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# FABRICATION AND EVALUATION OF SIMVASTATIN NANO SPONGES FOR ORAL DELIVERY

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**ABSTRACT**

The present work is to enhance bioavailability of drugs from BGS class II drugs like simvastatin by incorporating them in Nano sized drug delivery. Nano sponges are mesh like structures with a size range of below 1µm. Due to their small size and porous structure they can easily bind poorly soluble drugs, which leads to improve the solubility and ultimately the bioavailability of the same. Nanosponges is water soluble. This does not mean the molecules chemically break up in water, but it means that Nanosponges particles can mix with water and use it as transport fluid, for example to be injected. So, in theory Nanosponges has several advantages over other delivery methods. In this work poorly soluble drug i.e. simvastatin is formulated in Nanosponges for solubility enhancement.it is formulated in four batches by using Pluronic F68 and PVA.in this article preparation and evaluation of Nanosponges is described as per obtained results.

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## INTRODUCTION [1, 3]

The term "Nanosponge" means the nanoparticles having porous structures. Nanosponges are tiny sponges with a size of a virus with an average diameter below 1µm.Owing to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability by modifying the pharmacokinetic parameters of actives. Nanosponges are three dimensional, solid, porous, biocompatible adaptable drug delivery systems that can entrap both hydrophilic and hydrophobic drugs and conquer the problem of drug toxicity and poor bioavailability. The invention of the Nanosponges has become a significant step towards overcoming the complexity associated with the newly developing systems. Owing to their small size and porous nature Nanosponges can bind poorly- soluble drugs within the matrix and improve their bioavailability at specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. Simvastatin is Hydroxy Methyl Glutaryl Co-enzyme A (HMG CoA) inhibitor having antihyperlipidemic activity. This anticholesteremic agent is used in the treatment of dyslipidaemia. Absolute bioavailability of simvastatin is just about 5% due to high intestinal clearance and first pass metabolism. Inclusion complex formation enhanced the solubility, dissolution rate of poorly soluble BCS class II drugs and ultimately improved bioavailability of drug molecule. In this work novel approach was used for inclusion complex formation that was Nano sponge formation of poorly soluble simvastatin. This Nanosponges formation focuses on improvement in bioavailability of simvastatin.

### Advantages [41]

1. These formulations are stable over range of pH 1 to 11.
2. These formulations are stable at higher temperatures.
3. These formulations are compatible with most vehicles and ingredients.
4. These are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
5. These formulations are free flowing and can be cost effective.
6. This technology offers entrapment of ingredients and reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility.
7. Nanosponges are non-irritating, non-mutagenic, non-allergenic, and non-toxic.
8. Extended release action up to 12 hrs. can be attained.
9. Allows incorporation of immiscible liquid, Improves material processing as liquid can be converted to powders.
10. Easy scale up for commercial production.
11. Size of the Nanosponges can be varied by modifying the proportion of crosslinker to polymer.
12. Depending on the dosing requirement, the drug release profiles can be varied from fast, medium to slow release.
13. Predictable release.
14. Regeneration of Nanosponges can be done by washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating, changing pH or ionic strength.
15. Less harmful side effects because of drug having less contact with healthy tissue.

### Disadvantages [41]

1. Nanosponges have ability to include only small molecules.
2. Nanosponges could be either paracrystalline or in crystalline form.
3. The loading capacity of Nanosponges depends mainly on degree of crystallization.
4. Paracrystalline Nanosponges can show different loading

## MATERIAL AND METHODS

Simvastatin was gifted by Biocon Limited, Bangalore, India. Dichloromethane, Poly Vinyl Alcohol (PVA) and Pluronic f68 was of lab grade. Lab made distilled water was used throughout study.

### Preparation of Simvastatin loaded Nanosponges [1, 2, 3, and 8]

Nanosponges using different proportions of Pluronic f68 as polymer and co polymers like polyvinyl alcohol was prepared by solvent evaporation method. Disperse phase consisting of Simvastatin (1gm) and requisite quantity of Pluronic f68 dissolved in 10 ml solvent (dichloromethane or ethanol) was slowly added to a definite amount of PVA in100ml of aqueous continuous phase, prepared by using microwave oven. The reaction mixture was stirred at 1000 rpm for three hours on a magnetic stirrer. The Nanosponges formed were collected by filtration through Whatmann filter paper and dried in oven at 50°C for 2 hours. The dried Nanosponges were stored in vacuum desiccator to ensure the removal of residual solvent.

