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Formulation and Evaluation of Simvastatin Loaded Solid Lipid Nanoparticles

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ABSTRACT:

The current research work validates the preformulation, formulation, development, evaluation and improvement of solid lipid particles containing simvastatin as an Antihyperlipidemic drug. Various mixtures were obtained using active ingredient Simvastatin, Glyceryl monostearate and Gelucire 48/16 as solid lipids, tween 80 as hydrophilic surfactant and Span as lipophilic surfactant. Formulation of Solid lipid nanoparticles loaded simvastatin product was prepared by high-speed homogenization and ultrasonication. The composite formulations were evaluated based on various parameters such as particle size, absorption ratio, zeta potential measurement, FTIR and in vitro dissolution investigations. The products were found to be within standard limit. Reports based on FTIR investigations show no interaction between simvastatin and other additives. Zeta sizer showed that the size of the nanoparticles ranged from 143 $\pm$5 nm to 377 $\pm$2.57 nm. Based on the results of nanoparticle entrapment and particle size, sample F5 is considered the best formulation. The optimal formulation showed a drug release of 94.74 after 12 hours. The optimal formulation had an average zeta potential of 26.7 mV.

Key words: Anti hyperlipidemic drug, Solid lipid nanoparticle, entrapment efficiency, Zeta Potential, Particle size.

1. INTRODUCTION:

Lipid-based drug delivery systems have been increasingly utilised to improve the bioavailability of BCS class 2 drugs. Nano-medicine offers unique properties for nano-scale and nano structured material and able to overcome several limitations in drug delivery as poor oral bioavailability, and adverse drug reactions. A solid lipid nanoparticle (SLNs) is one of the most commonly used efficient tools for drug delivery, which provides better stability for several drugs with minimal toxicity and improved biocompatibility. Solid lipid nanoparticles (SLNs) developed in early nineties, are sub-micron colloidal carriers (50-1000 nm) which are composed of physiological lipid dispersed in water or in an aqueous surfactant solution. SLNs are advantageous over other colloidal systems with regards to biocompatibility and scale up.

Simvastatin chemically names as 2.2- dimethylbutanoic acid (4R,6R)-6-21S,2S,6R,8S,8aR)-1,2,6,7,8,8a-hexahydro-2,6-dimethyl-1-(2-(tetrahydro-4-hydroxy-6-OXO-2H-pyran-2-yl)ethyl-1-naptha lenyl ester, molecular weight 418.56and molecular formula $C_{25}H_{38}O_5$ .Simvastatin (SIM) is a potent inhibitor of 3-hydroy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which converts HMG CoA into mevalonate, a precursor in cholesterol synthesis.

Glyceryl Monostearate is an organic molecule and it is used in food industries as a thickener, a preservative agent, an emulsifying agent for food and also for oils, waxes, and solvent in pharmaceuticals and cosmetics industries. Also used as a plastic lubricant.

Hot homogenization technique was used; the drug was incorporated into the melted lipid. The drug loaded lipidic phase was dispersed in a hot aqueous surfactant solu tion under continuous stirring to form a coarse o/w emulsion. It was then homogenized at the temperature above the melting point of the lipid using high pressure homogenizer to form o/w nanoemulsion which was cooled to room temperature for solidification and formation of solid lipid nanoparticles.

Present literature focuses on for enhancement in oral bioavailability of statins using Nanoparticulate drug delivery system. Simvastatin loaded SLN's were successfully prepared by Hot homogenization method. The optimized formulations were evaluated for various parameters like Particle size, Percentage entrapment efficiency, Measurement of Zeta Potential, FTIR, in-vitro release study.

2. MATERIALS AND METHODOLOGY:

Simvastatin , Glyceryl monosterate was purchased from the Accord labs, Gelucire48/16 was purchased from the Accord labs Gattefosse SAS, Tween80 obtained from Finar and Span80 has taken from Fluka, Methanol(AR grade) was purchased from SLC Chemicals, Distilled water.

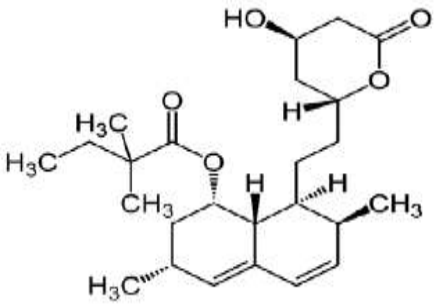


Fig.1.Structure of Simvastatin

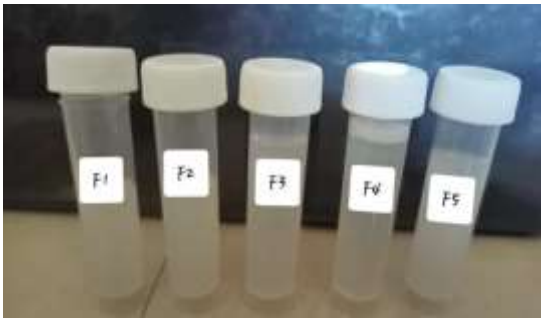
3. Methodology:

