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An Outlook for a Unique Strategy: Design and Expediting the Fabrication of Nanosponges

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Keywords

Nanosponges, RSM, DOE, QbD,QTPP,CQAs,CPPs

Abstract

Drug delivery systems (DDS) have been the focus of research for a long time in an effort to achieve desired outcomes. A variety of peerless obstacles can currently be overcome with DDS based on nanotechnology. A nanosponge is a type of modern material made up of tiny particles that can only transfer a few nanometers. Low-solubility drug delivery is very efficient with nano-formulations. The effective window for many medications can be widened by increasing their water solubility. Even that they can be used to focus and manage delivery has been asserted. A variety of formulations, including nanosponges, was combined to produce the ideal DDS. Analysts have examined into them and discovered that they have beneficial effects and can increase the stability of drugs that aren't very water-soluble. Drug delivery nanosponges can be identified by their features, preparation, contributing factors, and applications. Based on research papers about nanosponges, the article was written. A factorial design was used to gather information on nanosponges drug delivery devices from the past decade. According to study writers, factor design is crucial for maximizing drug dosage forms.

1. Introduction

Nanosponges are tiny mesh-like nonporous structures that can be used to encapsulate or suspend a variety of compounds before being combined into a dosage form. Both hydrophilic and lipophilic drug molecules materials can be transported by them. They are solid by nature. The nanosponges can be manufactured into dosage forms for oral, Parenteral, topical, or inhalation administration.[1] In contrast to all other nanoparticles, they are porous, non-toxic, and insoluble in both water and organic solvents. They are also stable at elevated temperatures up to 300°C. They possess a unique 3dimensional structure with nanometric-sized voids and variable polarity that enables them to capture, transport, and release a wide range of substances. In addition, nanosponges exhibit a noteworthy advantage over typical nanoparticles in that they are easily

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regenerable using a variety of processes, including washing with environmentally friendly solvents, light heating, stripping with relatively innocuous hot gases, or adjusting pH or ionic strength. The Crystalline or paracrystalline nanosponges are also possible. The load-bearing capacity of nanosponges is significantly influenced by the degree of crystallization. [2, 3]