**FORMULATION TABLE**

**For Nanosponges**

**Table no. 1 -formulation of simvastatin loaded Nano sponge.**

| Sr. no. | Excipient | A1 | A2 | A3 | A4 |
|---|---|---|---|---|---|
| 1 | Simvastatin | 1gm | 1gm | 1gm | 1gm |
| 2 | Poly Vinyl Alcohol (PVA) | 2% | 2% | 2% | 2% |
| 3 | Dichloromethane | 10ml | 10ml | 10ml | 10ml |
| 4 | Pluronic f68 | 1gm | 1.5g | 2gm | 2.5gm |
| 6 | Distilled Water | 100ml | 100ml | 100ml | 100ml |

**For tablets**

**Table no. 2 tablet formula.**

| Sr.no. | Ingredients | Quantity |
|---|---|---|
| 1 | Simvastatin loaded Nanosponge batch A2 | 50 mg |
| 2 | Starch | 5%w/w |
| 3 | Lactose | q.s |
| 4 | Povidone | 3%w/w |
| 5 | Magnesium stearate | 0.035%w/w |

**PREFORMULATION STUDIES OF PURE DRUG** [3, 23, 32, 39]

**Solubility studies of pure drug**

Solubility of Simvastatin was carried out in different solvents like- distilled water, 0.1 N NaOH & ethanol and methanol.

**Estimation of calibration curve**

Accurately weighed 10mg Simvastatin was dissolved in 0.1 N NaOH taken in a clean 10ml volumetric flask. The volume was made up to 10ml with 0.1 N NAOH which gives a concentration of 1000µg/ml. From this standard solution, 1ml was pipette out in 10ml volumetric flask and volume was made up to 10ml using 0.1 N NaOH to obtain a concentration of 10µg/ml. From the above stock solution, aliquots of 0.2, 0.4, 0.6, 0.8,1.0 and 1.2 ml each was transferred to a separate 10ml volumetric flask and solution was made up to 10ml using 0.1 N NaOH to obtain a concentration of 2, 4, 6, 8,10 and 12µg/ml respectively. The absorbance of each solution was measured at 247nm.

**Drug excipient compatibility studies**

The drug and excipient compatibility were observed using Fourier Transform – Infra Red spectroscopy (FT-IR).It was performed by Thermofischer scientific Nicolet IS-10.

**EVALUATION TESTS** [1, 3, 8]

**FOR NANOSPONGES**

**Drug Entrapment efficiency**

100mg of the Nano sponge suspension was analysed by dissolving the sample in 10ml of distilled water. After the drug was dissolved 10mL of clear layer of dissolved drug is taken. There after the amount of drug in the water phase was detected by a UV-spectrophotometric method at 247nm. The test was repeated with another Nano particulate sample. The amount of the drug in the suspension was analysed by centrifugation at 500rpm for 5min and by measuring the concentration of the drug in the clear supernatant layer by the UV-spectrophotometric method. The test was again repeated with another sample.

$$\% \text{ of Drug entrapment} = \frac{\text{Mass of drug in Nano sponge}}{\text{Mass of drug used in formulation}} \times 100$$

***In-vitro* drug release study**

*In vitro* release studies were performed in using dialysis membrane method at 100 rpm and 37±0.2oC in 100ml of 6.8 buffer.100 mg of the formulated Nanosponges is used for each experiment. Samples were taken at appropriate time intervals for 30, 60, 90, 120, and 150 up to 360 min. The samples were measured spectrophotometrically at 239 nm. Fresh dissolution medium was replenished each time when sample is withdrawn to compensate the volume.

**Scanning electron microscopy**

The morphological features of prepared Nanosponges are observed by scanning electron microscopy at different magnifications.it was studied at Savitribai Phule University, Pune.It was studied at 100µm and 50 µm. The instrument used EVO MA15 Scanning Electron Microscope, Germany.

**DSC**

The thermal behaviour of drug- Pluronic f68complex was studied in order to confirm the formation of complex. Thermal analysis was carried out by using SDT Q600V20.9 Build 20 Differential scanning calorimeter.

**XRD**

It was performed by using Bruker D5 at Savitribai Phule University, Pune. The samples were run over range from 0 ˚C to 80 ˚C. The step scan mode was performed at 25 ˚C.