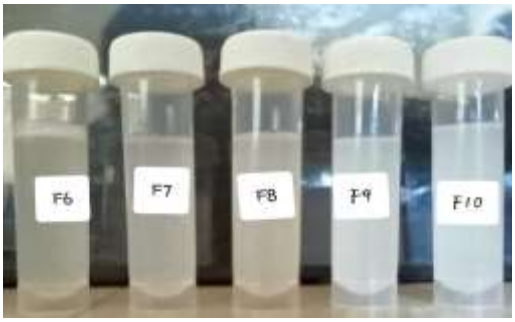
A solid lipid nanoparticle (SLNs) was prepared by the hot homogenization & ultrasonication method. The level of lipid mixture and surfactant seems to be a critical parameter for particle size determination. The reduction in the particle size is due to cavitations and turbulences during homogenization process. In this method amount of solid lipid (GMS & Gelucire 48/16)taken in a china dish and melted, to this drug (Simvastatin) was added and dispersed, then lipophilic surfactant (Span80) was added, this is considered as oil phase. In a beaker 25ml of water and hydrophilic surfactant (Tween80) taken and kept under homogenizer and stirred at 2700rpm, this is aqueous phase. Oil phase is added to aqueous phase under high pressure homogenization and homogenized for 3 to 4 hrs. After homogenisation the SLNs were subjected to sonication for 30-40 mins. The obtained SLNs were collected and stored.

3.1. Formulation of Nanoparticles by Hot Homogenization Method by using various Ingredients:

Table 1: List of formulations prepared by using GMS and Gelucire48/16

MATERIALS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug (mg)	20	20	20	20	**20**	20	20	20	20	20
GMS (mg)	500	500	500	500	**500**	---	---	---	---	---
Gelucire 48/16 (mg)	---	---	---	---	**---**	300	300	300	300	300
Tween 80 (mg)	100	200	300	400	**500**	100	200	300	400	500
Span 80(mg)	25	50	75	100	**125**	25	50	75	100	125
Distilled water	Q.S	Q.S	Q.S	Q.S	**Q.S**	Q.S	Q.S	Q.S	Q.S	Q.S





3.2. Evaluation of Nanoparticles:

3.2.1. Determination of λ-max of Simvastatin in Methanol and pH.7.4.PBS:

In quantitative UV analysis, it is important to determine the wavelength that produces maximum absorption. In general, solutions with absorbance values less than 1 are considered good for determining the absorption wavelength. Solutions prepared in methanol and pH.7.4.PBS buffer respectively were scanned in the 400–200 nm range using a co-solvent system equipped with a light emitting diode. This scanning process was performed at full scan speed using full control mode. After significance is obtained, λ-max is determined. The above procedure was given 3 times. And Calibration curve was constructed by using solvents methanol and pH.7.4.PBS buffer respectively.

3.2.2. FTIR study of prepared Simvastatin nanoparticles:

FTIR study of optimized batch of prepared Simvastatin nanoparticles was carried out on FTIR spectrophotometer. Appearance or disappearance of any peak in the spectra indicates the formation of any new compound in prepared nanoparticles. As a result, we can say that there is no interaction between the components found.

3.2.3. 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 236 nm

For determination of % drug content following formula:

% Yield = (Practical yield)/ (Theoretical yield) × 100

3.2.4. Drug entrapment efficiency:

The entrapment efficiencies of prepared systems were determined by measuring the concentration of free drug in the dispersion medium. The unentrapped drug was determined by adding 0.1 ml of the nano suspension to 9.9 ml water (95%) in order to dissolve the unentrapped drug; the obtained suspension was centrifuged for 45 min at 17,000 rpm. The supernatant was separated and then filtered through filter paper (0.2- µm). The filtrate was diluted using water and measured spectrophotometrically at 236nm. The entrapment efficiency was calculated using the following equation.

% EE= [(total drug content-unentrapped drug)/ total drug content] × 100

3.2.5. 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.

3.2.6. Measurement of Zeta Potential:

Zeta potential is the most important parameter for physical stability of nanoparticle. The higher the electrostatic repulsion between the particles the greater is the stability. Zeta potential measurement of the optimized nanoparticle suspension was done by using the (Malvern zeta nano). For the measurement, 1ml of the sample was diluted to 10ml with water, 5ml of this diluted sample was transferred to a cuvette and the zeta potential was measured.

3.2.7. In vitro Drug Release Studies

The in vitro drug release of Simvastatin nanoparticles was determined by dissolution apparatus using USP II. An accurately weighed amount of Simvastatin nanoparticles containing the drug equivalent to 20mg 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. Aliquotes were collected at each 30min upto 12 hours and the same was replaced with the fresh buffer. The drug content was determined spectrophotometrically by measuring the absorbance at 236nm using the same buffer solution as the blank.

4. Results and Discussions:

4.1. Determination of λ-max of Simvastatin in Methanol:

For the selection of analytical wavelength, standard solution of Simvastatin was scanned in the spectrum mode from 200 nm to 400 nm separately. From the spectra of drug, λmax of Simvastatin,236 nm was selected for the analysis of samples. Aliquots of standard stock solution were made and calibration curve was plotted using concentrations between 1µg-5µg for methanol solvent and the same buffer solution as the blank.