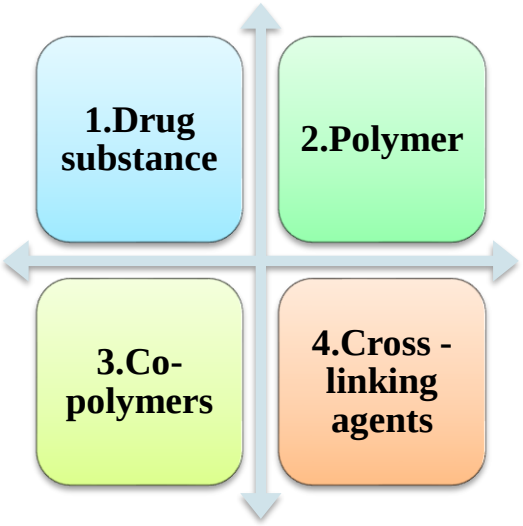
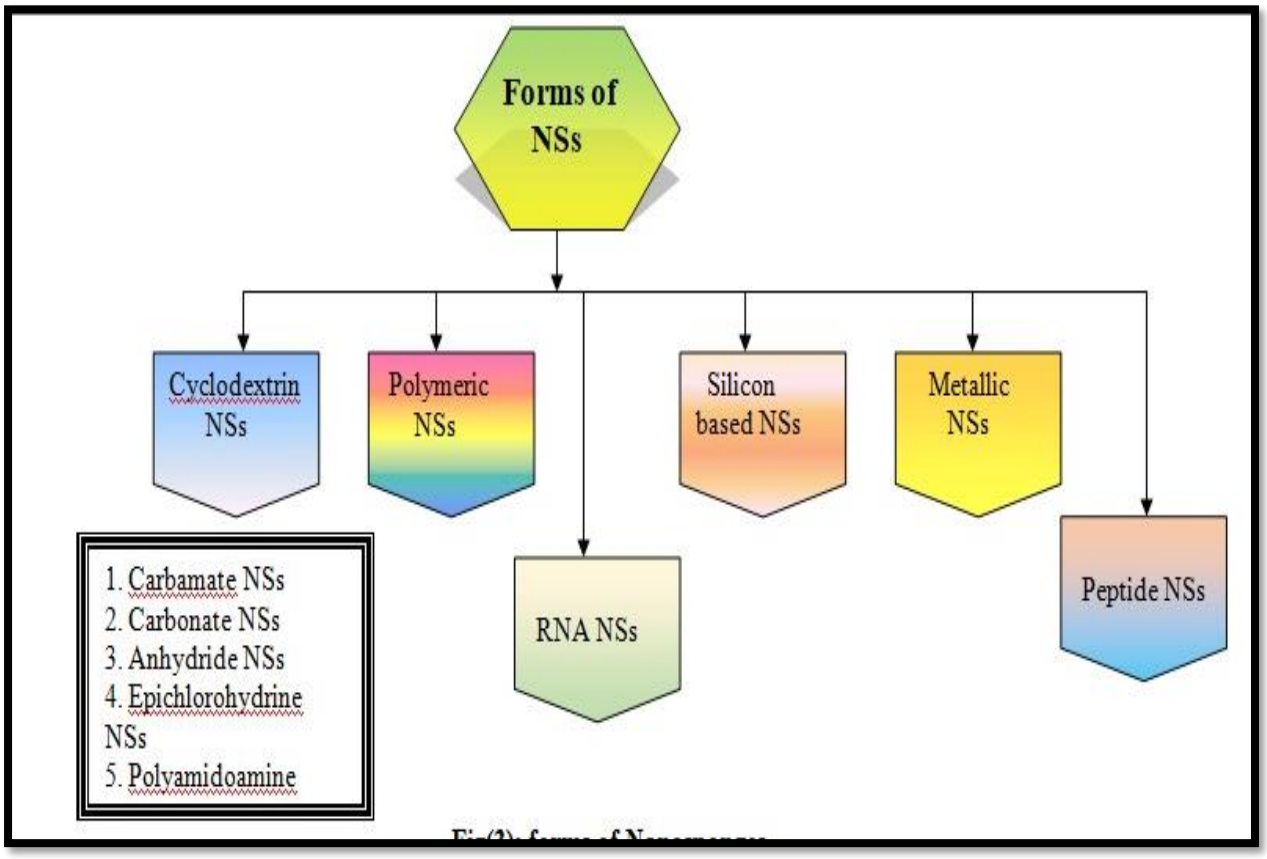


Fig (1): Composition of NSs



Fig(2): Preparation process for nanosponges

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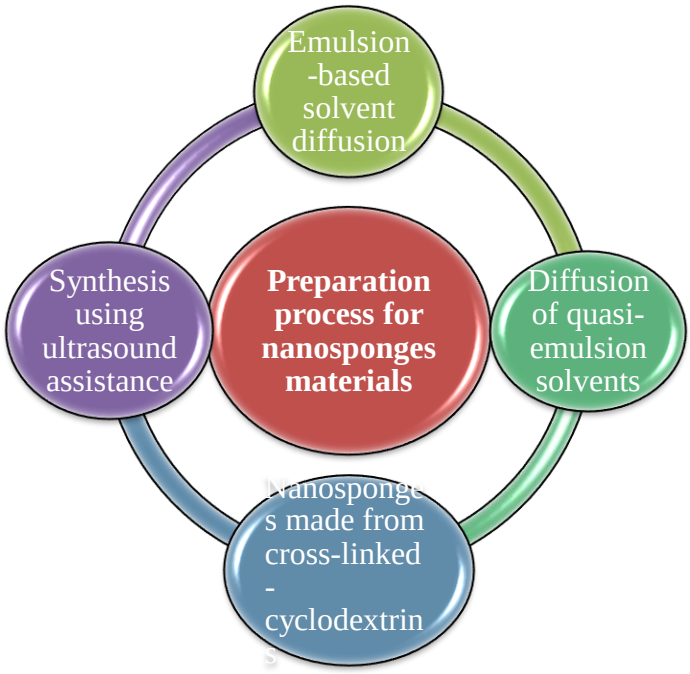
What nanosponges are made of? [4]



