Research Article

Formulation and Evaluation of Nanosuspension as an Alternative Approach for Solubility Enhancement of Simvastatin

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Received: 14-08-2021; **Revised:** 21-10-2021; **Accepted:** 28-10-2021; **Published on:** 15-11-2021.

ABSTRACT

Solubility is an essential factor for drug effectiveness. Simvastatin is poorly water-soluble drug and its bioavailability is very low. Nanosuspension is one of those approach which can tremendously enhance the effective surface area of drug particles by reducing the particle size and there by increases the rate of dissolution and hence improve bioavailability. The main purpose of the present investigation was to increase the saturation solubility of simvastatin by preparation of nanosuspension. Nanosuspension of simvastatin were prepared by nanoprecipitation method using hydroxypropyl cellulose as stabilizer and sodium lauryl sulphate as surfactant. Prepared nanosuspension was evaluated for its particle size, total drug content, entrapment efficiency and saturation solubility study. On the basis of the evaluation, the best batch F8 formulation demonstrated highest drug content and entrapment efficiency with average particle size of 0.004µm. The saturation solubility studies show the solubility of the prepared nanosuspension has increased as compared to the pure drug due to the particle size reduction. The nanosuspension of simvastatin could be successfully prepared and can be concluded that the nanosuspension formulation is a promising approach to enhance the solubility. The nanoprecipitation is a simple and effective method to produce nano sized particles of poorly water-soluble drugs with enhance solubility.

Keywords: Simvastatin, Nanosuspension, Saturation solubility, Particle size, Dissolution, Bioavailability, Nanoprecipitation.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2021.v71i01.012

DOI link: http://dx.doi.org/10.47583/ijpsrr.2021.v71i01.012

INTRODUCTION

Solubility is a vital factor for developing drug delivery systems for hydrophobic drugs. One of the major problems associated with poorly soluble drugs is very low bioavailability[1]. This problem is more worsen because of more than the 40% of the newly discovered drug product are poorly water soluble. BCS Class II and IV Drugs are poorly water soluble and their pharmacokinetic studies shows low oral bioavailability[2]. So, they show problems in formulating them in conventional dosage forms. Formulation of these mainly the BCS class II and IV drug into the conventional dosage form is a challenging problem faced by the pharmaceutical researcher. In this cases, preparing nanosuspension is preferred for such compounds that are insoluble in water but soluble in oil[3]. Nanosuspension is one those approach used to solve the problems of poor solubility which is based on size reduction mechanism. Reduction of drug particles in nanosized range leads to enhance faster dissolution rate and increased surface area[4]. Recently, nanoscale systems have received much interest as a way to resolve solubility issues because of their technical simplicity compared to liposomes and other colloidal drug carriers. Nanosuspensions have proven to be a better alternatives over other approaches currently available for improving solubility of number of drugs[5]. Nanosuspension consist of dispersed solid drug particles in an aqueous vehicle with average particle sizes below 1µm. they are stabilized by polymers and surfactants. The potential advantage of nanosuspension technology is to enhance the saturation solubility and consequently increase the dissolution rate of the drug[6,7].

Simvastatin is a hydrophobic and highly lipophilic drug belonging to the BCS Class II drug, the dissolution process of this drug acts as the rate controlling step and therefore it is necessary to improve the solubility[8]. Simvastatin is a lipid lowering agent shows 5% bioavailability due to poor solubility, decreased in bioavailability due to rapid first pass metabolism. Approximately 95% of an oral dose is not absorbed. Therefore, it is important to enhance the aqueous solubility and improving bioavailability. Simvastatin is a potent inhibitor of HMG-COA Reductase which is rate limiting step in cholesterol biosynthesis[9,10].

The main intention of this research is to enhance the aqueous solubility and therefore improved the bioavailability of poorly aqueous soluble drug like simvastatin. Formulation as simvastatin nanosuspension is an attractive and promising alternatives to solve these problems. Improvement of aqueous solubility in such case is a valuable goal to improve therapeutic efficacy.