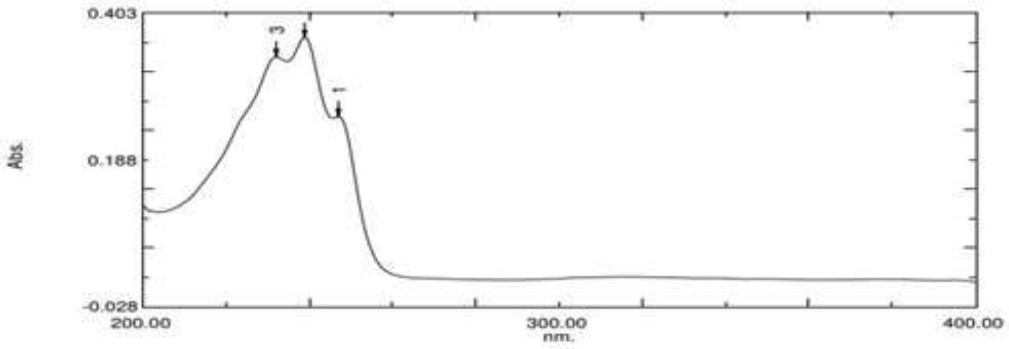


Fig.2. UV Spectrum of Simvastatin in Methanol

Table.2. Simvastatin Standard in Methanol

Concentration(µg/ml)	Absorbance
1ppm	0.124
2ppm	0.172
3ppm	0.225
4ppm	0.271
5ppm	0.318

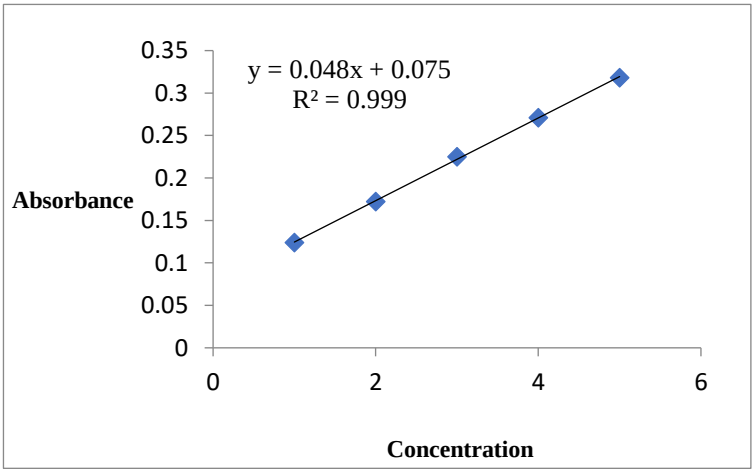


Fig.3. Calibration curve of Simvastatin in methanol

Discussion: The maximum wavelength of simvastatin solutions at a concentration of 100 µg/mL was determined using the comprehensive inspection mode of the UV-visible spectrophotometer, taking into account the required level of accuracy. The λ-max of simvastatin maximum absorption is optimized as 236nm.

4.2. Determination of λ-max of Simvastatin in pH.7.4.PBS buffer solution:

For the selection of analytical wavelength, standard solution of Simvastatin was scanned in the spectrum mode from 200 nm to 400 nm separately. From the spectra of drug, λmax of Simvastatin, 236 nm was selected for the analysis of samples. Aliquots of standard stock solution were made and calibration curve was plotted using concentrations between 5µg-25µg forpH.7.4.PBS buffer solution and the same buffer solution as the blank.

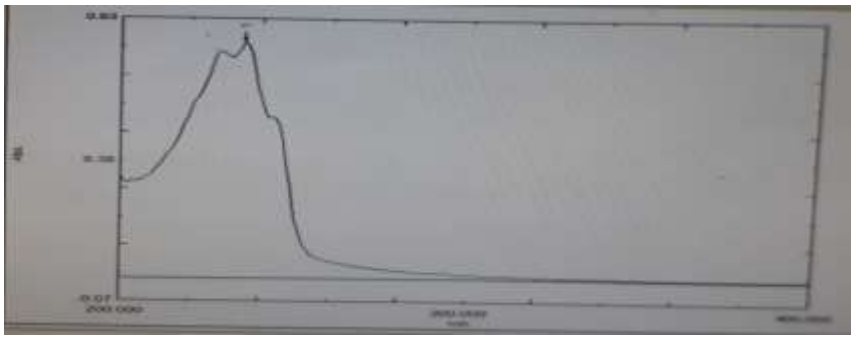


Fig. 4.UV spectrum of Simvastatin in 7.4 PBS

Table.3. Simvastatin Standard in PBS

Concentration(µg/ml)	Absorbance
5ppm	0.052
10ppm	0.182
15ppm	0.308
20ppm	0.427
25ppm	0.568

