqueous phase}}{\text{Amount of total drug}} \times 100$$

### Measurement of Particle Size

The mean diameter of polymeric nanoparticles in the dispersion was determined by Malvern Zeta-sizer. It

measures Brownian motion of particles, which are suspended in a liquid through the changes in the intensity of light scattered from particles through time. Consequently, if the motion is slow ultimately larger the particle size will be, since smaller particles are more affected by interactions with the solvent<sup>6</sup>.

### Measurement of Zeta Potential

It is an important factor to be considered in understanding the electric double layer repulsion and it can be measured by phase analysis light scattering when the electric field is applied across an electrolyte, the charged particles in the preparation are attracted towards the electrode of opposite charge while the viscous forces acting on the particle tend to oppose the movement. When equilibrium is reached, the particles move with constant velocity, also known as electrophoretic mobility, and zeta potential can be measure. The magnitude of zeta potential gives an indication of the potential stability of the particular system. If modules of zeta- potential are large, the particles in preparation will tend to repel each other. Hence, there will be no tendency to agglomerate and vice versa<sup>7</sup>



**In vitro Drug Release Studies**

The in vitro drug release of fluvastatin nanoparticles was determined by dissolution apparatus using USP II. An accurately weighed amount of fluvastatin nanoparticles containing the drug equivalent to 10mg was taken into the dialysis bag and sealed. This sealed dialysis bag was then suspended into the dissolution basket containing 900ml of phosphate buffer solution of pH 7.2 at the temperature of 37± 2°C and stirred at a constant speed of 100rpm. Aliquots were collected at each hour upto 24 hours and the same was replaced with the fresh buffer. The drug content was determined spectrophotometrically by measuring the absorbance at 302nm using the same buffer solution as the blank<sup>8</sup>.

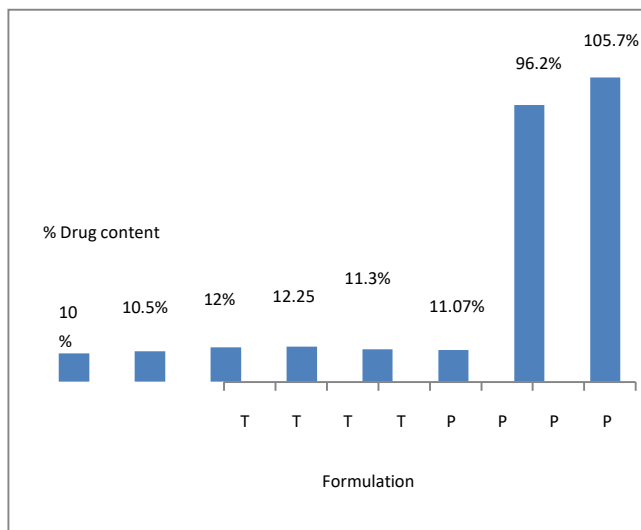
**Stability Studies**

Stability studies were carried out by storing the formulation at two different temperatures, in refrigerated condition and at room temperatures. The samples were analyzed for their physical appearance, drug content, entrapment efficiency and percent drug release after a time period like at 0, 1, 2, and 3 months<sup>9</sup>.

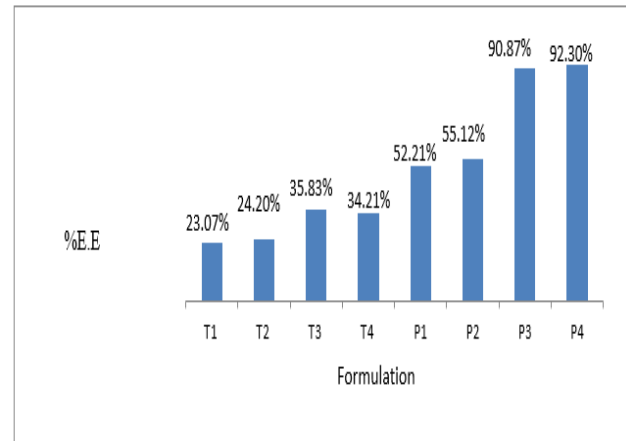
**RESULTS AND DISCUSSION**

**TABLE 3:** Percentage of Drug content and Entrapment efficiency of Compritol as a lipid and Tween-80 and PEG-400 as a surfactants

