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. Nanosponge is water soluble. This does not mean the molecules chemically break up in water, but it means that nanosponge particles can mix with water and use it as transport fluid, for example to be injected. So, in theory nanosponge 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 Betacyclodextrin and Ethyl cellulose.in this article preparation and evaluation of Nanosponges is described as per obtained results.*

Key Words: *Nano sponge, simvastatin, poorly soluble drug, drug delivery, β-cyclodextrin*

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 nanosponge formation of poorly soluble simvastatin. The present research work focuses on improvement in solubility and bioavailability of simvastatin to provide an efficient way of oral administration.

MATERIAL AND METHODS

Simvastatin was obtained as a gift sample from Biocon Limited, Bangalore, India. Dichloromethane, ethyl cellulose was of lab grade and betacyclodextrin was ordered online from ChemCenter La Jolla, California. Lab made distilled water was used throughout study.

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

Nanosponges using different proportions of Beta cyclodextrin as polymer and co polymers like betacyclodextrin was prepared by solvent evaporation method. Disperse phase consisting of Simvastatin (1gm) and requisite quantity of ethyl cellulose dissolved in 10 ml solvent (dichloromethane or ethanol) was slowly added to a definite amount of betacyclodextrin 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

Table No.1: Formulation of simvastatin loaded nanosponge

Sr. no.	Ingredients	A1	A2	A3	A4
1	Simvastatin	1gm	1gm	1gm	1gm
2	Ethyl cellulose	1gm	1gm	1gm	1gm
3	Dichloromethane	10ml	10ml	10ml	10ml
4	B-cyclodextrin	1gm	2g	3gm	4gm
6	Distilled Water	100ml	100ml	100ml	100ml

PREFORMULATION STUDIES OF PURE DRUG [3, 5, 6, 7]

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 STUDIES OF PREPARED NANOSPONGES [1, 3, 8]

Drug Entrapment efficiency:

100mg of the nanosponge suspension was analysed by dissolving the sample in 10ml of Ethanol. 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 239 nm. 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.

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

***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, and 90,120,150 minup 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.

Evaluation studies of nanosponge tablets:

Performed various evaluation tests like Hardness, WeightVariation, Friability, disintegration time according to I.P.

Drug content

Take 10 tablets. Determine average weight of 10 tablets. Triturate tablets in mortar. Takequantity of powder equivalent to 10 mg simvastatin. Dissolve powder in solvent in whichSimvastatin gets dissolved. Determine drug content by using UV 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:

Nanosponges were characterized by various preformulation parameters such as solubility of simvastatin in water, 0.1 M NaOH, ethanol and methanol. Maximum wavelength of absorbance was determined by calibration curve.

Solubility study

Table no.2-solubility results

Sr.no	Solvent	Solubility(mg/ml)
1	Water	Insoluble
2	0.1M NaOH	69
3	Ethanol	158
4	Methanol	195

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.3-callibration curve studies of simvastatin

Sr. no.	Concentration (µg/ml)	Absorbance(nm)
1	10	0.098
2	15	0.2194
3	20	0.276
4	25	0.371
5	30	0.457
6	35	0.513