**Particle size analysis**

Particle size analysis was performed by using SAGLO SOFT-SGL Micro-imaging Adapter.

**FOR TABLET**

Performed various evaluation IPQC (In Process Quality Control) tests like Hardness, Weight Variation, Friability, disintegration time according to I.P.

**Drug content**

Take 10 tablets. Determine average weight of 10 tablets. Triturate tablets in mortar. Take quantity of powder equivalent to 10 mg simvastatin. Dissolve powder in solvent in which Simvastatin gets dissolved. Determine drug content by using U.V spectrophotometer.

**In vitro Dissolution studies**

In vitro dissolution studies of tablets were performed in 900 ml of 0.1 N HCL for 1 hour at 75 rpm by using USP type II apparatus.

**RESULT AND DISCUSSION**

**Pre-formulation study**

**Solubility study**

**Table no.3 -solubility results.**

| Sr.no | Solvent | Solubility (mg/ml) |
|---|---|---|
| 1 | Water | Insoluble |
| 2 | 0.1M NaOH | 70 |
| 3 | Ethanol | 160 |
| 4 | Methanol | 200 |

**Calibration curve data of Simvastatin**

The linearity was found to be in the range of 2- 12µg/ml. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

**Table no.4 -calibration curve studies of simvastatin.**

| Sr. no. | Concentration (µg/ml) | Absorbance(nm) |
|---|---|---|
| 1 | 10 | 0.249 |
| 2 | 15 | 0.432 |
| 3 | 20 | 0.572 |
| 4 | 25 | 0.694 |
| 5 | 30 | 0.829 |
| 6 | 35 | 0.976 |