Ingredients	%Drug present	Ingredients	%E.E
T1	10%	T1	23.07%
T2	10.5%	T2	24.2%
T3	12%	T3	34.21%
T4	12.25%	T4	35.83%
P1	11.3%	P1	52.94%
P2	11.07%	P2	55.12%
P3	96.2%	P3	90.87%
P4	105.7%	P4	92.30%



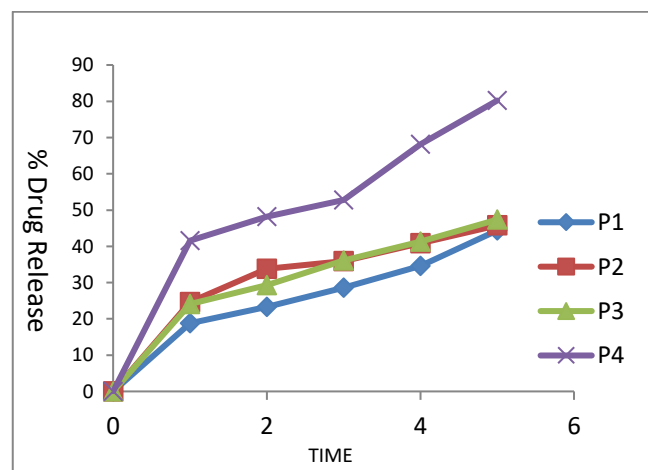
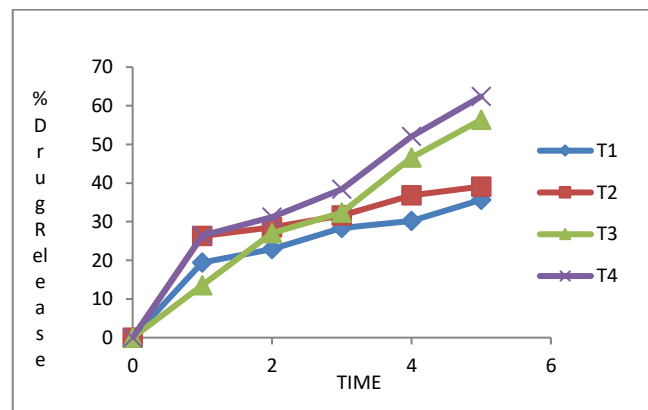
**Figure 1:** % Drug content of Compritol as lipid and tween-80, PEG-400 as a surfactant



**Figure 2:** Entrapment efficiency of Compritol as lipid and tween-80, PEG-400 as a surfactant

**Percentage of Drug Release for solid lipid nanoparticles with Tween-80 and PEG-400 as surfactant and compritol as lipid.**