Fig(3): forms of Nanosponges

Several forms of Nanosponges

DOE application in the production of nanosponges

The idea of Quality by Design (QbD), which is a conservative, risk-based, and upbeat approach to the production of nanosponges, is discussed in this article, has been suggested as a means of achieving the greatest quality attainable for pharmaceuticals. The deliberate development and design of formulations is embraced by QbD, which also acknowledges the relationship between the qualities and methods of both dependent and independent variables and the performance of the product. A strategic process called QbD begins with a quality target product profile (QTPP), which is used to identify

1) CQAs
2) QRA
3) CPPs

The subsequent stage of the design involves experimental design (DoE), which is supported by CPPs and signifies the selection of significant product quality characteristics, resulting in the selection of an efficient method.[7, 8, 9]

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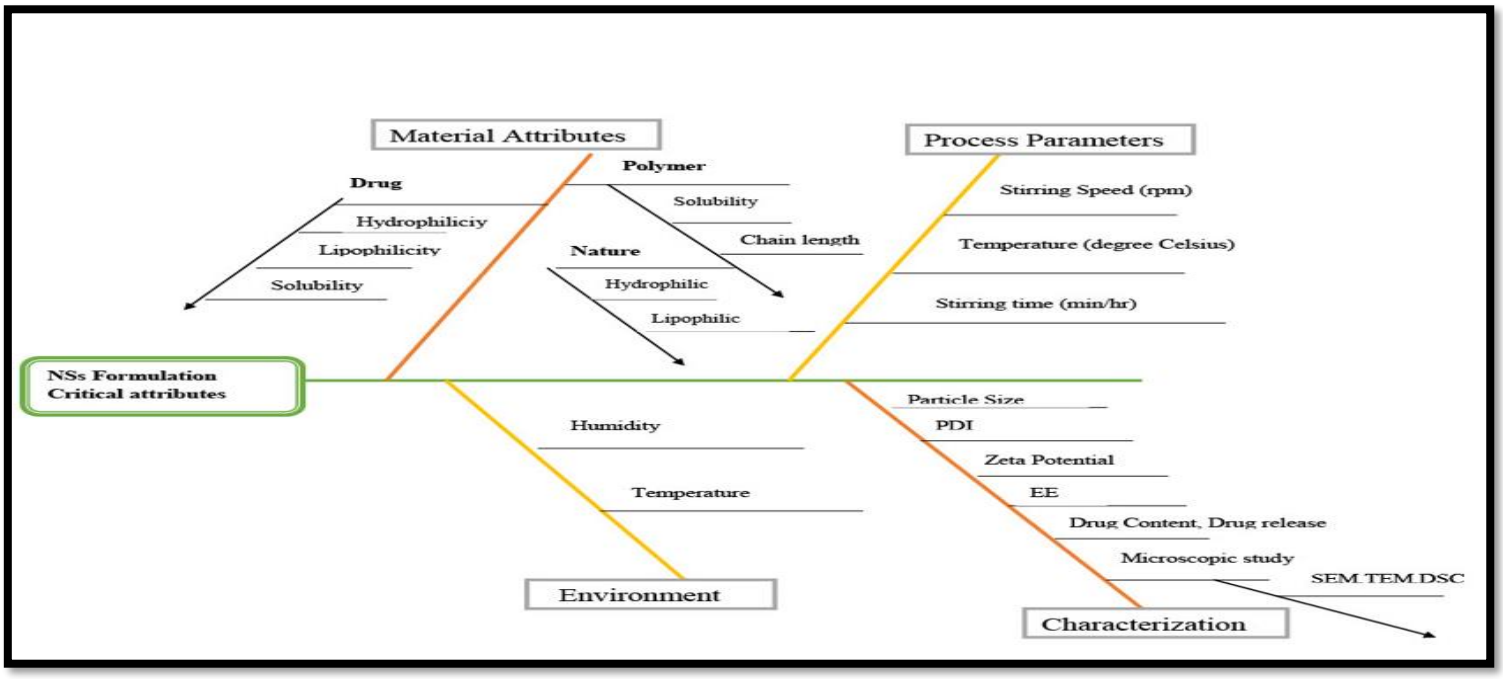