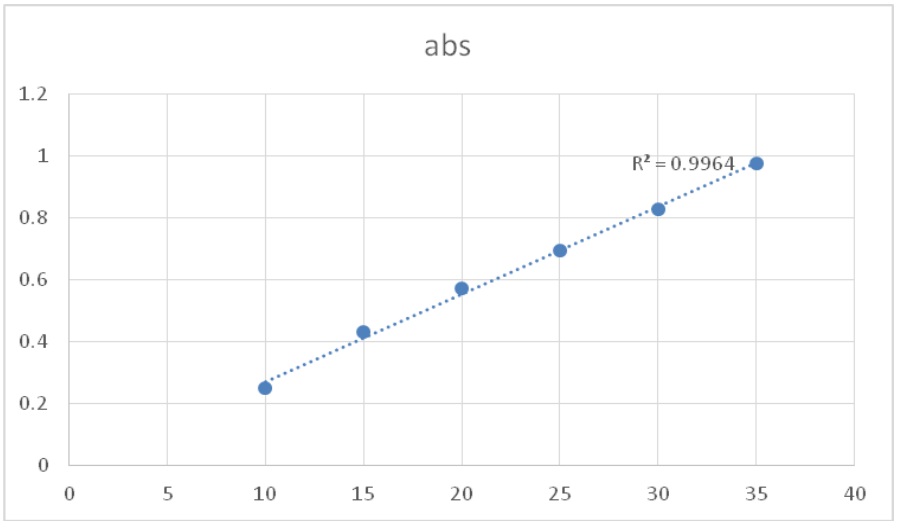


**Fig.2-calibration curve of simvastatin.**

**Drug excipient compatibility studies**

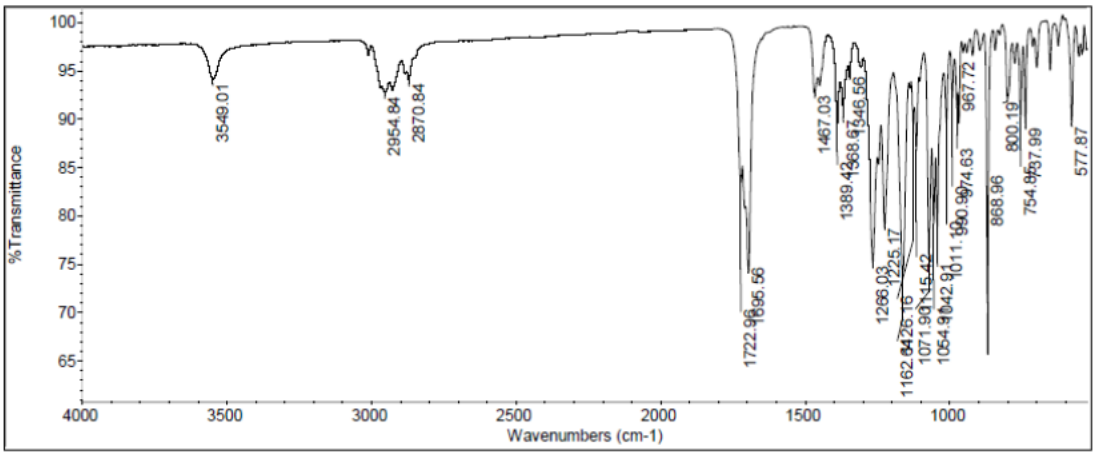


**Fig.3 Drug compatibility study of pure simvastatin.**

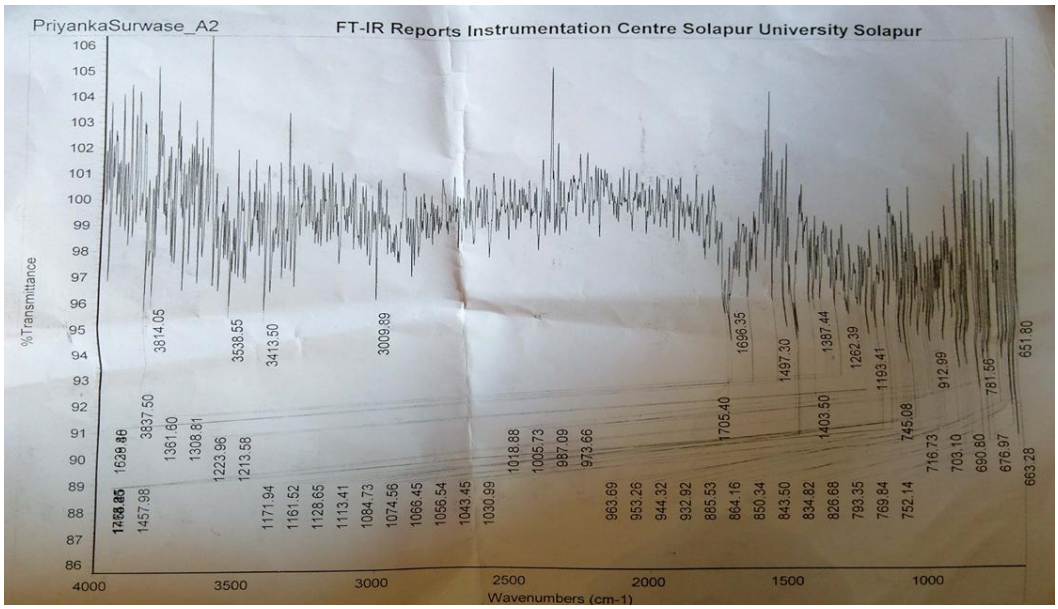


**Fig.4 Result showing drug excipient compatibility profile by FTIR.**

Figure 3 showed FT-IR spectra of pure Simvastatin and Figure 4 showed FT-IR spectra of Simvastatin Nanosponges. The FT-IR spectrum of pure Simvastatin was equivalent to the FT-IR spectra obtained by the Simvastatin Nanosponges. This indicated that no interaction occurred between Simvastatin and inclusion complex of Pluronic F68. The results revealed no considerable changes in the IR peaks of Simvastatin, when mixed with Pluronic F68.

**Evaluation study of prepared Nano sponges**
**Drug entrapment efficiency**

**Table no. 5-drug entrapment efficiency.**

| Sr. no. | Formulation code | % drug entrapped |
|---|---|---|
| 1 | A1 | 57.55 |
| 2 | A2 | 83.26 |
| 3 | A3 | 42.08 |
| 4 | A4 | 71.86 |