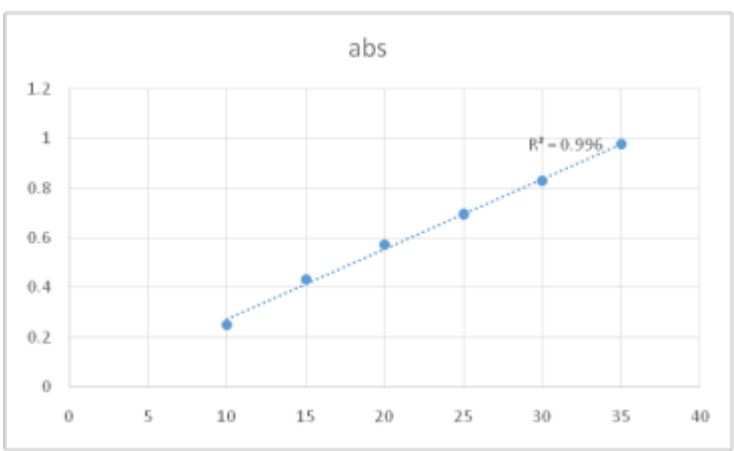

Fig1-calibration curve of simvastatin

Drug excipient compatibility studies

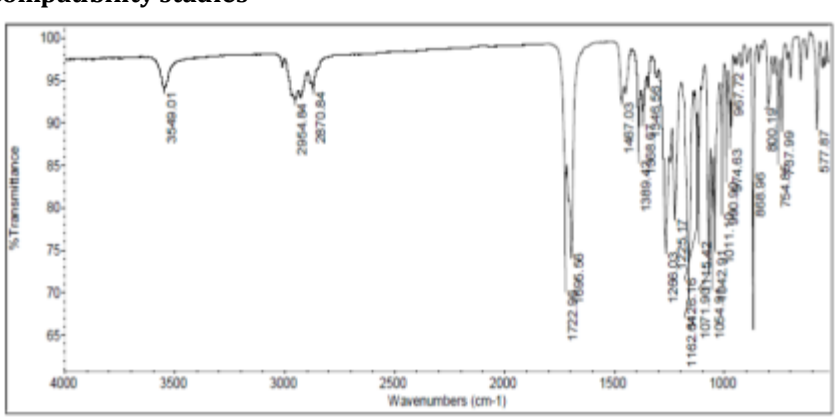

Fig. 2: FTIR spectra of pure simvastatin

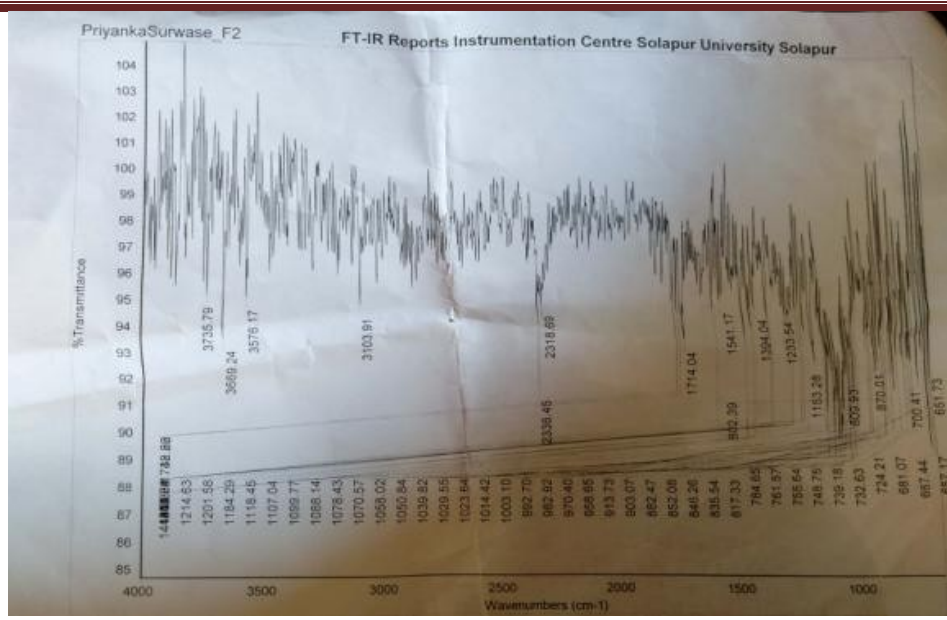

Fig.3: FTIR spectra of F2 Batch of Nanosponges.

Evaluation study of prepared Nanosponges:

Drug entrapment efficiency:

Entrapment efficiency of Nanosponges ranges from 44.87% to 89.99%.

Table No. 4: Drug entrapment efficiency of nanosponges

Sr. no.	Formulation code	% drug entrapped
1	A1	67.08
2	A2	89.99
3	A3	73.64
4	A4	44.87

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

Table No.5: *in-vitro* drug release

Sr. no.	Time (in min)	A1	A2	A3	A4
1	30	10.89	15.25	05.00	00.90
2	60	22.57	27.34	10.98	03.51
3	90	36.31	38.77	17.86	15.36
4	120	42.1	47.07	19.12	21.88
5	150	47.51	59.36	26.71	33.39
6	180	56.30	62.88	33.20	41.44
7	210	63.65	70.55	39.10	54.36
8	240	78.58	75.00	44.06	61.69
9	270	83.00	81.07	57.88	76.82
10	300	88.22	85.90	68.09	86.92
11	330		93.08	72.11	98.57
12	360		100.02	82.48	120.00

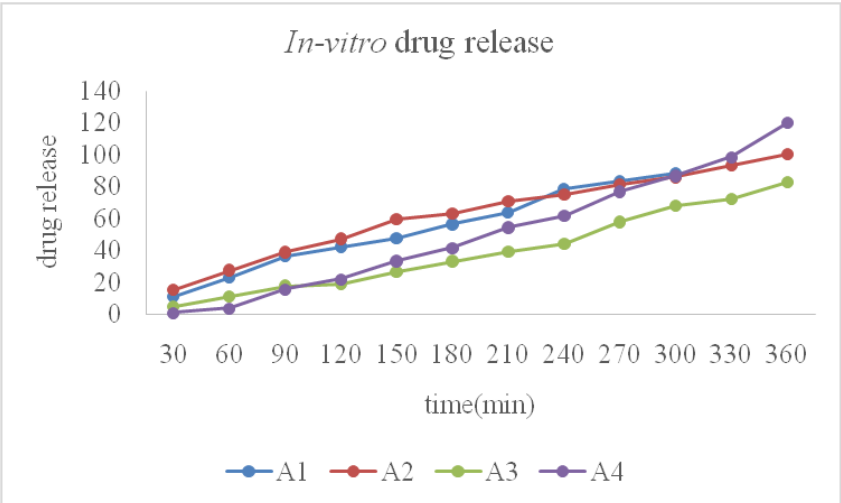

Fig.4:*In-vitro* drug release profile

Scanning Electron Microscopy

It was performed on JEOL JSM 6360A, mfg. Japan. The Nanosponges was found to be spherical and smooth in nature.