Fig(4): Fishbone diagram

- **Screening of variables using DOE:** Following the initial risk assessment, an initial screening design experiment is conducted to evaluate the relevance of formulation and process factors. This experiment may use fractional factorial designs, Placket-Burman designs, or Taguchi-orthogonal arrays. The Ishikawa diagram was used in the current review to identify the potential risk variables for product quality (CQAs, such as ps and entrapment efficiency).[9]
- **Formulation optimization using DOE:** In order to reduce the discrepancy in formulation development and eventually create nanosponges with high product yield and constant particle size, the design of experiments (DoE) has been employed as a powerful strategy. Traditional methods including Box-Behnken and Central Composite designs, which are frequently utilized in the formulation of NSs, were applied to optimize the formulation.[10,11]
- The following dependent and independent variables are frequently employed in the formulation of nanosponges using factorial design.

Sr. No	Design	Drug	Preparation method	Independent variables	Dependent variables	Ref
1.	3^2 full factorial design	Caffeine and Curcumin	Hot melt method	X_1 Carbapol934 X_2 β-CD	Y_1 Viscosity Y_2 % drug release	12
2.	3^2 full factorial design	Lornoxicam	Emulsion solvent evaporation method	X_1 Ethyl cellulose X_2 PVA	Y_1 EE Y_2 % drug release	13
3.	3^2 full factorial design	Terbinafine	Emulsion solvent diffusion method	X_1 Ethyl cellulose X_2 Stirring rate	Y_1 Particle size Y_2 EE	14

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4.	3^2 full factorial design	Aceclofenac,paracetamol,caffeine	Hot melt compression method	X_1Polymer conc. X_2 Cross -linker X_3reaction time	Y_1 Particle size Y_2 EE	15
5.	3^2 full factorial design	Acyclovir	quasi-emulsion solvents diffusion method	X_1 PVA X_2Eudragit X_3 Stirring rate	Y_1 EE Y_2 % yield Y_3 Particle size Y_4 % drug release	16
6.	3^2 full factorial design	Nifidipine	Solvents evaporation method	X_1 EC X_2 PVA X_3 β-CD	Y_1 DC Y_2 % yield Y_3 EE	17

Sr. No	Design	Drug	Preparation method	Independent variables	Dependent variables	Ref
7.	3^2 full factorial design	Clotrimazole		X_1 Pluronic F-127 X_2 Pluronic F-68	Y_1 gelatin temp Y_2 gelatin time Y_3 % drug release	18
8.	2^4 factorial design	paclitaxel	Spray drying method	X_1 Bovine serum albumin X_2 Stirring rate	Y_1 EE Y_2 Particle size Y_3% drug release	19
9.	3^2 full factorial design	Voriconazole	Emulsion solvent evaporation method	X_1 Pluronic F-68 X_2 PMM X_3 EC X_4 PVA X_5 Carbopol 971P	Y_1 EE Y_2 % drug release	20
10.	3^2 full factorial design	Flubriprofen	Solvents evaporation method	X_1 β-CD X_2 PVA	Y_1 EE Y_2 % drug release	21
11.	3^2 full factorial design	Indomethacin	Solvent diffusion method	X_1 EC X_2 PVA	Y_1 EE	22
12.	3^2 full factorial design	Glipizide	Solvents evaporation method	X_1 EC X_2 PVA X_3 β-CD	Y_1 DC Y_2 EE Y_3 Particle size Y_4% drug release	23
13.	2^3 full factorial design	Praziquantel	Emulsion solvent diffusion method	X_1 EC X_2 PVA X_3 Stirring rate	Y_1 % drug loading Y_2 Particle size Y_3 % drug release	24