MATERIALS AND METHODS

Materials

Simvastatin was acquired as a gift sample from Artemis Biotech, Hyderabad. Hydroxy propyl cellulose and Sodium lauryl sulphate were procured from Research Lab Mumbai, whereas Methanol was purchased from Fischer Scientific, Mumbai. All the ingredients used in the research work were of analytical grade.

Preparation of simvastatin nanosuspension

The nanoprecipitation technique is used for the preparation of simvastatin nanosuspension[11]. The pure drug of simvastatin (10mg) was dissolve in (1ml) of methanol to produced uniform organic phase. (Solution 1) The Stabilizers (HPC, SLS) was dissolved in water (40ml) to form aqueous phase. (solution 2) The solution 1 added into solution 2 dropwised with the help of syringe under the magnetic stirrer for 15 min. to get desired nano dispersion. After the magnetic stirring the formulation is subjected to agitation with the help of lab stirrer at 1500 rpm at 1 hr. to evaporate the organic solvent.

Table 1: Formulation batches of Simvastatin Nanosuspension.

Ingredients	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Simvastatin (mg)	10	10	10	10	10	10	10	10	10
HPC (%)	1	2.5	5	-	-	-	1	2.5	5
SLS (%)	-	-	-	0.1	0.3	0.5	0.1	0.3	0.5
Methanol (ml)	1	1	1	1	1	1	1	1	1
Water (ml)	40	40	40	40	40	40	40	40	40
Stirring Speed (RPM)	1500	1500	1500	1500	1500	1500	1500	1500	1500

Particle size analysis

The average particle size of all NS formulations was determined by the motic digital microscopy. The nanosuspension showing the lowest particle size was selected for further studies. The particle size of the formulated batches was measured in micrometers[12].

Total drug content

Prepared Nanosuspensions was analyzed for drug content by UV spectroscopic method. Different batches of nanosuspensions equivalent to 10 mg of drug Simvastatin weighed accurately and diluted up to 100 ml with methanol. Stock solutions will be diluted with methanol and analyze by UV spectroscopy at 238 nm[13].

Entrapment efficiency

The method suitable for determining entrapment efficiency of nanosuspension when fairly high concentration of free drug is present in the supernatant after centrifugation[14,15]. 10 ml portion of the freshly prepared nanosuspension was centrifuged at 1000 rpm for 10 min. using centrifuge. the supernatant was removed and the amount of incorporated drug was measured by taking the absorbance of supernatant solution at 238 nm by using UV spectrophotometer. (LABINDIA 3000^{+}).

Entrapment efficiency was calculated by following formula:

Entrapment Efficiency (%) =

(W initial drug –W free drug / W initial drug ×100

Saturation solubility studies

The saturation solubility studies were carried out for both the unprocessed pure drug and its nanosuspension[16,17]. The solubility of simvastatin in powder form was determined by a shake flask method. Briefly, an excess amount of drug simvastatin was suspended in 10 ml of water, and the suspension were shaken and filter through a 0.22µm whatman filter. The filtered solution was suitably diluted and the simvastatin concentration in the filtrate was analysed by UV analysis method at 238nm. The solubility of best batch of formulation was measured by centrifugal method. Briefly, 10 ml of nanosuspension was loaded into centrifugal tubes. Samples were centrifuged at 10000 rpm for 10 min. The supernatant solutions were analyzed using UV spectrophotometer at 238 nm.

Stability studies

The final formulation was subjected to stability studies as per ICH guidelines. Samples were stored at 40ºC ± 2ºC and 75% ± 5% RH for 1 month to access their stability. The Various parameters such as drug content, entrapment efficiency was measured before and after 30 days of stability.

RESULTS AND DISCUSSION

Particle size analysis

The particle size of the NS produced systems was analysed by motic digital microscopy. the particle size of each formulation was carried out and results indicates that all formulations was found in the nanosized range. The F8 formulation shows better results because of low particle

size compared to other formulations. The batch F8 had a average particle size of 0.004µm which indicate the particles are in uniform distribution. The best formulation is select on the basis of particle size. The particle size of all formulations as shown in Table 2.