***Invitro* drug release study**


**Image no.1-invitro drug release in procedure.**

**Table no.6-*invitro* drug release.**

| Sr. no. | Time (in min) | A1 (%) | A2 (%) | A3 (%) | A4 (%) |
|---|---|---|---|---|---|
| 1 | 30 | 21.46 | 15.25 | 05.00 | 00.90 |
| 2 | 60 | 33.20 | 29.78 | 10.98 | 03.51 |
| 3 | 90 | 36.31 | 38.77 | 17.86 | 08.36 |
| 4 | 120 | 42.1 | 46.08 | 19.12 | 21.88 |
| 5 | 150 | 49.9 | 59.36 | 26.71 | 36.39 |
| 6 | 180 | 56.30 | 62.88 | 33.20 | 41.44 |
| 7 | 210 | 62.42 | 69.9 | 39.10 | 50.36 |
| 8 | 240 | 78.58 | 75.00 | 44.06 | 61.69 |
| 9 | 270 | 98.59 | 81.07 | 57.88 | 78.36 |
| 10 | 300 | 98.59 | 88.98 | 68.09 | 86.92 |
| 11 | 330 | 105.01 | 93.08 | 72.11 | 98.57 |
| 12 | 360 | 105.66 | 98.59 | 89.08 | 102.00 |

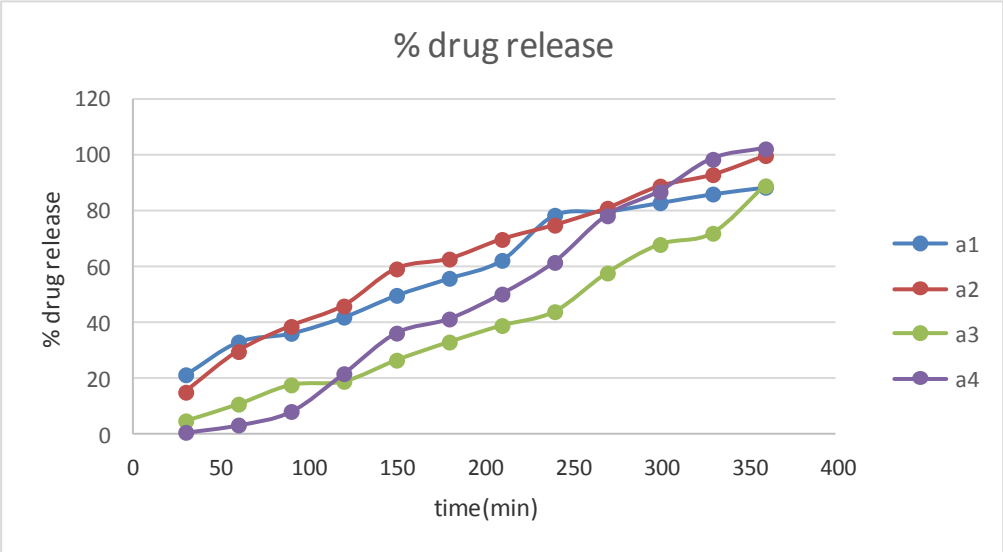


**Fig.5- *invitro* drug release profile.**

**Scanning electron microscopy**

Scanning electron microscopy is performed at physics department, Savitribai Phule Pune University. It was performed on JEOL jsm 6360A, mfg. Japan.