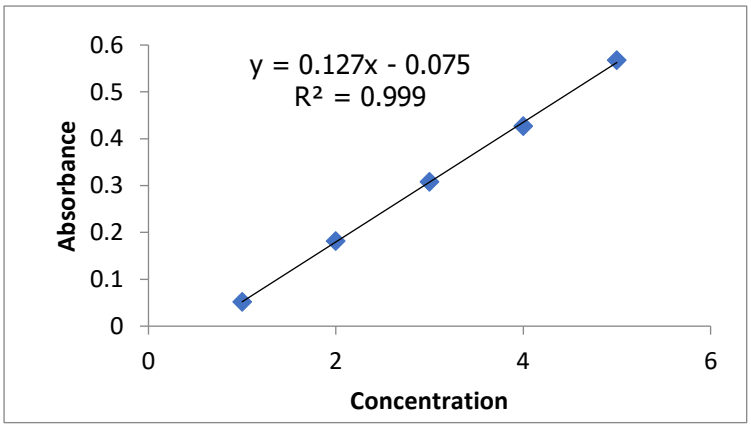


Fig.5.Calibration Curve of Simvastatin in pH 7.4 PBS

Discussion: The maximum wavelength of simvastatin solutions at a concentration of 100 µg/mL was determined using the comprehensive inspection mode of the UV-visible spectrophotometer, taking into account the required level of accuracy. The λ-max of simvastatin maximum absorption is optimized as 236nm.

4.3. FTIR:

FTIR spectroscopy was performed to confirm pure drug samples by FTIR spectra. The existence of electro -nic and chemical interactions between samvastatin and nanoparticles was clearly ruled out by FTIR spectra. This structure retains its medicinal properties. The absence of new peaks is a clear indication that there are no new active groups. As a result, we can say that there is no interaction between the components found.

Wave length(cm^{-1})of pure drug	**Wave length(cm^{-1})of optimized formulation**	**Functional Group**
3549 cm^{-1}	3548 cm^{-1}	O−H stretch vibration
3416 cm^{-1}	3176 cm^{-1}	O−H stretch vibration
2961 cm^{-1}	2963 cm^{-1}	C−H stretch vibration
1701 cm^{-1}	1701 cm^{-1}	−C−O stretch vibration
1120 cm^{-1}	1165 cm^{-1}	−C=O stretch vibration
1066 cm^{-1}	1066 cm^{-1}	−C=O stretch vibration

