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Design and Characterization of Atorvastatin Calcium-Loaded Nanosponges for Enhanced Solubility

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ABSTRACT

Atorvastatin calcium, a widely prescribed statin for hyperlipidemia, exhibits poor solubility and bioavailability. This study aimed to develop drug-loaded nanosponges (NSGs) to enhance solubility and achieve controlled release. Preformulation studies confirmed drug's physicochemical properties, including solubility, melting point, and spectral characteristics. Nanosponges were prepared using ethyl cellulose (EC) as the polymer and dimethyl carbonate (DMC) as the cross-linker, with whey protein isolate (WPI) as a stabilizer. A 3^2 factorial design optimized the formulation, evaluating particle size, entrapment efficiency (EE), and drug release. The optimized formulation (F6) exhibited a particle size of 106 nm, EE of 93.89%, and significantly improved solubility (17-fold in distilled water, 21-fold in pH 1.2 buffer). In vitro release studies demonstrated sustained drug release (93.98% in pH 6.8 buffer) compared to plain drug (37.81%) and marketed tablets (59.56%). Stability studies confirmed the formulation's robustness under ICH guidelines. The developed drug-NSGs offer a promising approach to enhance solubility and therapeutic efficacy.

INTRODUCTION

Atorvastatin calcium is a potent HMG-CoA reductase inhibitor used to manage hypercholesterolemia. Despite its efficacy, drug suffers from poor aqueous solubility, leading to low bioavailability. Nanosponges, porous polymeric nanoparticles, have emerged as a novel drug delivery system to improve solubility, stability, and controlled release of poorly soluble drugs.

This study focused on developing drug-loaded nanosponges using EC and DMC, optimized via a factorial design. The objectives included:

Standardizing ATRC and evaluating its physicochemical properties.Developing and characterizing NSGs for enhanced solubility.Optimizing the formulation using a 3^2 factorial design.Assessing stability under accelerated conditions.

Materials

Atorvastatin calcium (Vitalife Laboratories, India).Ethyl cellulose (EC), dimethyl carbonate (DMC), whey protein isolate (WPI).Solvents: Methanol, ethanol, dimethyl sulfoxide (DMSO).

Buffers: pH 1.2, 6.8, and 7.4 phosphate buffers.

METHODS

Preformulation Studies

Standardization: Evaluated appearance, solubility, melting point, UV/FTIR spectra, loss on drying, and assay.

Analytical Method Development: UV spectrophotometry at λmax 246 nm; validation for linearity, precision, accuracy, and robustness.

Formulation of Nanosponges

Solvent Method: ATRC, EC, and DMC were dissolved in DMSO, cross-linked, and stabilized with WPI.

Optimization: A 3^2 factorial design evaluated EC:DMC ratios (1:5 to 1:15) for particle size, EE, and drug release.

Characterization

Particle Size and Zeta Potential: Dynamic light scattering (Malvern Zetasizer).

Entrapment Efficiency (EE): Centrifugation and UV analysis of free drug.

Morphology: FESEM and TEM for surface and internal structure.

Solid-State Analysis: FTIR, DSC, and PXRD for compatibility and crystallinity.

In Vitro Release: USP Type II apparatus in pH 6.8 buffer.

Stability Studies: ICH guidelines (25°C/60% RH, 40°C/75% RH for 6 months).

RESULTS AND DISCUSSION

Preformulation Studies:

Spectral analysis:*UV Spectroscopy:*

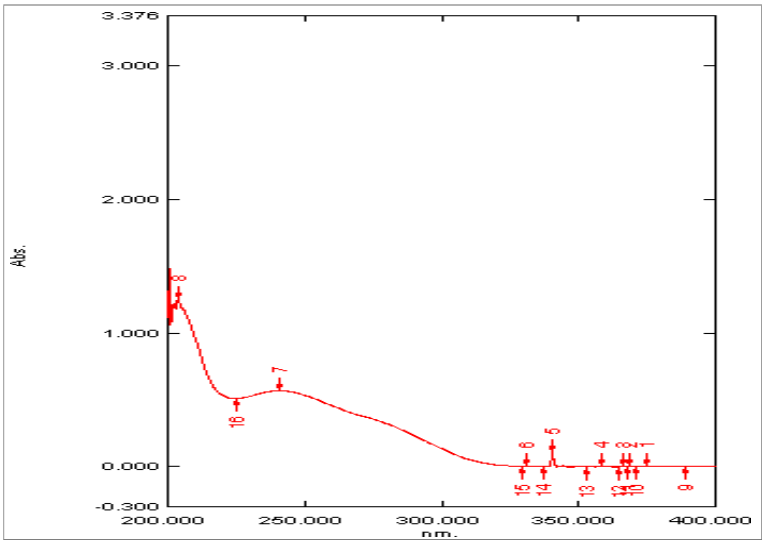

Fig 1: UV-visible spectrum of Atorvastatin calcium

Field Emission Scanning Electron Microscopy (FESEM):

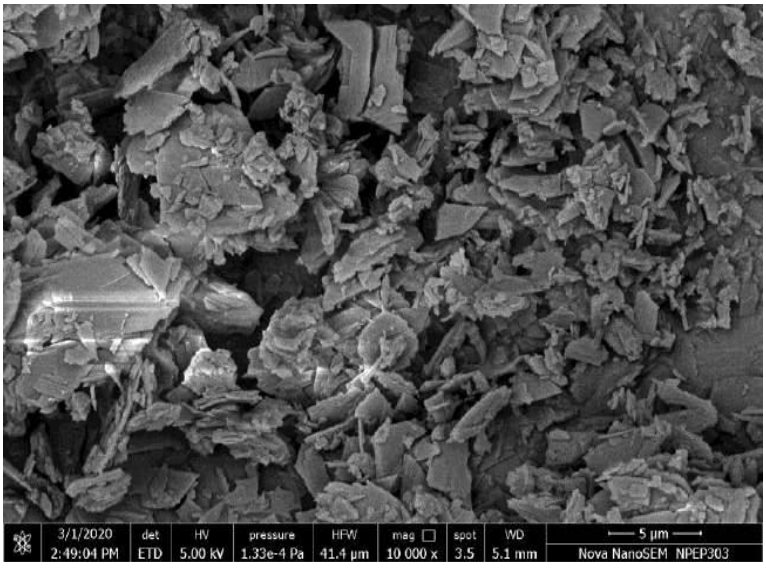

Fig 2: FESEM micrograph of Atorvastatin calcium

Fourier Transform Infrared (FTIR) spectroscopy:

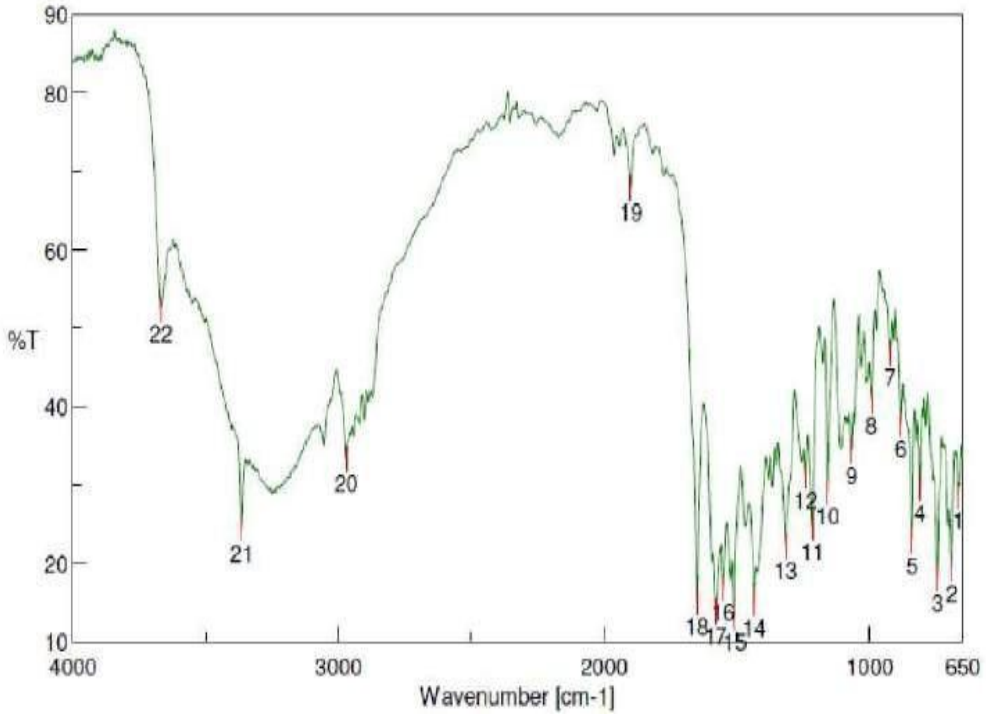

Fig 3: FTIR spectra of Atorvastatin calcium

DifferentIl Scanning Calorimetry (DSC) (Melting temperature range):

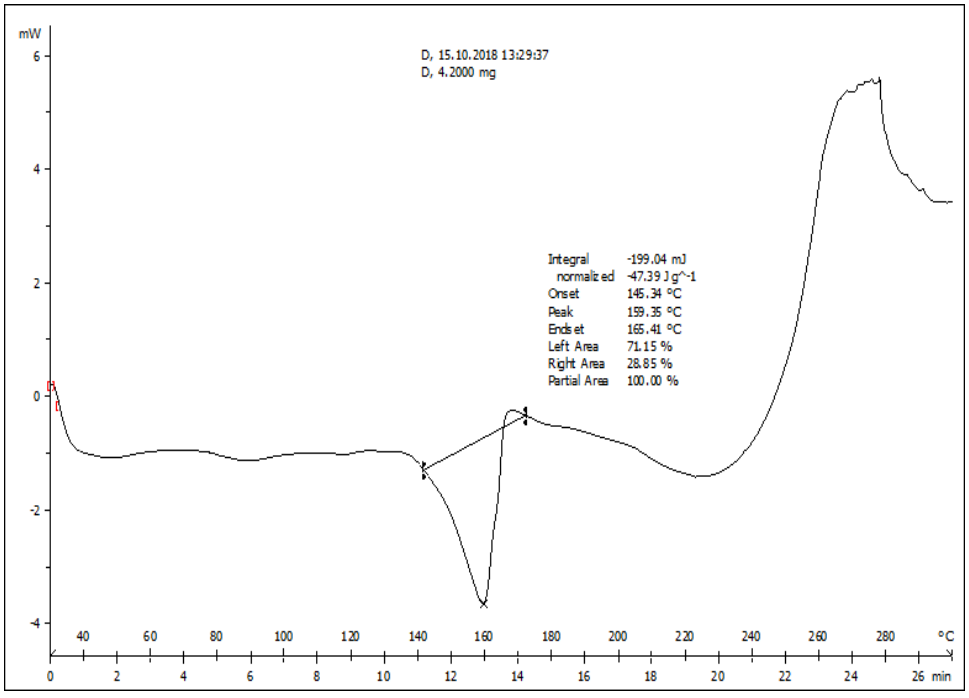

Fig 4: DSC thermogram of Atorvastatin calcium

ANALYTICAL STUDIES

Determination of Calibration curve by UV visible spectrophotometer

Study of spectra and selection of analytical wavelength:

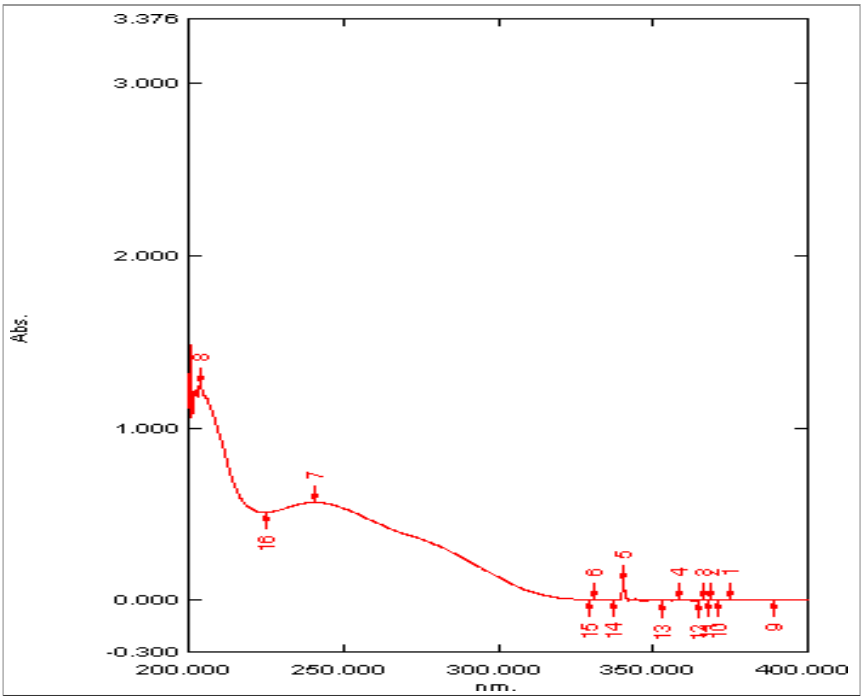

Fig 5: UV-absorption spectrum of Atorvastatin calcium

DRUG-EXCIPIENT COMPATIBILITY STUDIES:

FT-IR Spectroscopy (Vibrational spectroscopy):

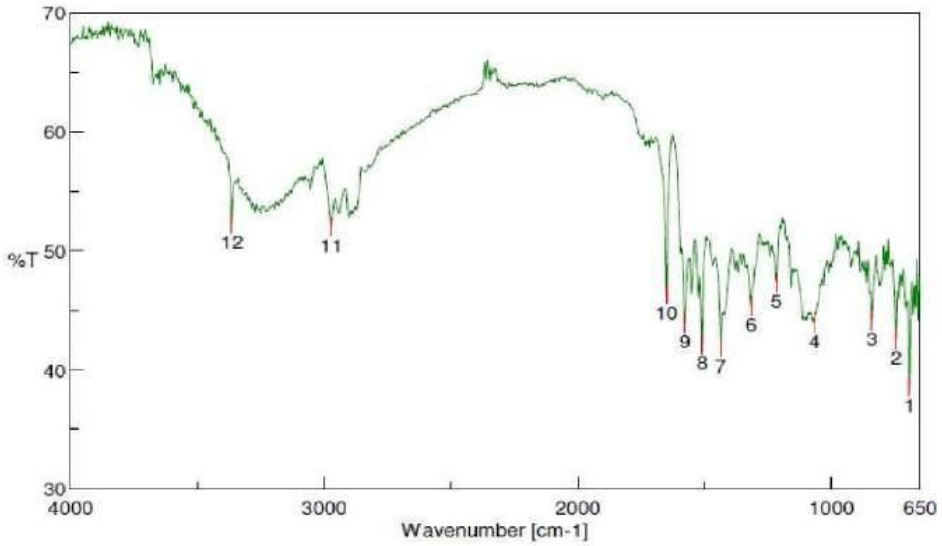

Fig6 : FT-IR spectra of physical mixture

FORMULATION AND DEVELOPMENT STAGE

Method of Nanosponges Formulation (NSGs): I.2.2.1. I.3.1. Optimization Study:Response Surface Analysis (RSA):
Response surface plots for measured responses

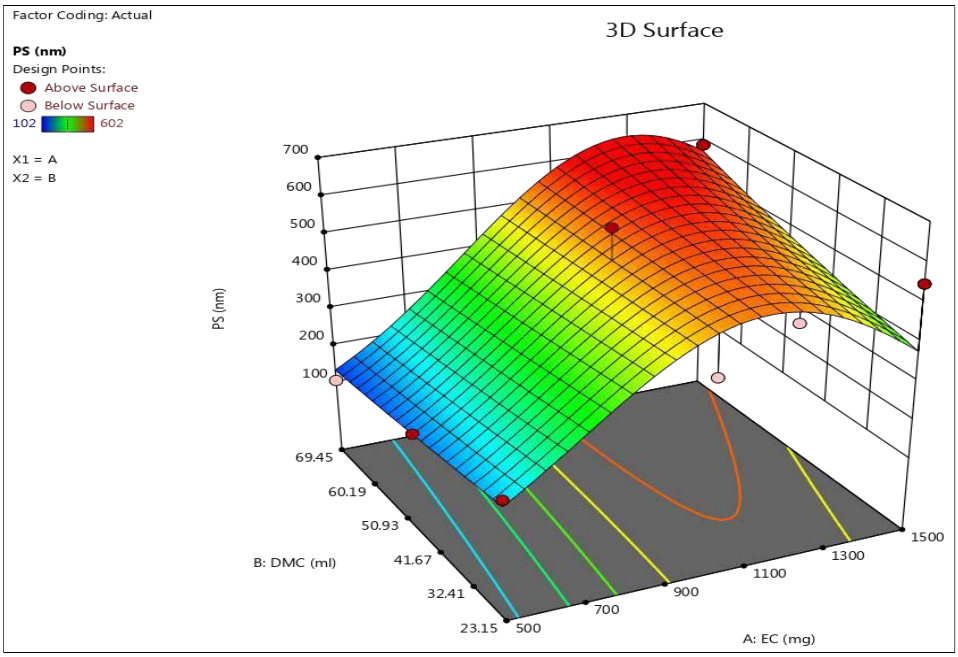

Fig 7: Response surface plot showing the effect of EC and DMC ratios on the PS from formulation.

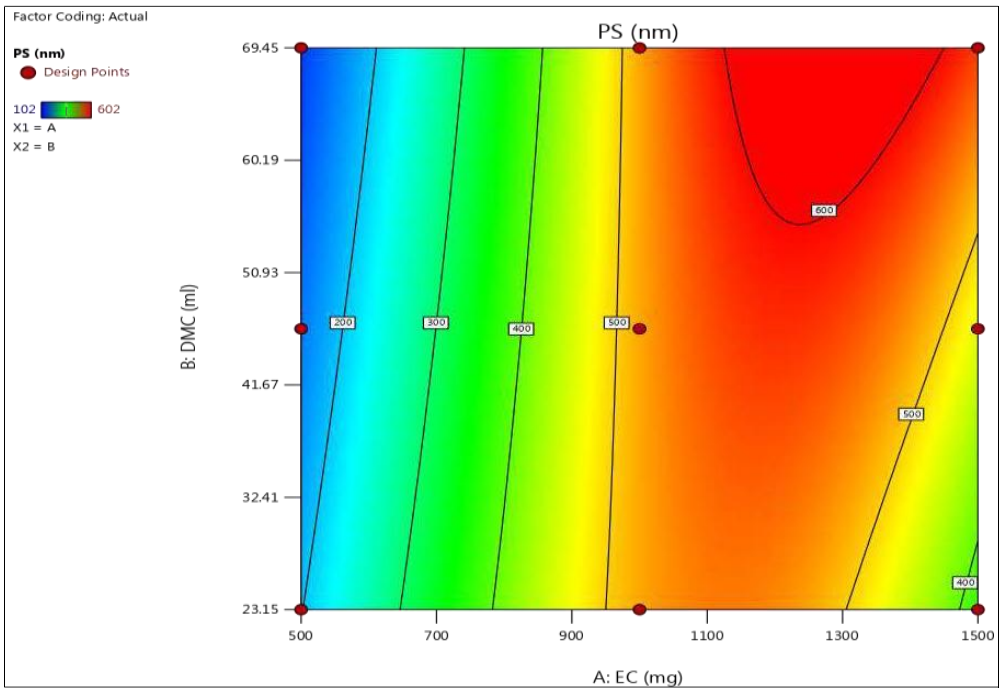

Fig 8: Counter plot showing the effect of EC and DMC ratios on the PS from formulation

Response surface plots for measured responses:

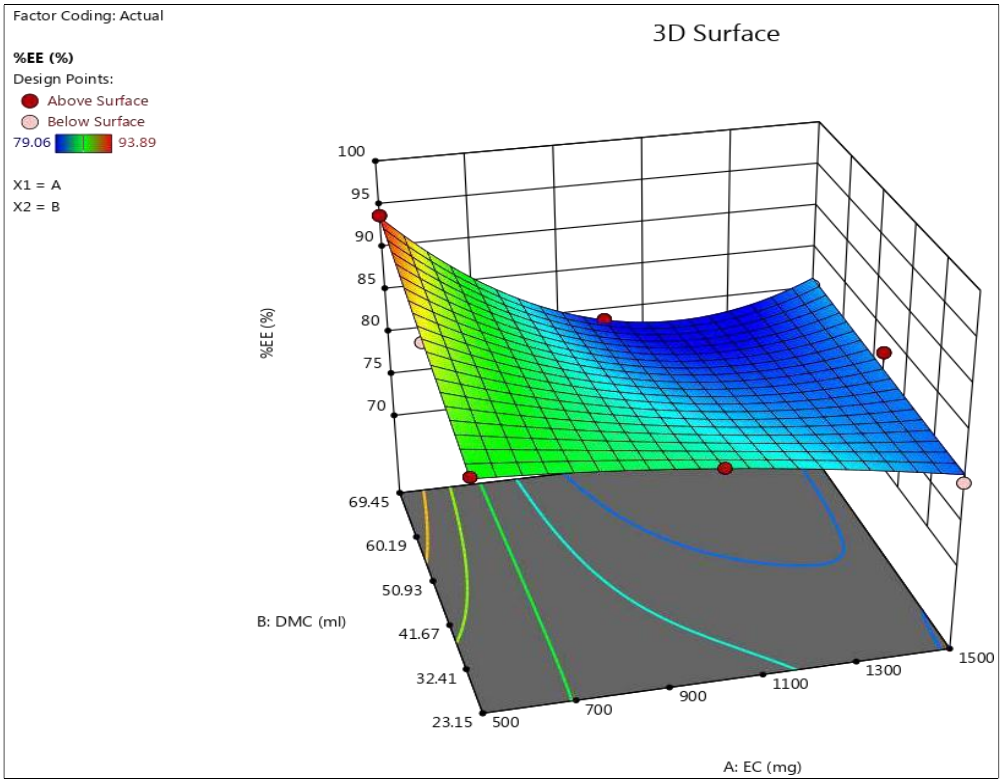

Fig 9: Response surface plot showing the effect of EC and DMC ratios on the % EE from formulation

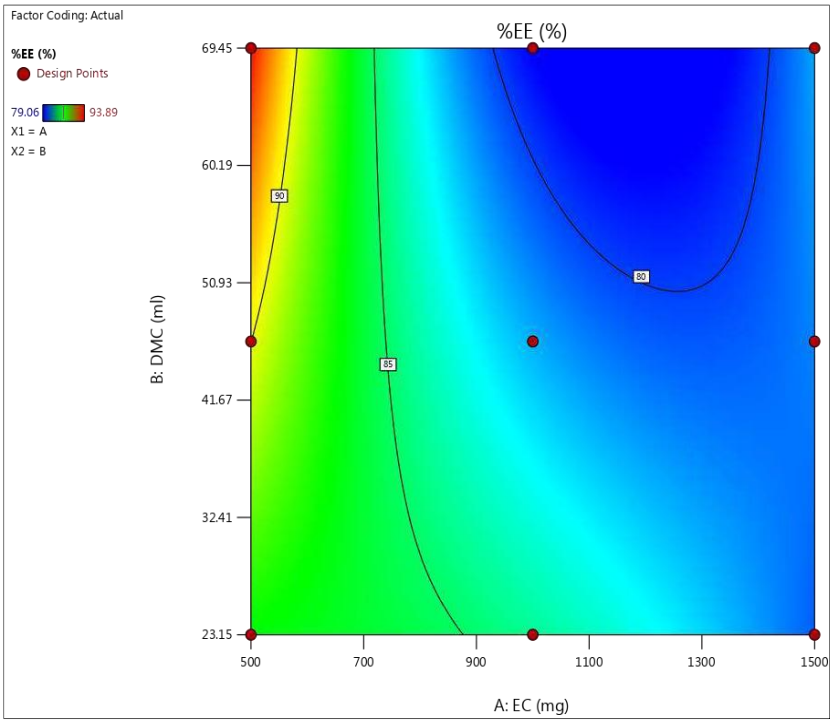

Fig 10: Counter plot showing the effect of EC and DMC on the % EE from formulation

Response surface plots for measured responses.

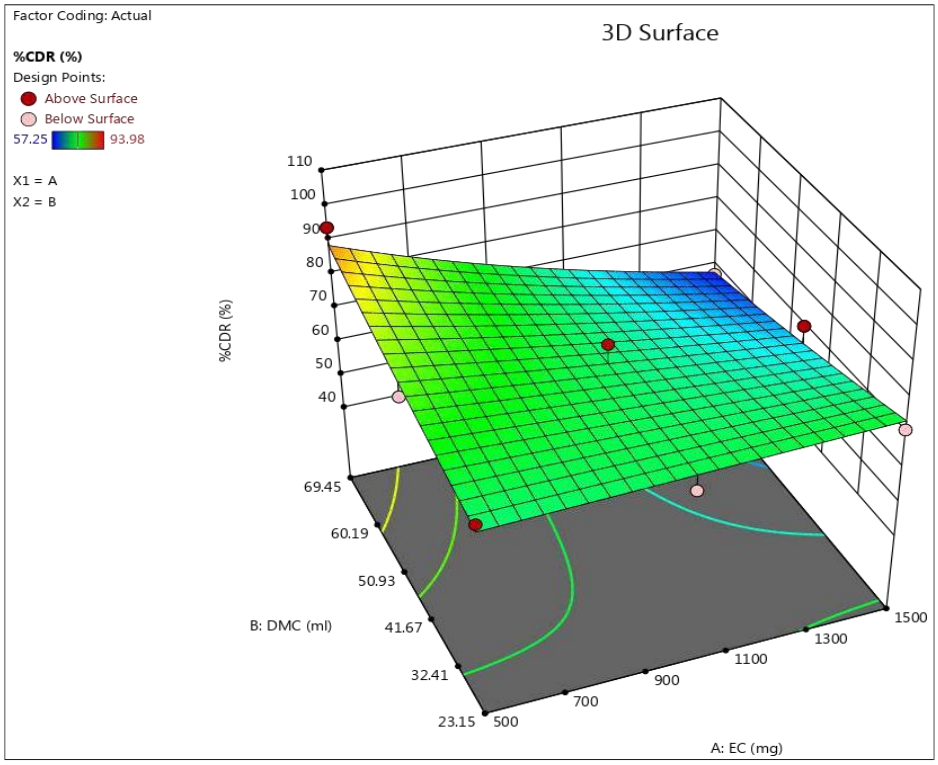

Fig 11: Response surface plot showing the effect of EC and DMC on the % CDR from formulation