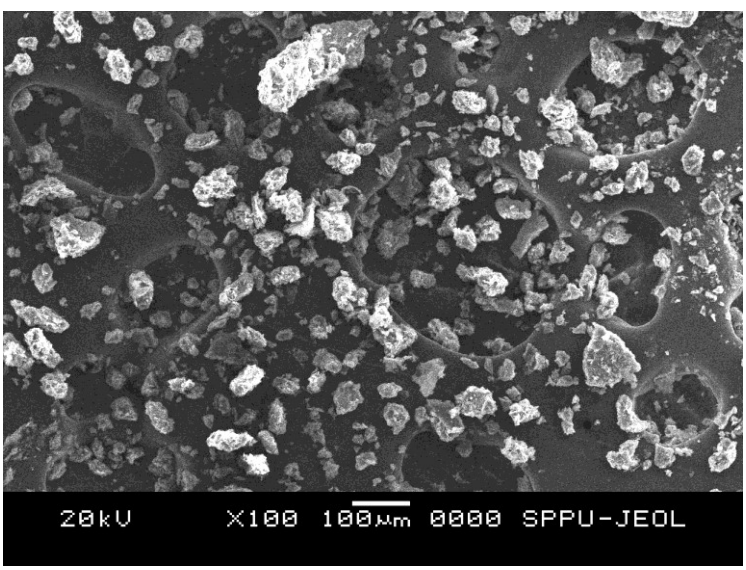

Fig.5-SEM image of batch F2 at 100µ

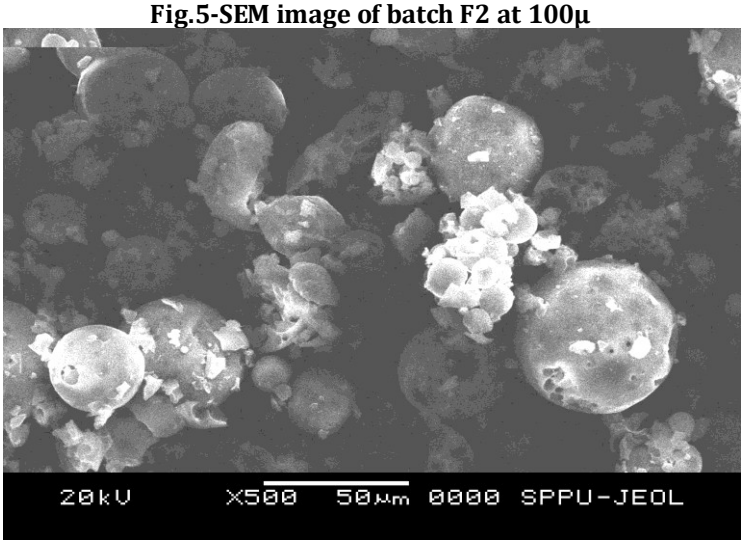

Fig.6-SEM image of batch F2 at50µ

Differential Scanning Coloroemetry:

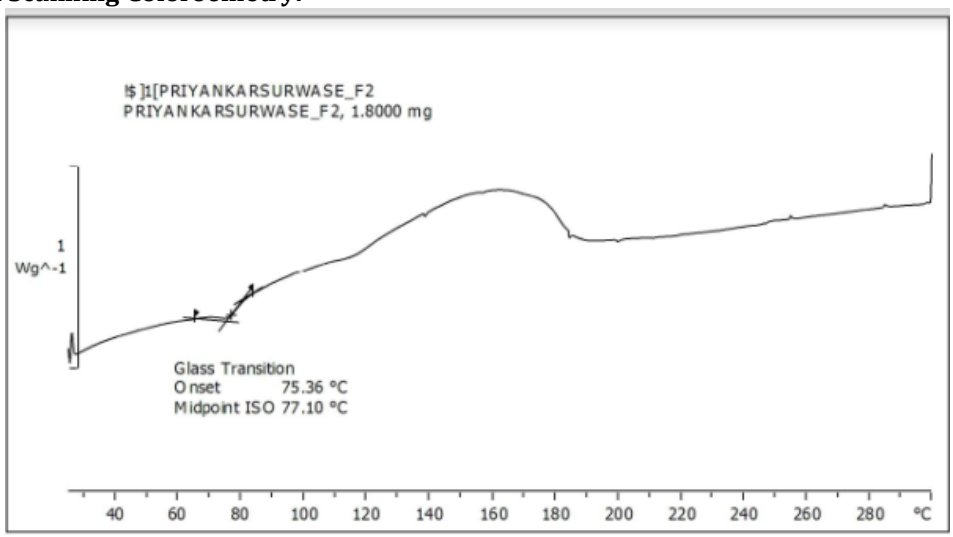

Fig no. 7. DSC graph

Powder X-Ray diffraction:

No sharp peaks are observed in XRD graph hence it shows paracrystalline nature.

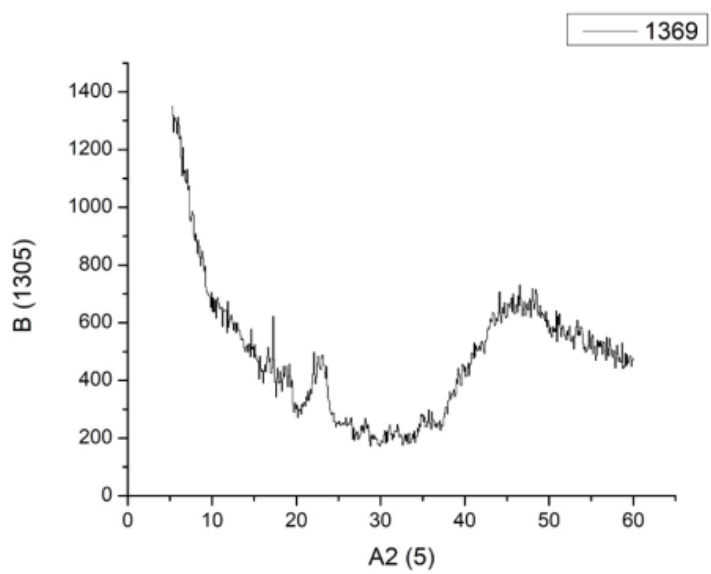

Fig. 8: XRD graph of F2 batch

Evaluation studies of tablets

Table 7 shows results for various parameters like Hardness, Weight variation, friability, disintegration time.

Table 6: IPQC Parameters

Parameters Inference	Found value
Hardness	3.06kg/cm2
Weight variation test	Passes
Friability	0.1-0.35%
Disintegration time	65 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 No. 7:% drug release data from tablet of batch F2

Sr. No.	Time (min)	% Release
1	5	1.65
2	10	7.12
3	15	15.26
4	20	26.48
5	25	34.00
6	30	42.95
7	35	54.00
8	40	61.01
9	45	70.55
10	50	78.26
11	55	84.42
12	60	99.56

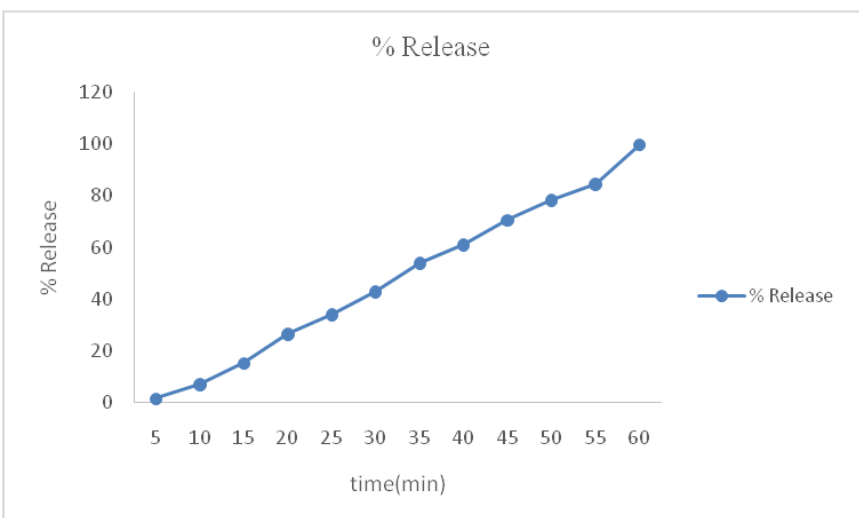

Figure.8: %drug release graph

CONCLUSION

One of the most significant property of Beta cyclodextrin based Nanosponges is that they are able to encapsulate a variety of different types of drug molecules. Beta cyclodextrin 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.

ABBREVIATIONS

1. XRD- X-Ray Diffraction
2. DSC- Differential scanning calorimetry
3. SEM- Scanning Electron Microscopy
4. UV- Ultraviolet Visible
5. FTIR- Fourier Transform – Infra Red spectroscopy
6. Fig.no.-Figure Number

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