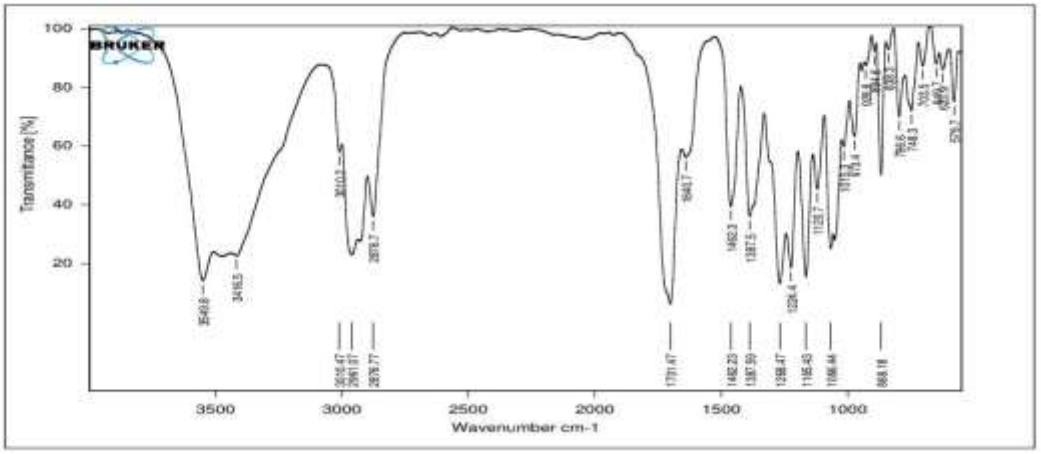


Fig.6. FTIR spectrum of Simvastatin

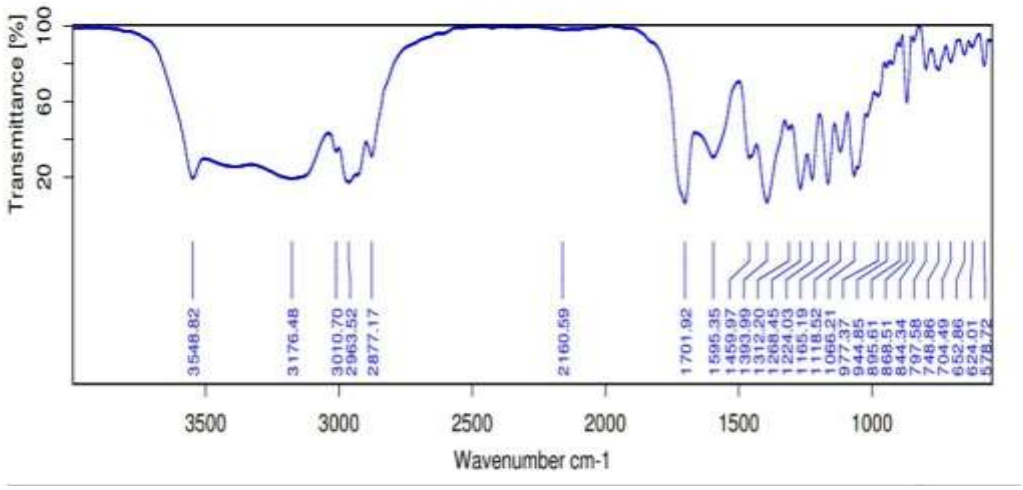


Fig.7 FTIR spectrum of Optimised Formulation

4.4. Drug content:

The results of percent practical yield studies of Simvastatin Nanoparticle are prepared by hot homogenization method. From the different ratio of drug (20mg), GMS (500mg), Tween(125mg), Span(125mg) shows maximum practical yield. It was found that hot homogenization method gives the practical yield in the range of 91.59-94.74%. The maximum yield was found 94.74% in batch F5.

4.5. Entrapment efficiency of nanoparticles:

The entrapment efficiency of prepared nanoparticles was carried out by ultracentrifugation method. The drug (20mg), GMS (500mg),Tween(125mg),Span(125mg) found to be maximum drug entrapped. The batch F5 shows maximum drug content capacity. The drug entrapment efficiency was found to be 85.34 ± 2.47.

4.6. Determination of Particle Size:

The particle size of the best formulation F5 was done with the help of nanoparticle analyzer Malvern zeta nano . The formulation contained particles of size of 420 nm. Thus it was observed that formulation was found to be in nano range.

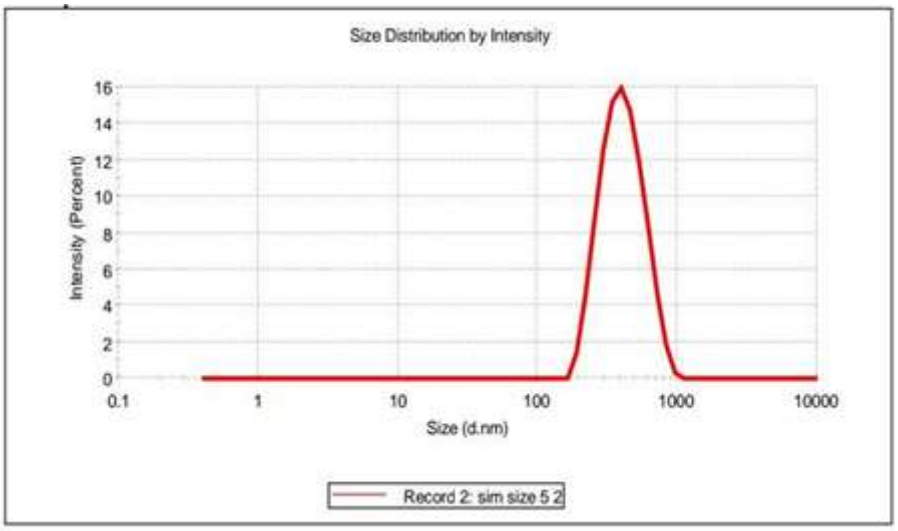


Fig.7.Size of optimized formulation

4.7. Determination of Zeta Potential:

The zeta potential value indicates about the stability of nanoparticles. It was determined by Malvern zeta nano nanoparticle analyzer. And the best formulation F5 showed the zeta potential value of -26 mV. Thus, it was found that the prepared formulation was stable.

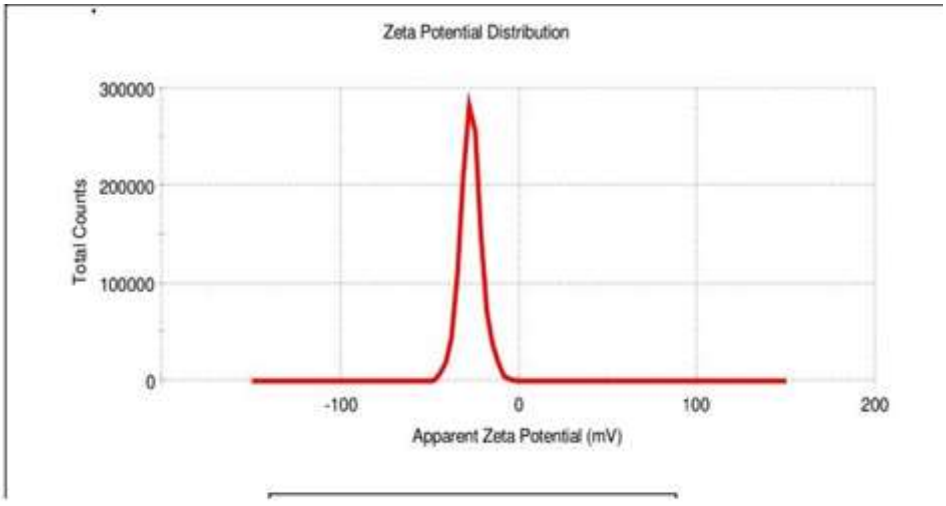


Fig.8.Zeta potential of optimized formulation

Table. 4.Drug Content,Characterization Of Size,PDI, Zeta Potential Of The Prepared SLN