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Sr. No	Design	Drug	Preparation method	Independent variables	Dependent variables	Ref
14.	3^2 full factorial design	Fluconazole	Emulsion solvent diffusion method	X_1 EC X_2 PVA	Y_1 EE Y_2 Particle size Y_3% drug release	25
15.	3^2 full factorial design	Doxorubicin	Emulsion solvent evaporation method	X_1 EC X_2 PVA	Y_1 DC Y_2 Particle size Y_3PDI Y_4 EE Y_5% drug release	26
16.	3^2 full factorial design	Naproxen & Ibuprofen	Emulsion solvent diffusion method	X_1 EC X_2 PVA	Y_1 % yield Y_2 EE Y_3 DC Y_4 Particle size Y_5 PDI Y_6 Zeta potential	27
17.	3^2 full factorial design	Miconazole nitrite	Emulsion solvent diffusion method	X_1 Sodium CMC X_2 Carbopol 934 X_3 HPMC X_4 MC	Y_1Mucoadhesive time	28
18.	3^2 full factorial design	Lemongrass	Emulsion solvent evaporation method	X_1 EC X_2 PVA X_3 Stirring rate	Y_1 Particle size Y_2% drug release	29
19.	3^2 full factorial design	Ciprofloxacin	Solvent evaporation method	X_1 EC X_2 PVA	Y_1 PVA	30

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Sr. No	Design	Drug	Preparation method	Independent variables	Dependent variables	Ref
20.	3^2 full factorial design	Itroconzole	Emulsion solvent diffusion method	X_1 EC X_2 PVA	Y_1 EE Y_2 DC Y_3% yield	31
21.	3^2 full factorial design	Atorvastatin	Emulsion solvent diffusion method	X_1 EC X_2 PVA X_3 β-CD	Y_1% yield Y_2% drug release Y_3 EE	32
22.	Box Behnken design	Trimethoprem	Hot melt extrusion	X_1 β-CD	Y_1 DC Y_2 DS Y_3 EE	33
23.	3^2 full factorial design	Risidronate sodium	Emulsion solvent diffusion method	X_1 EC X_2 PVA	Y_1 Particle size Y_2 EE	34
24.	3^2 full factorial design	5 Fluoro uracil	Emulsion solvent diffusion method	X_1 EC X_2 PVA X_3 Poloxamer-407	Y_1 DC Y_2 EE Y_3 Zeta potential	35
25.	3^2 full factorial design	Tizanidine HCL	Emulsion solvent diffusion method	X_1 β-CD X_2 Carbopol 934	Y_1 Particle size Y_2% yield Y_3 EE Y_4 Zeta potential	36
26.	3^2 full factorial design	Quercetin	Emulsion solvent diffusion method	X_1 EC X_2 PVA X_3 HPMC X4 Carbopol 934	Y_1 Particle size Y_2 PDI Y_3 Zeta potential Y_4 EE	37

Sr. No	Design	Drug	Preparation method	Independent variables	Dependent variables	Ref
27.	Box Behnken design	Felodipine	Physical mixture, solvent evaporation	X_1 amount of polymers HPMC X_2 amount of polymers of surfactant	Y_1 Maximum solubility after 24 hr Y_2 dissolution efficiency	38
28.	Plackett Burman design	Cyclosporine -A	Emulsion solvent diffusion method	X_1 Drug:polymer :surfactant ratio	Y_1 Encapsulation efficiency Y_2 particle size, Y_3 zeta potential Y_3burst release	39

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					Y_4Dissolution efficiency	

Table 1: Factorial design and Variables considered in NSs Formulation

❖ **Effect of variables on formation of NSs:**

Sr.No	Variables	Effect	Ref
1.	Drug and polymer ratio	Nanosponges' particle size decreases up to a certain point when the drug-polymer ratio is increased, but after that, polymer-polymer interaction takes precedence and causes particle size to increase.	40
2.	concentration of polymers	Lower percentage drug release and slower penetration rates are due to a higher polymer concentration.	41
3.	Stirring time & speed	The production yield and particle size both increased with speed	42
4.	Temperature Effect	Temperature inversions can influence the formation of a drug-nanosponges combination. In general, the apparent stability constant of a drug-nanosponges complex decreases with temperature in both magnitude and value. This could be explained by the reduction of drug-nanosponges interaction forces such Vander Waal forces and hydrophobic forces as temperature increases.	42
5.	Nature of substitution	Type, number, and position of substituent's on the parent molecule can have a significant impact on the nanosponges' capacity to complex.	43
6.	cross linking agent	Viscosity and porosity of the formulation will increase further with an increase in the cross-linking agent's concentration, decreasing the efficiency of entrapment. Crosslinker for topical treatments are frequently made of dichloromethane. Because of the internal phase's decreased viscosity, as the volume of the internal phase grew, drug entrapment and particle size did not follow any particular patterns.	44
7.	Surfactant	A typical surfactant used to prepare nanosponges, polyvinyl alcohol is necessary for producing nanosponges with smaller particle sizes. It was observed that the particle size increased as the surfactant concentration increased. Higher surfactant concentrations cause foaming, which leads to the production of aggregates. As the concentration of surfactant increased, the effectiveness of drug entrapment decreased. This could be as a result of the drug's specific polymer concentrations not being high enough to encapsulate its particle.	45