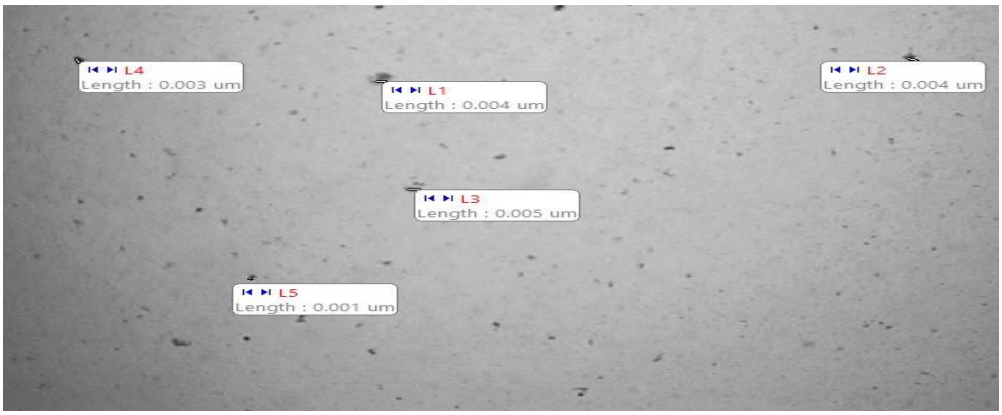

Figure 1: Particle size analysis by motic microscope of F8 Formulation.

Table 2: Particle size, total drug content and entrapment efficiency data of all formulations.

Formulation Code	Particle size (µm)	Total drug content (%)	Entrapment efficiency (%)
F1	0.013	83.64	81.69
F2	0.015	85.79	83.98
F3	0.018	83.96	81.33
F4	0.016	85.23	84.20
F5	0.014	87.79	85.46
F6	0.017	81.64	79.11
F7	0.006	91.54	87.44
F8	**0.004**	**95.19**	**93.28**
F9	0.007	93.24	90.88

Total drug content

The drug content of all NS formulations was found to be greater than 81%. Indicating suitability of these methods for particle size reduction. the Formulation batch F8 shows drug content 95.19%. The total drug content of all formulations are recorded in Table 2.

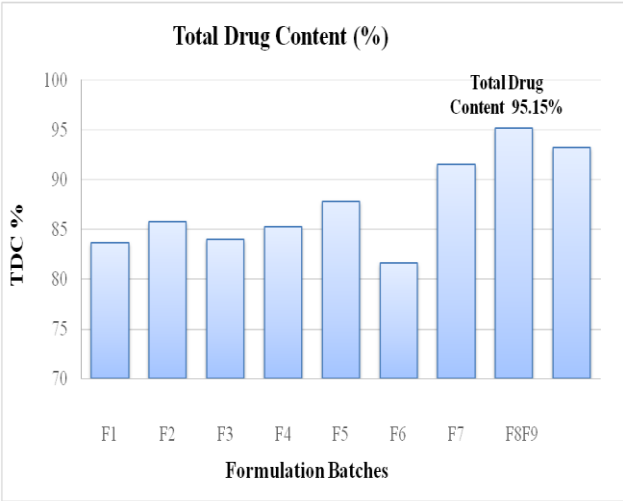

Figure 2: Total drug content of formulated nanosuspensions.

Entrapment efficiency

The entrapment efficiency of all formulations was found to be in the range of (79.11- 93.28%) the entrapment efficiency of formulation F8 was high when compared to other formulations. The entrapment efficiency of all nanosuspensions are recorded in Table 2.