FORMULATION	DRUG CONTENT (%)	PARTICLE SIZE(nm)	PDI	ZETA POTENTIAL(mV)	ENTRAPMENT EFFICIANCY
F1	91.59	355.5 ± 2.75	0.148 ± 0.005	-25.8 ± 1.18	75.26 ± 2.45
F2	91.62	384.1 ± 3.00	0.099 ± 0.002	-24.5 ± 0.89	68.98 ± 1.84
F3	92.26	388.1 ± 3.51	0.300 ± 0.003	-23.4 ± 1.08	71.11 ± 3.17
F4	91.68	458.2 ± 2.72	0.097 ± 0.002	-20.4 ± 1.76	73.4 ± 3.31
F5	**94.74**	**377.6 ± 2.57**	**0.103 ± 0.001**	**-26.7 ± 1.32**	**85.34 ± 2.47**
F6	92.10	358.1 ± 3.04	0.204 ± 0.004	-18.4 ± 1.72	60.26 ± 3.17
F7	91.64	338.8 ± 2.61	0.533 ± 0.010	-19.3 ± 1.97	64.43 ± 1.89
F8	92.27	336.8 ± 3.57	0.198 ± 0.001	-19.9 ± 1.77	50.35 ± 2.72
F9	93.86	417.1 ± 3.51	0.098 ± 0.004	-24.6 ± 2.41	49.85 ± 1.70
F10	92.82	350.1 ± 4,05	0.181 ± 0.005	-22.1 ± 2.55	58.54 ± 2.99

Discussion: All the prepared formulations were evaluated for drug content, particle size,zeta potential and entrapment efficiency. The drug content values ranged from 91.59 to 94.74. With highest drug content value of 94.74% for F5 formulation. The entrapment efficiency values ranged from 49.85-85.34% with highest entrapment efficiency value of 85.34% for F5 formulation. The results of F5 formulation particle size was 377.6±2.57 nm and zeta potential was 26.7mV are also sync with the above studies.

4.8. in Vitro Drug Release Studies:

The in vitro drug release profile of Simvastatin from various prepared nanoparticles formulations by hot homogenization. The drug release samples were collected over a period of 30mins to 12 hrs from all the formulations and there are scanned by using uv-spectrometry.

Table.5.Developed formulation and in vitro data

TIME	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	F10 (%)	Std
30mins	20.3	18.22	20.11	17.82	**21.88**	16.11	14.79	20.44	25.88	18.34	23.33
1hr	25.96	20.28	24.77	22.59	**35.30**	19.5	20.10	24.31	30.55	22.12	31.19
2hr	33.42	26.52	35.15	33.32	**49.95**	20.78	27.88	29.73	42.12	31.12	42.55
4hr	50.11	30.03	47.22	41.90	**57.81**	28.66	34.44	33.81	50.52	35.21	50.32
6hr	56.00	44.66	59.56	49.45	**68.99**	34.88	47.73	40.81	61.22	40.13	61.92
8hr	60.43	59.11	67.40	58.19	**75.55**	44.15	51.09	51.22	67.11	48.93	69.50
10hr	62.09	66.81	75.91	64.77	**89.65**	52.90	56.73	57.99	70.32	55.76	71.69
12hr	66.22	71.24	79.58	73.33	**91.71**	58.32	60.05	63.65	73.01	61.47	72.8

Discussion: The in vitro drug release over a period of 12 hrs from all the formulations was observed to be in the range of 21.80-91.71% .Among all the formulations F5 is showing 91.71% of drug release in 12 hrs.