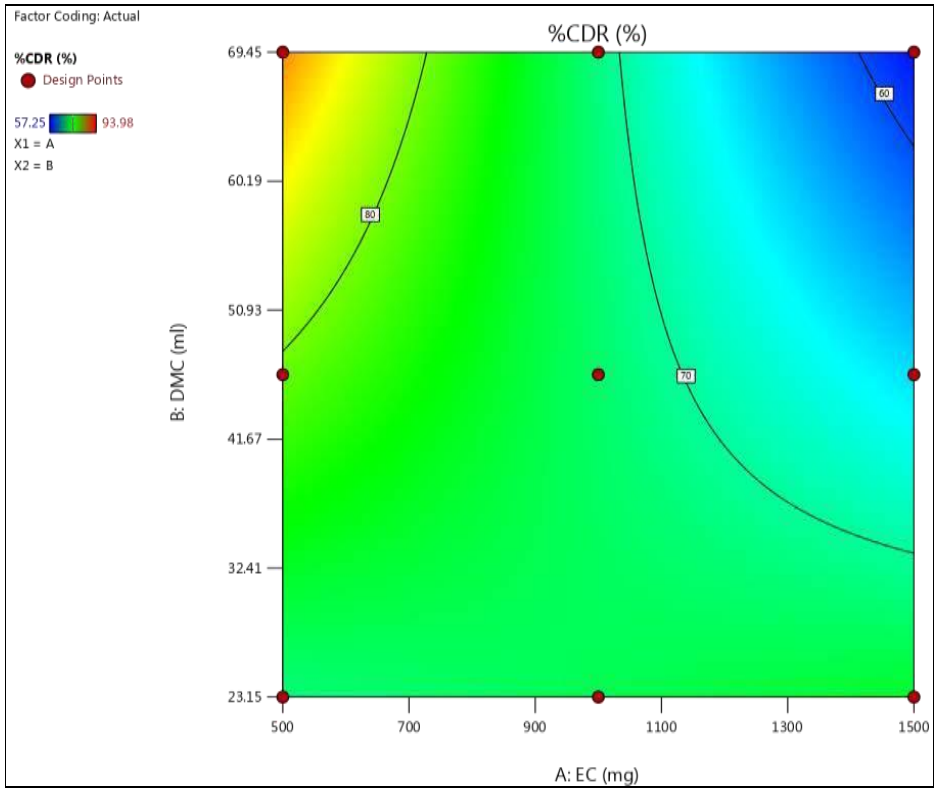

Fig 12: Counter plot showing the effect of EC and DMC on the % CDR from formulation

EVALUATION AND CHARACTERIZATION OF NSGS

Saturation solubility study:

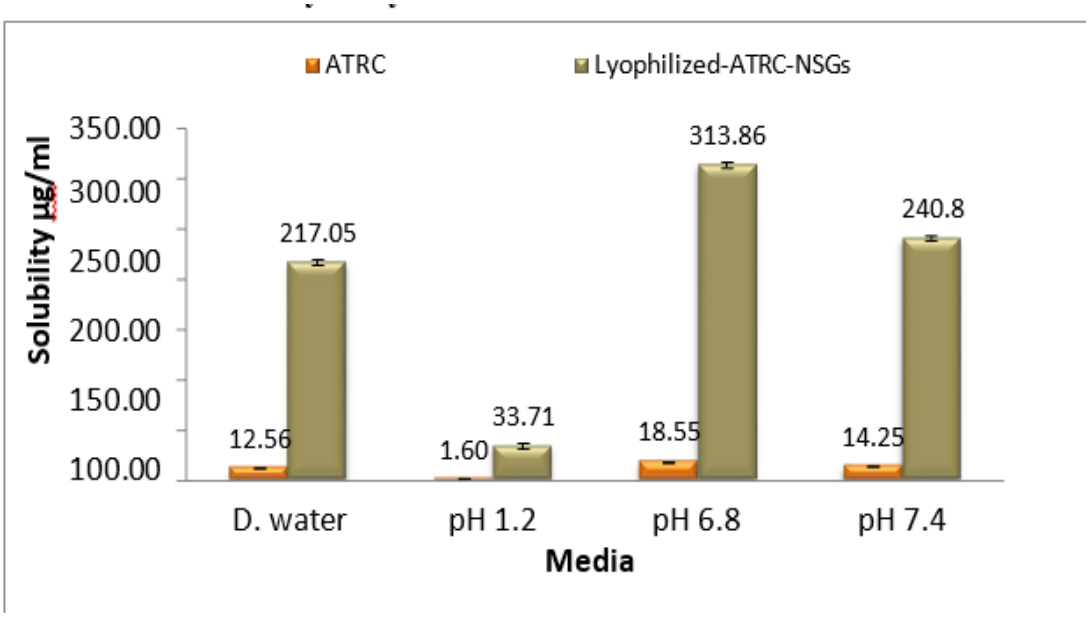

Fig 13: Solubility Comparison of pure ATRC and lyophilized NSGs in different medI

Entrapment efficiency and Drug loading:

Table 1: Percent drug encapsulation and drug loading of NSGs[a]

Run	ATRC: EC (% w/w)	Percent drug encapsulation(%	Unentraped drug (%)	Drug Loading (%)	Solubility (µg/ml)
F1	1: 15	80.56	19.43	14.39	75.42
F2	1: 10	79.06	20.94	21.96	89.63
F3	1: 10	84.36	15.64	23.43	107.57
F4	1: 15	82.87	17.13	14.8	133.32
F5	1: 5	86.6	13.4	39.36	163.46
F6	1: 5	93.89	6.11	42.68	313.86
F7	1: 5	89.62	10.38	40.74	184.69
F8	1: 10	81.53	18.47	22.65	226.96
F9	1: 15	79.49	20.51	14.2	139.73

Particle size and zeta potentIl analysis:

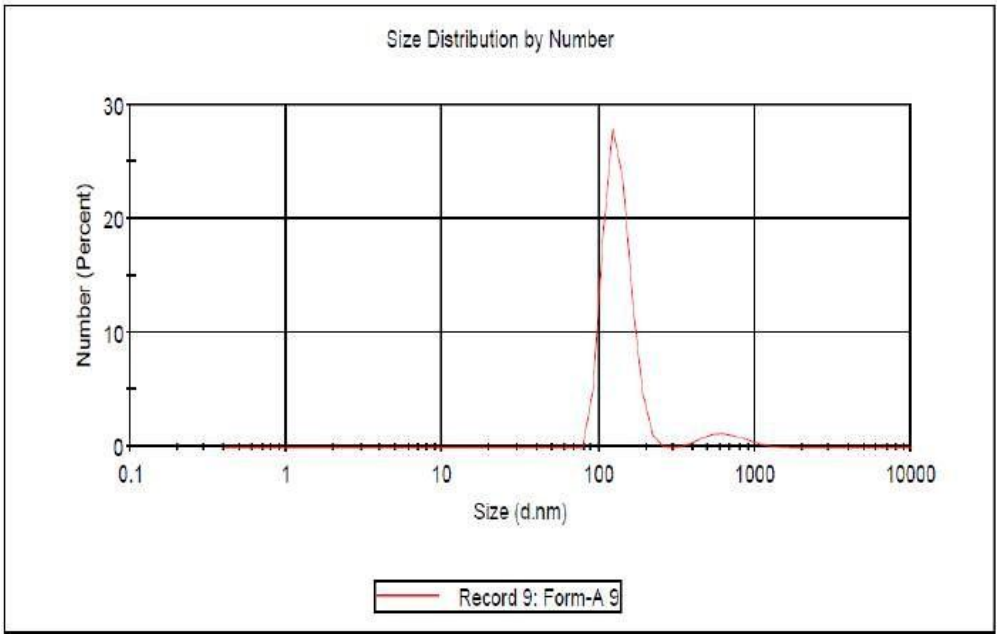

Fig 14: Particle size analysis of formulation (F6)

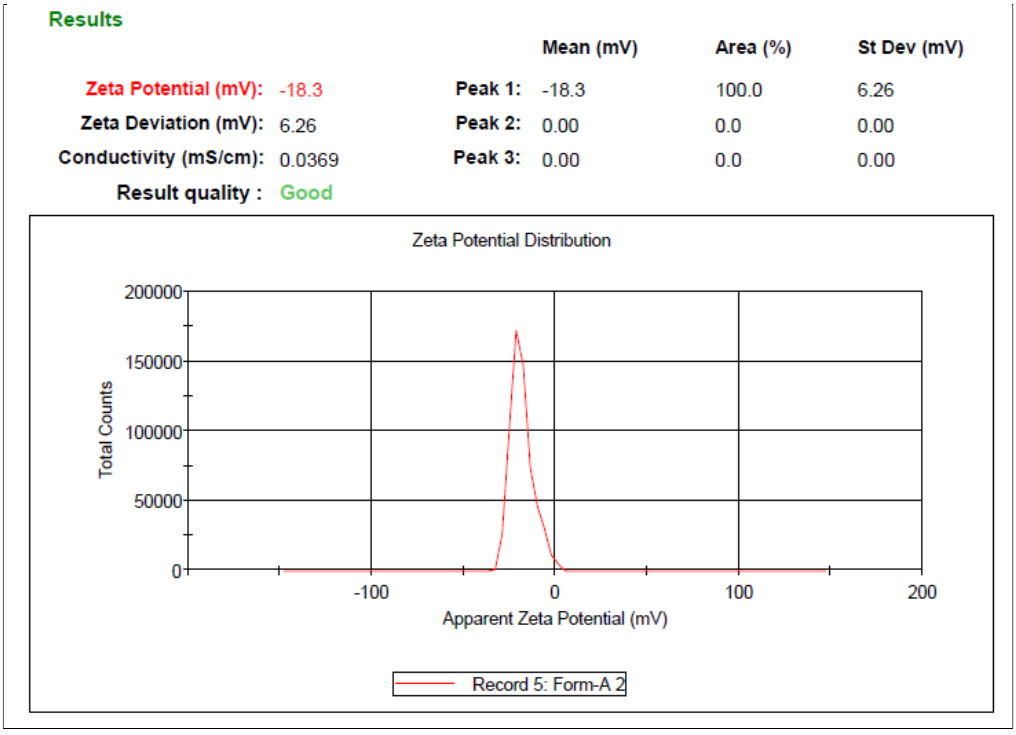

Fig 15: Zeta potentIl plot of formulation (F6) I.4.5. FT-IR spectrum interpretation:

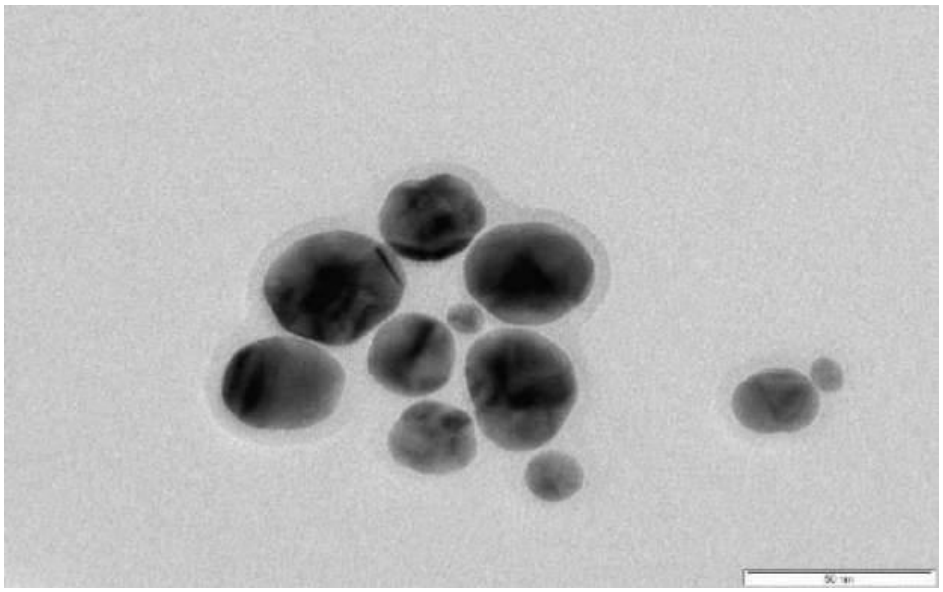

Fig 16: FTIR spectra of optimized lyophilized ATRC-NSGs (F6)

Transmission electron Microscopy and Selected area diffraction pattern (TEM and SAED):