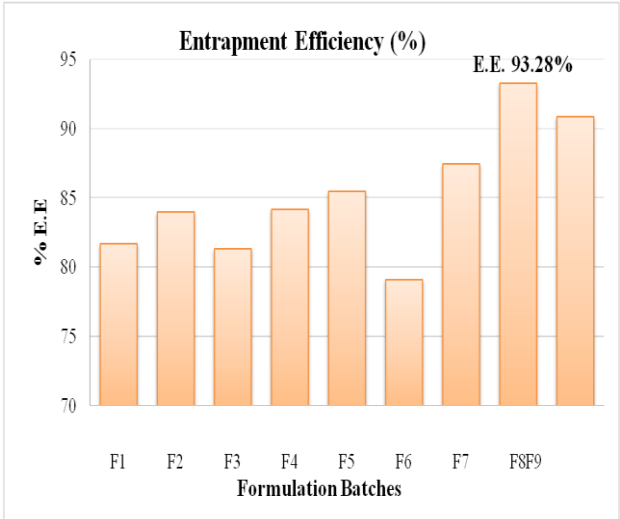

Figure 3: Entrapment efficiency of formulated nanosuspensions.

Saturation solubility studies

The saturation solubility studies indicating that nanosuspension showing maximum solubility compared to unprocessed drug. the optimized batch F8 shows highest solubility than pure drug. It may be observed that solubility of prepared nanosuspension has been increased due to the formation stabilized nanoparticles. It may be due to decreased in particle size and increased solubilization.

Table 3: Saturation Solubility of Simvastatin and its nanosuspension.

Formulations	Saturation solubility (µg/ml)
Pure drug	12.60
Nanosuspension	64.74

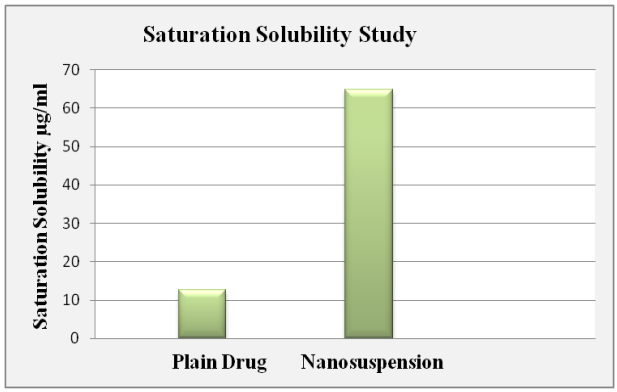

Figure 4: Comparison of solubility of Simvastatin and its Nanosuspension.

It may be observed that the solubility of prepared simvastatin nanosuspension has been increased up to 5.12 fold due to formation of stabilized nanoparticles.

Stability studies

The stability studies were carried out on final formulation. The samples were stored at 40°C ± 2°C and 75 % ± 5 % RH for 30 days to access best formulation their stability. After 30 days were withdrawn and rested for entrapment efficiency and total drug content. The F8 formulation did not show any significant difference in both parameters. It indicates that this formulation was able to retain its stability up to 30 days.

Table 4: Stability data of F8 formulation of nanosuspension.

Time period	Entrapment efficiency	Total drug content
Initial (0days)	93.28%	95.19%
After storage		
1 month	92.65%	95.02%

It may be observed that the solubility of prepared simvastatin nanosuspension has been increased up to 5.12 fold due to formation of stabilized nanoparticles.

CONCLUSION

The above investigation suggests the suitability of simvastatin nanosuspension as a promising drug delivery system. Simvastatin nanosuspension was successfully prepared by a nanoprecipitation method with a lower particle size. The comparison study of the simvastatin nanosuspension with pure drug (simvastatin) also indicate that the solubility of nanosuspension is higher than the pure drug. Hence, it can be good alternative to the solubility enhancement. In conclusion, the appropriate selection of process parameter and formulation parameters we can conclude that nanoprecipitation method is a simple and effective approach to produce nanosized particles of poorly water-soluble drugs with enhance solubility. It can be concluded that formulating poorly water-soluble drugs in the form of nanosuspension would be a promising approach in the delivery of poorly water-soluble drug.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.