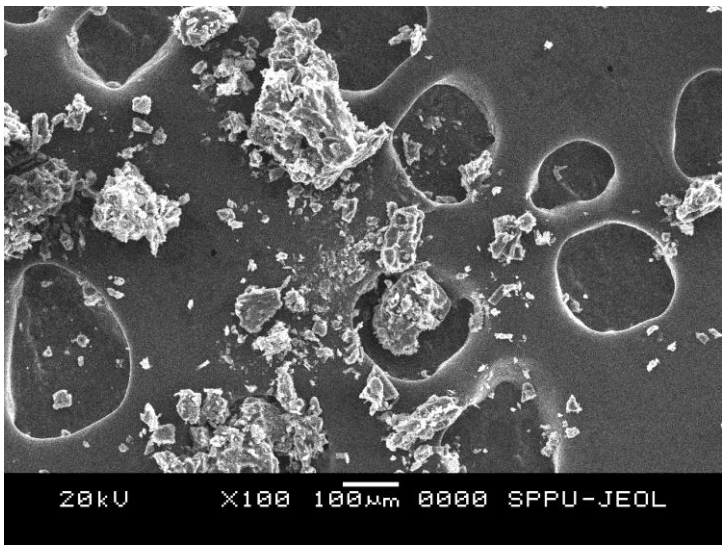


**Fig.4-SEM image of batch A2 at 100µ.**

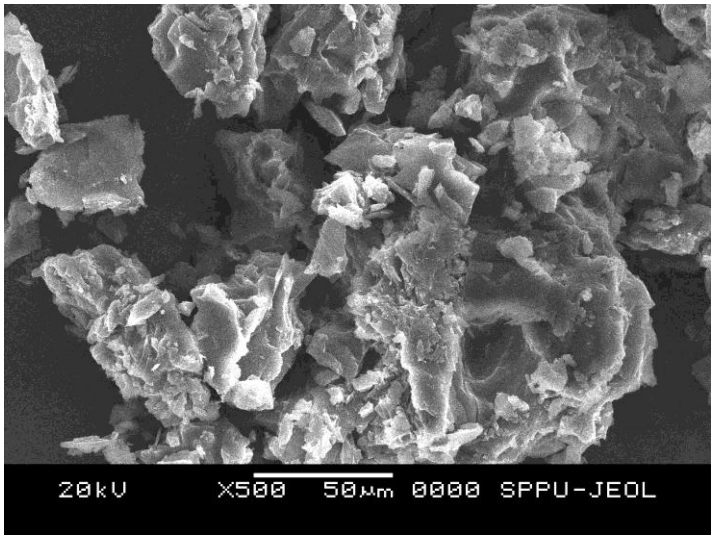


**Fig. 5-SEM image of batch A2 at50µ.**

**XRD**

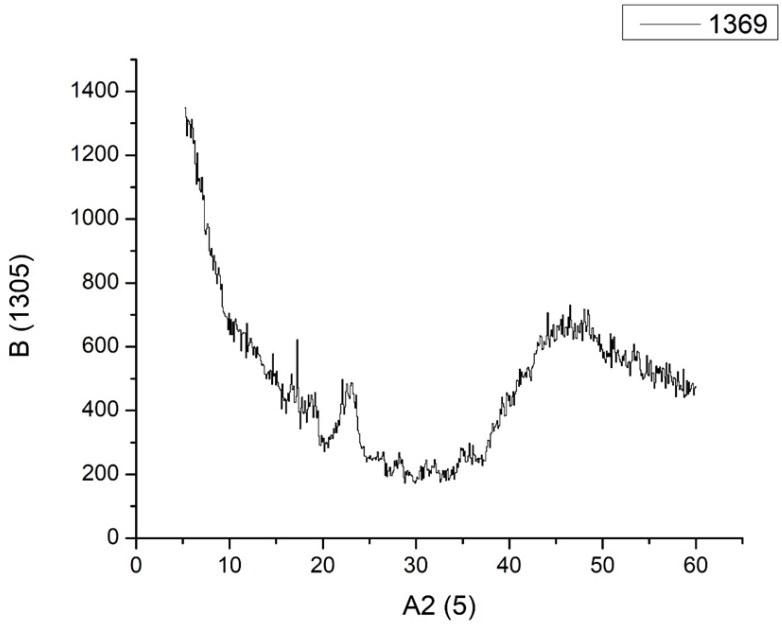


**Figure 7.XRD graph.**

**DSC**

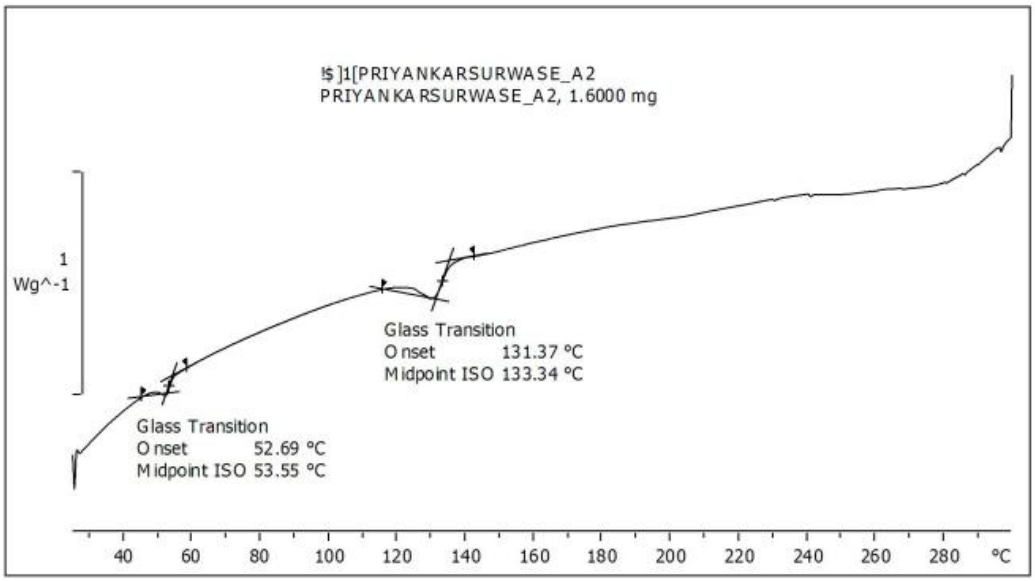


**Figure 8. DSC graph.**

**Particle size analysis**

**Evaluation studies of tablets**

Table 6 shows results for various IPQC (In Process Quality Control) parameters like Hardness, Weight variation, friability, disintegration time.

**Table 7: IPQC Parameters.**

| Parameters Inference | Found value |
|---|---|
| Hardness | 3 kg/cm2 |
| Weight variation test | Passes |
| Friability | Passes |
| Disintegration time | 70 seconds |

**Drug Content**

Drug content was found to be 99.8 % using Systronics UV 2102.

**In vitro dissolution studies**

Dissolution test were conducted using Electro Lab 8 station machine USP II apparatus.it is observed that at 60 min drug released from tablet is 98.05 %.it reveals that tablet form for prepared Nanosponges is suitable.