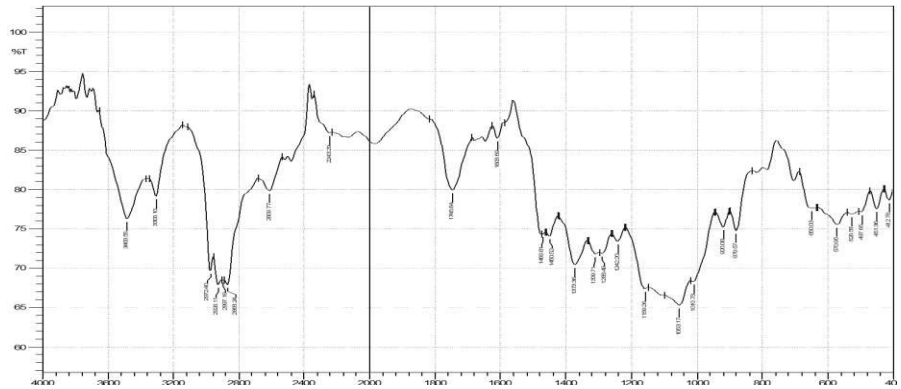

Fig 17: Micrographs of ATRC-NSGs by transmission electron microscope for Optimized Formulation F6 (110 nm)

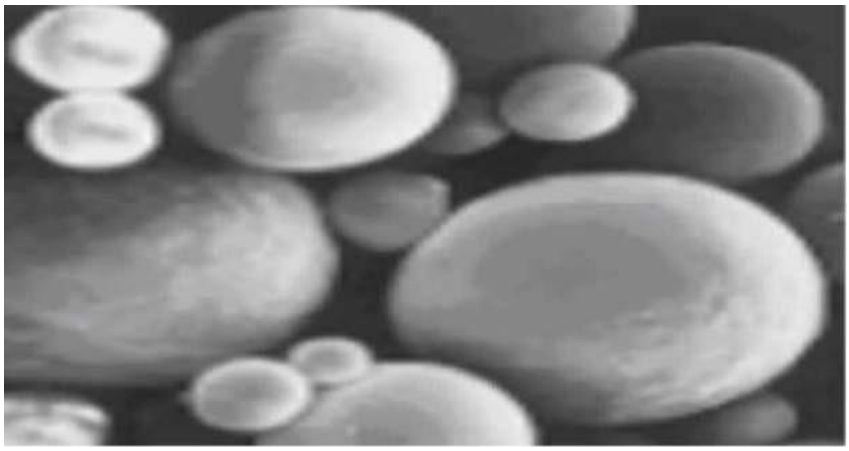

Fig 18 : Micrographs of ATRC-NSGs by transmission electron microscope for Optimized Formulation F6 (110 nm)

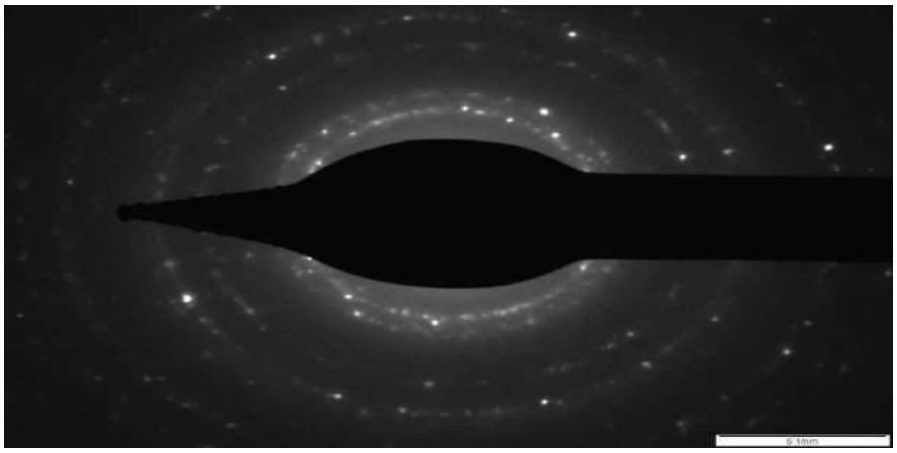

Fig 19: SAED in TEM of optimized batch F6 Nanosponge

***In Vitro* Release Study:**

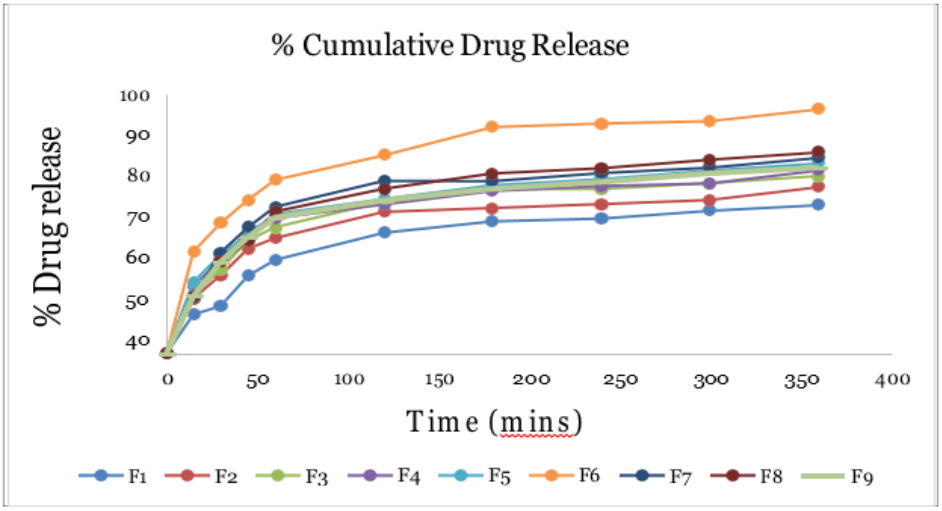

Fig 20: Release profile of different formulations of ATRC-NSGs.

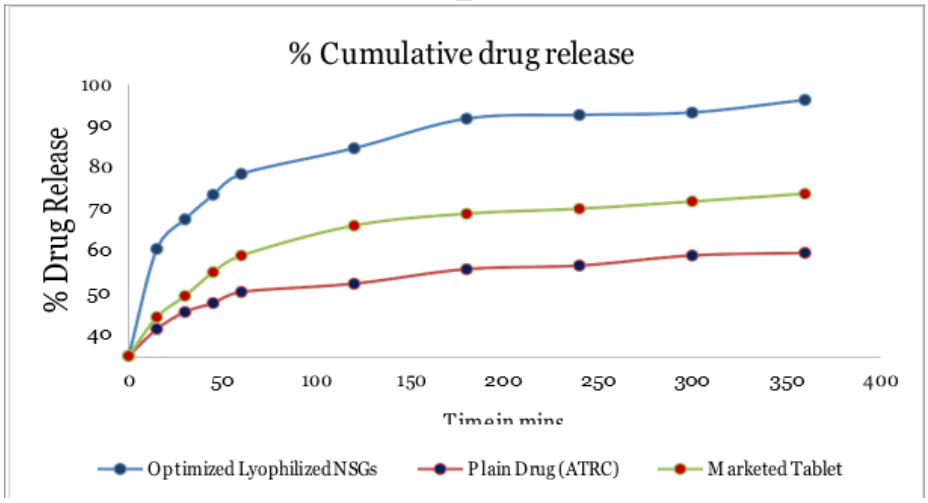

Fig 21 : Release profile of Plain drug-ATRC, Marketed tablet and optimized lyophilized ATRC-NSGs.