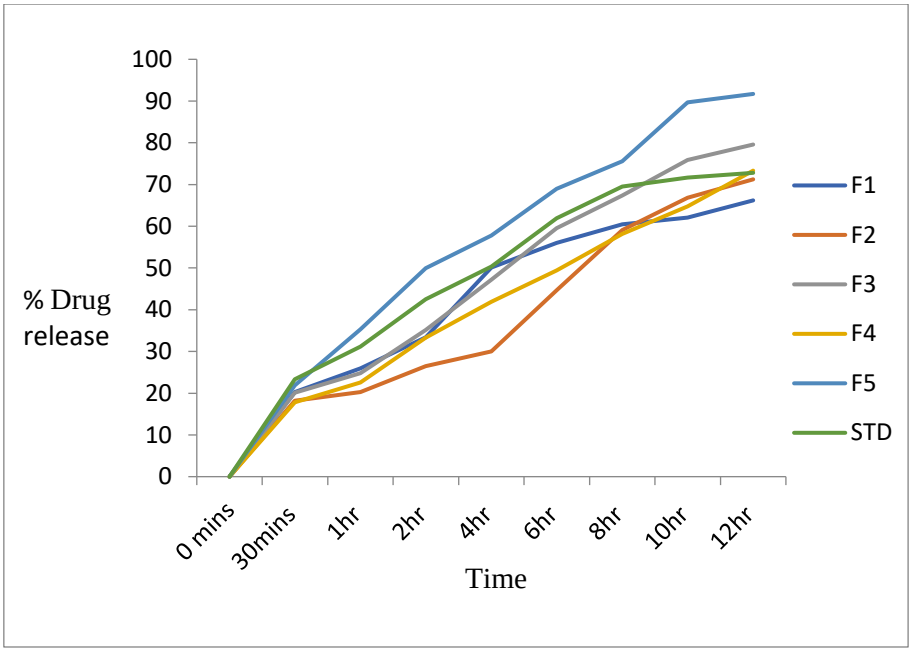


Fig.9.Invitro-drug release Studies of F1-F5 Formulations

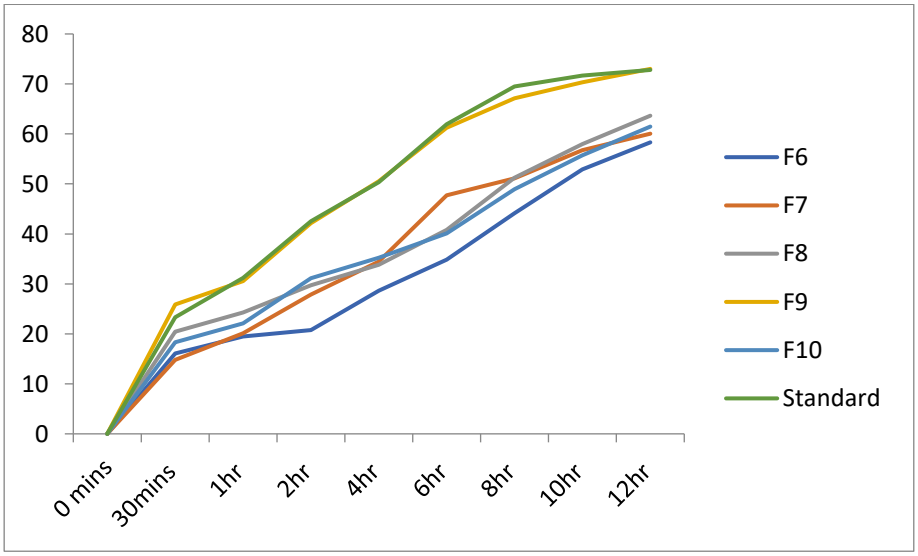


Fig.10.Invitro-drug release Studies of F6-F10Formulations

4.9. Kinetic Analysis of Dissolution:

The drug release data was fitted in various kinetic plots in order to determine the order and mode of drug release.

Table.6. Kinetic Data

Formulation	**Zero order plot(R^2)**	**First order plot(R^2)**	**Higuchi plot(R^2)**	**Peppas plot(R^2)**
F5	0.969	0.705	0.982	0.95