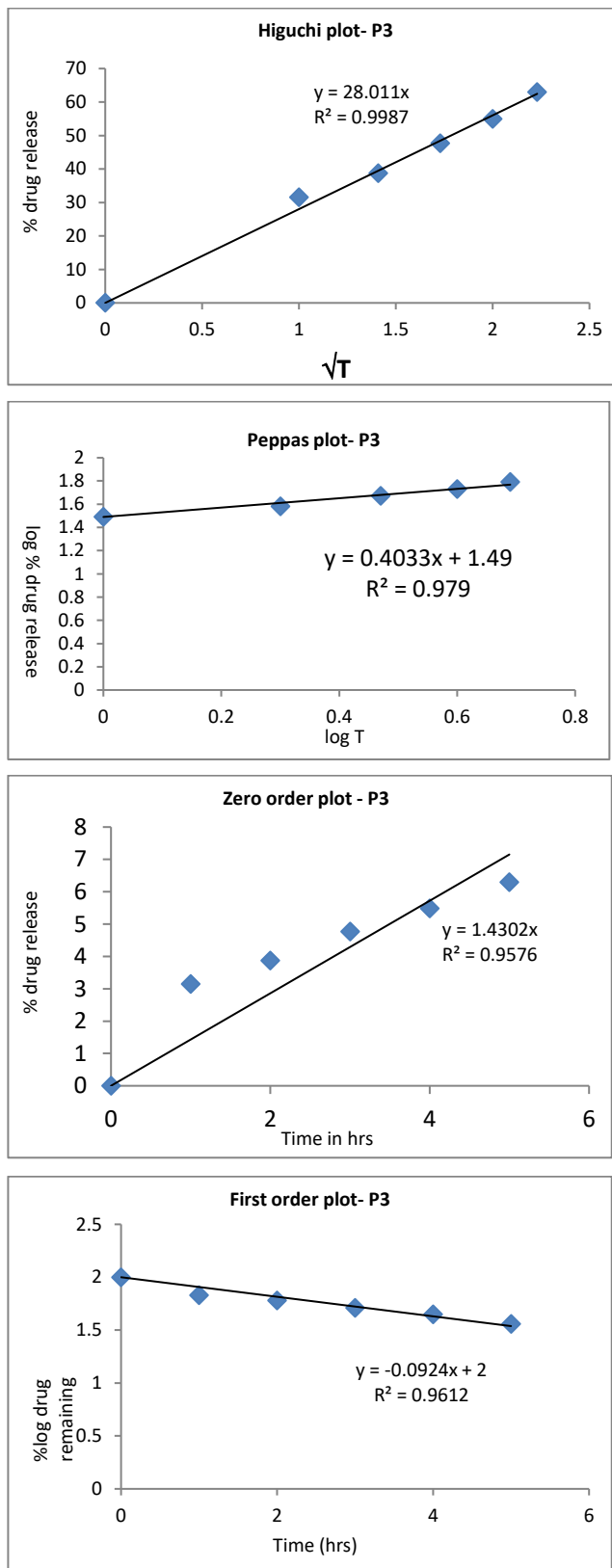
The in vitro drug release profile of Fluvastatin from various prepared nanoparticles formulations by hot homogenization. The drug release over a period of 5 hrs from all the formulations was observed to be in the range of 35-80% Among all the formulations P3 is showing 35% of drug release in 5 hrs.



**Figure 3:** Percentage of Drug Release for solid lipid nanoparticles with Tween-80 and PEG-400 as surfactant and compritol as lipid.

**Fitting of data into kinetic plots of Fluvastatin solid lipid nanoparticles for Optimised formulation**

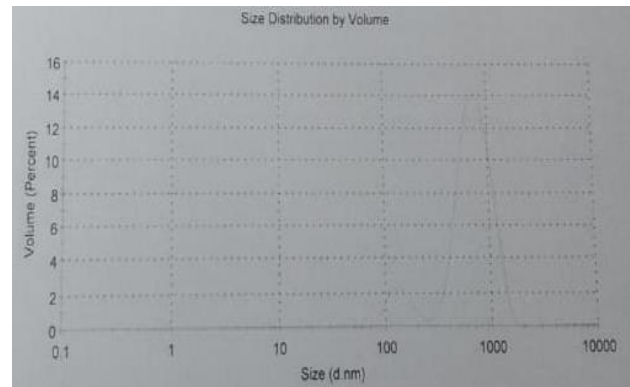
The drug release data was fitted in various kinetic plots (zero order, first order, Higuchi and Peppas) in order to determine the order and mode of drug release.