STABILITY STUDY

Table 2 : 1) Stability study of ATRC-NSGs

Time (Month/)	Physical Appearance	Particle size (nm)	Entrapment Efficiency (%)	% CDR	Solubility (µg/ml)
25±2ºC/65± 5% RH					
0	white crystalline powder	108.39±1.99	93.13±0.13	93.81	311.26±2.17
3	white crystalline powder	109.61±0.94	93.01±0.12	93.44	310.03±0.23
6	white crystalline powder	110.43±1.37	93.18±0.1	93.27	309.39±0.82
30±2ºC/70±5% RH					
0	White crystalline powder	109.50±2.28	93.34±0.19	93.45	311.15±1.62
3	white crystalline powder	109.67±1.24	93.22±0.19	93.26	310.82±1.23
6	White crystalline powder	111.16±0.90	93.09±0.18	92.91	309.90±0.14
40±2ºC/ 75±5% RH					
0	White crystalline powder	110.29±2.26	93.18±0.4	93.27	312.78±0.94
3	white crystalline powder	111.03±1.52	93.09±0.37	92.73	311.26±0.22
6	white crystallinepowder	111.56±1.45	92.95±0.4	92.55	311.01±0.21

FTIR:

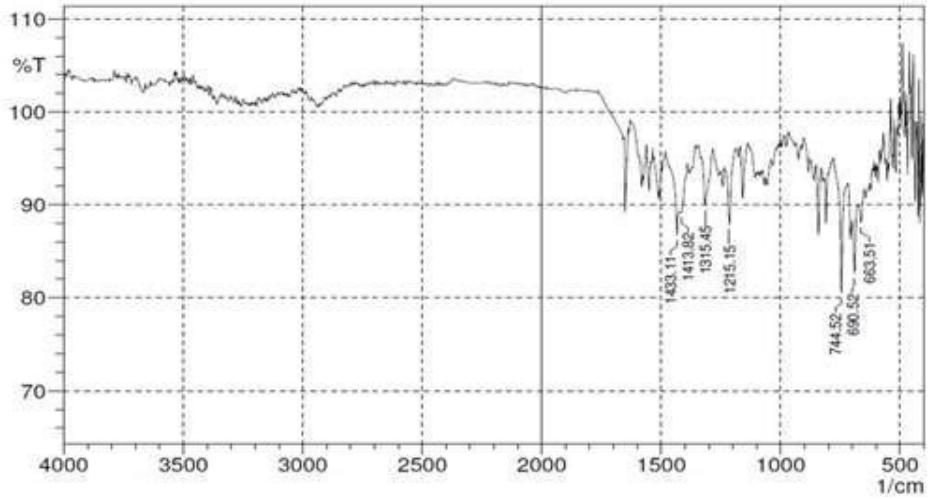

Fig 22: FTIR spectrum of freeze dried ATRC-NSGs 40ºC ± 2ºC and RH 75% ± 5 % after 6 months

CONCLUSION

The study successfully developed Atorvastatin calcium-loaded nanosponges with enhanced solubility and controlled release. The optimized formulation (F6) demonstrated nanoscale particle size, high entrapment efficiency, and stability under accelerated conditions. The factorial design effectively optimized critical parameters, ensuring reproducibility. These findings suggest that NSGs are a promising delivery system to overcome solubility limitations and improve therapeutic outcomes.

REFERENCES

[1]. Abdelwahed, W. et al., (2006). Freeze-drying of nanoparticles: formulation, process and storage considerations. *Advanced Drug Delivery Reviews* **58**:1688– 1713.
[2]. Aderem A (2002). How to eat something bigger than your head. *Cell* **110:**5–8
[3]. Aderem A, Underhill D (1999). Mechanisms of phagocytosis in macrophages.
[4]. *Annu Rev Immunol* **17:**593–623.
[5]. Akbarieh M, Besner JG, Galal A, Tawashi R et. al., (1992). Liposomal system for the targeting and controlled release of praziquantel. *Drug Dev Ind Pharm* **18:**303– 317.

[6]. Anwar M, Warsi MH, Mallick N et. al., (2011). Enhanced bioavailability of nano- sized chitosan–atorvastatin conjugate after oral administration to rats. *Eur J Pharm Sci* **44:** 241-249.
[7]. Allen TM, Austin GA, Chonn A, Lin L, Lee KC (1991). Uptake of liposomes by cultured mouse bone marrow macrophages: influence of liposome composition and size. *Biochim Biophys Acta Biomembranes* **1061:**56–64.
[8]. Anderson JM, Shive MS (1997). Biodegradation and biocompatibility of PLA and PLGA microspheres. *Adv Drug Deliv Rev* **28:**5–24.
[9]. Arkas M, Allabashi R, Tsiourvas D, Mattausch E, Perfle R (2006). Organic/inorganic hybrid filters based on dendritic and cyclodextrin nanosponges for the removal of organic pollutants from water. *Environ Sci Technol* **40:** 2771- 2777.
[10]. Amber V, Shailendra S, Swarnalatha S (2008). Cyclodextrin based novel drug delivery systems. *J Incl Phenom Macrocycl Chem* **62:** 23-42.
[11]. Ahmed R, Patil G, Zaheer Z (2013). Nanosponges–a completely new nano- horizon: pharmaceutical applications and recent advances. *Drug Dev Ind Pharm* **39:** 1263-72.
[12]. Ansari K, Torne S, Vavia P, Trotta F, Cavalli R (2011). Cyclodextrin -Based Nanosponges for Delivery of Resveratrol: In Vitro Characterization, Stability, Cytotoxicity and Permeation Study. *AAPS Pharm Sci Tech* **12:** 279-86.
[13]. Amsden B, Misra G, Gu F, Younes H (2004). Synthesis and characterization of a photo-cross-linked biodegradable elastomer. *Biomacromolecules* **5:** 2479-2486.
[14]. Ali R, Thirumaleshwar S, Bhosale R, Kulkarni P (2014). Nanosponges- The spanking Accession in Drug Delivery-An Updated Comprehensive Review. *Der Pharmacia Sinica* **5:** 7-21.
[15]. Amidon G, Lennern¨as H, Shah V, and Crison J (1995). A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical Research* **12:** 413–420,
[16]. Aulton M (2002). "Dissolution and solubility," in *Pharmaceutics: The Science of Dosage form Design*, M. E. Aulton, Ed., p. 15,Churchill Livingstone, 2nd edition