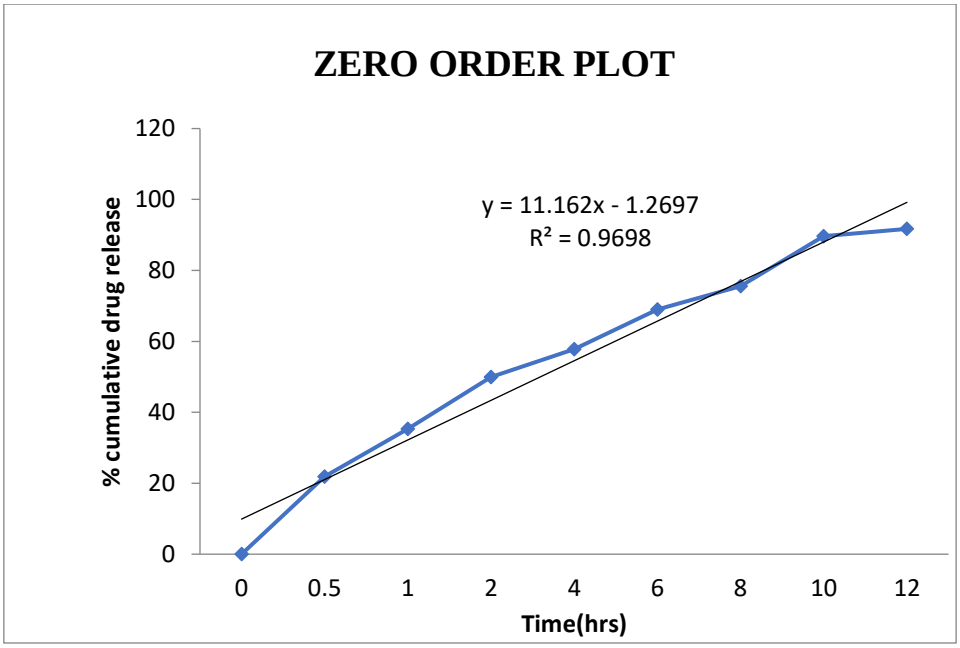


Fig.11. Zero order plot of Simvasatin loaded SLNP'S

Fig.12.First order plot of Simvasatin loaded SLNP'S

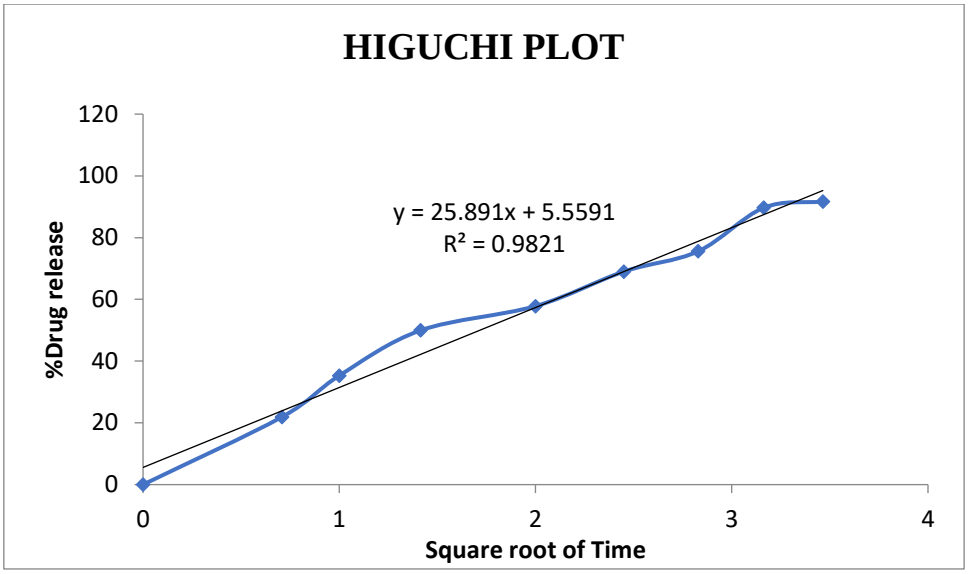


Fig.13.Higuchi plot of Simvasatin loaded SLNP'S

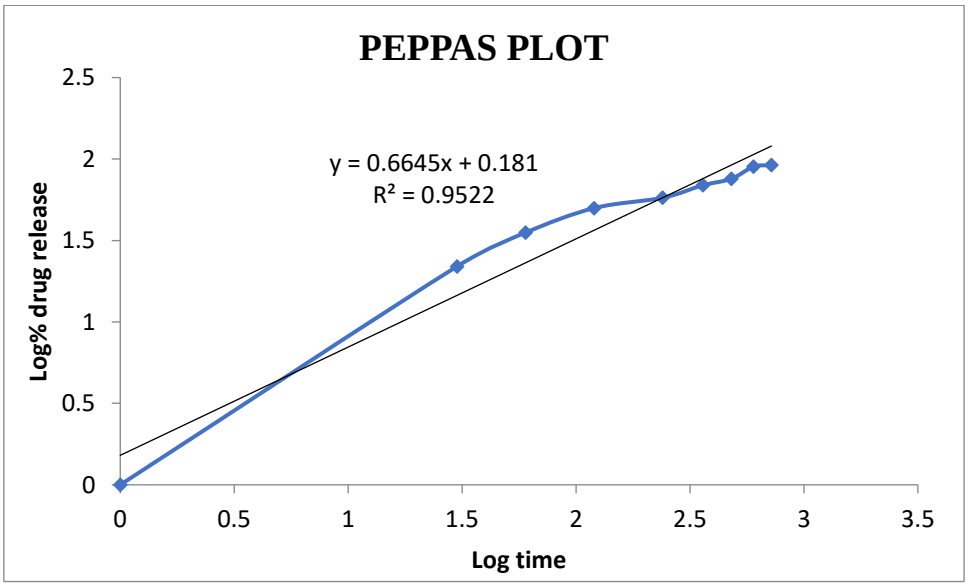


Fig.14.Peppas's plot of Simvasatin loaded SLNP'S

Drug release data obtained was extrapolated by and the release kinetics shows that the release of drug follows Higuchi model for the formulation F5 with an R^2 value of 0.98.

5. Conclusion:

It can be concluded that solid lipid nanoparticles provide controlled release of drug and these systems are used as drug carriers for lipophilic drugs, to enhance bioavailability of poorly water-soluble drugs through nanoparticles as a drug delivery system. Simvastatin loaded solid lipid nanoparticles by employing GMS and Gelucire were prepared by using hot homogenization method. Ten different formulations by varying the concentration of solid lipids, hydrophilic and lipophilic surfactants. All the prepared formulations were evaluated for drug content, entrapment efficiency, invitro drug release studies. The nanoparticles made of GMS showed good results compared to Gelucire 48/16.The drug content values ranged from 91.59 to 94.74 %. With highest drug content value of 94.74% for F5 formulation. The entrapment efficiency values ranged from 49.85-85.34%with highest entrapment efficiency value of 85.37% for F5 formulation. The percentage in vitro drug release values for 12 hrs are from 21%to 91.71 % range. The results of F5 formulation particle size was 377.6±2.57 nm and zeta potential was 26.7mV are also sync with the above studies. Promising results of the study indicated the applicability of Simvastatin solid lipid nanoparticles as potential tools to improve the bioavailability of poorly soluble drugs.

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