**Table 8. % drug release data from tablet.**

| Sr. No. | Min | % Release |
|---|---|---|
| 1 | 5 | 0.56 |
| 2 | 10 | 9.71 |
| 3 | 15 | 13.11 |
| 4 | 20 | 27.90 |
| 5 | 25 | 31.48 |
| 6 | 30 | 39.8 |
| 7 | 35 | 47.33 |
| 8 | 40 | 61.20 |
| 9 | 45 | 70.55 |
| 10 | 50 | 76.42 |
| 11 | 55 | 89.04 |
| 12 | 60 | 98.05 |

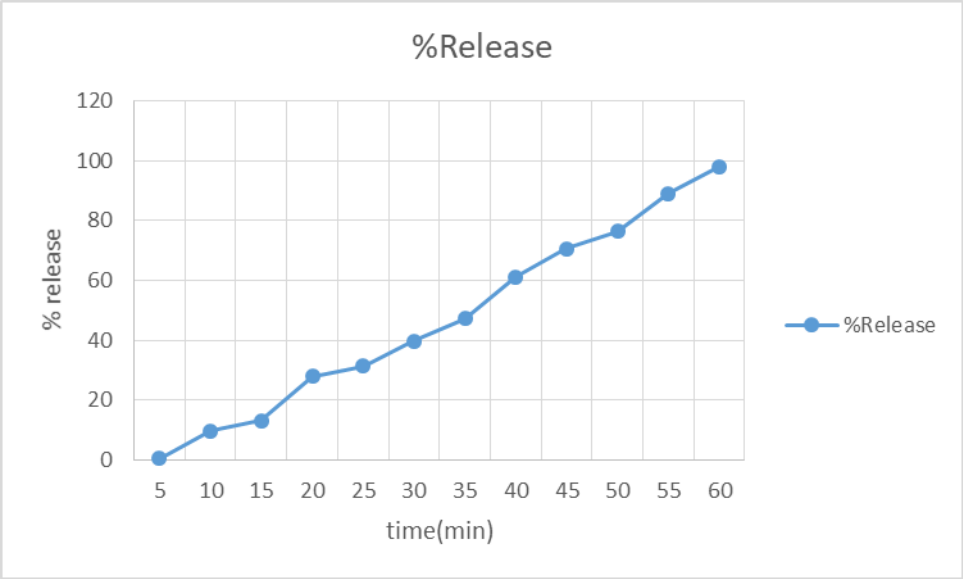


**Figure 9. %drug release graph.**

## CONCLUSION

One of the most significant property of Pluronic f68 based Nanosponges is that they are able to encapsulate a variety of different types of drug molecules. Pluronic f68 based Nanosponges of simvastatin are solid, porous, biocompatible Nano-particulate three dimensional structures whose production cost is less because of simple synthesis, purification procedures and use of limited number of reagents. Present work shows that Nanosponges prepared are efficient and fulfil the purpose for which it is prepared.

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