**Figure 4:** Higuchi, First Order, Peppas plot and Zero Order for P3 formulation

**Determination of Particle Size**

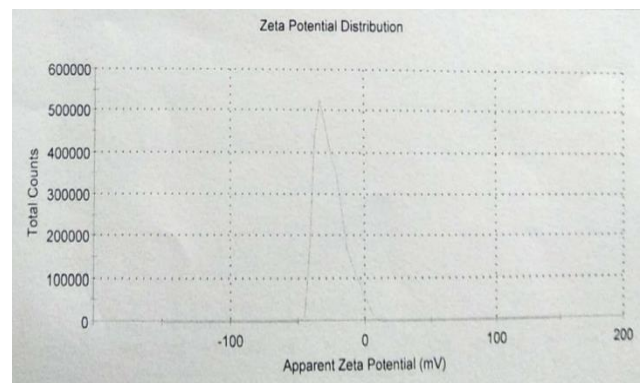
The particle size of the best formulation P3 was done with the help of nanoparticle analyzer HORIBA SZ 100 Z. The formulation contained particles of size of 578 nm. Thus it was observed that formulation was found to be in nano range.



**Figure 5:** Particle size report for P3 formulation of Fluvastatin

**Determination of Zeta Potential**

The zeta potential value indicates about the stability of nanoparticles. It was determined by HORIBA SZ 100 Z nanoparticle analyzer. And the best formulation P3 showed the zeta potential value of -26 mV. Thus, it was found that the prepared formulation was stable.



**Figure 6:** Zeta Potential report for P3 formulation of Fluvastatin

According to the kinetic plots, the drug release mechanism is observed to be Matrix diffusion by Higuchi plot, and Fickian diffusion by n value in peppas.

**DISCUSSION**

Fluvastatin is the drug used in cardiovascular diseases. It is used in patients with cardiovascular problems by reducing cholesterol in plasma for a chronic period. It is available commercially in 20mg, 40mg and 80mg strength as dose with bioavailability of 20-30% following oral administration. In the present study, solid lipid nanoparticles of Fluvastatin were prepared by hot homogenisation by employing Compritol, Precirol, Tween-80, PEG-400, Soyalecithin. All the prepared formulations were evaluated for Drug content, Entrapment efficiency,

Drug release studies. Total 16 formulations (P1-P8&T1-T8) were prepared by varying lipid to surfactant ratio. In this 8 formulations are with Compritol as lipid and Tween-80 as surfactants and named as (T1, T2, T3,T4) Compritol and PEG-400 as (P1, P2,P3,P4) and 8 formulations are with Precirol and Tween-80 as (T5,T6, T7, T8), Precirol and PEG-400 as (P5, P6, P7, P8) in ratio of (1:0.5,1:1, 1:2, 1:3) i.e., by increasing surfactant concentrations like 50mg, 100mg, 200mg, 300mg by keeping lipid concentration constant. The drug content values ranges from 10- 96.2% with 96.2% of drug content shown by formulation P3 formulation. Entrapment efficiency values ranges from 23.07- 90.87% with better entrapment efficiency value shown by P3 formulation. Drug release values ranged from 35- 61% for upto 5hrs with 61% of drug release shown by P3 formulation which is best suitable for sustained release formulations. The drug release mechanism is observed to be Matrix diffusion by Higuchi plot, and Fickian diffusion by n value in peppas.

### CONCLUSION

In the present study Fluvastatin loaded solid lipid nanoparticles were prepared. Solid lipid nanoparticles of Fluvastatin were prepared by hot homogenization method. In this Compritol used as solid lipid, soya lecithin used as lipid surfactant and stabilizing agent, Tween-80 and PEG-400 used as hydrophilic surfactants. Total 8 formulations were prepared varying surfactant ratios. All the formulations were evaluated for drug content, entrapment efficiency and drug release studies. Out of all formulations best formulation was found to be P3 formulation with drug content was found to be 96.2%, entrapment efficiency was 90.87% and drug release was 35-80% within 5hrs and it has shown particle size of 1190nm and zeta potential of -26mV. Hence they are the best suitable formulations for sustained release.

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