Table 2: Effect of variables on formation of NSs

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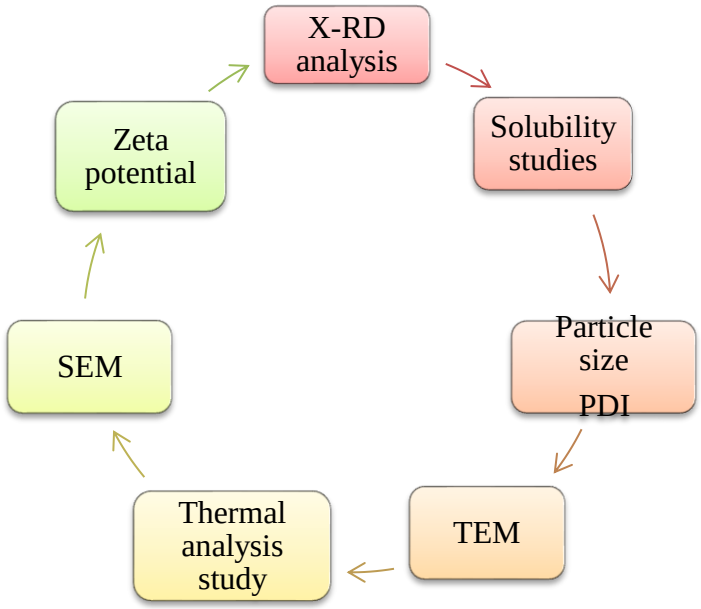

Nanosponges' evaluation parameters and their specifications

Fig (5) Evaluation parameters of NSs

❖ **Nanosponges' evaluation parameters and their specifications**

1.	X-RD analysis	Analysis of drug polymer complexation	The experiment was conducted in an x-ray diffractometer using Cu K radiation at a speed of 100 rad/min at an angle of 10–800. The effective encapsulation of the drug in the nanosponge core is shown by the masking of crystalline peaks.	46
2.	Zeta potential	Hydrodynamic diameter on average was measured.	It was carried out employing zeta sizer measurements of dynamic light scattering.	47
3.	Scanning electron microscopy (SEM)	For the purpose of determining surface morphology	The photos that were examined after it was operated at an accelerated voltage of 15 Kv showed that the nanosponges are homogeneous and spherical in nature.	48
4.	Thermal analysis study	Utilized to determine a substance's thermal properties	DSC and thermal gravimetric analysis (TGA), which involves heating materials from room temperature to 300°C while applying heat at a rate of 10°C per minute, are two of the methods employed. Drug encapsulation in nanosponges is successful when the DSC curve of the formulation shows there is no drug melting peak.	49
5.	Particle size	Using a 90 Plus particle sizer and MAS OPTION particle sizing software, it was possible to calculate the average nanosponges particle size.	The nanosponges' average particle size ranged from 400 to 800 nm, and the particle size increased as the amount of polymer decreased.	50
6.	Entrapment efficiency	Quantitative drug loading into nanosponges using UV	The total amount of drug is subtracted from the total amount of drug in the supernatant, which is divided by	51

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		spectrophotometer & HPLC techniques to determine how much drug is embedded and finding out how much drug is embedded in nanosponges .	the total amount of drug, to determine the quantity of drug entrapped in a certain nanosponges formulation. Ultracentrifugation is typically thought to be 9000 rpm for 30 min. It was discovered that changes in phase volume affected entrapment efficiency (%E.E), which depended on both internal and external phase volumes.	
7.	%Production yield	Knowing the yield of nanosponges that were obtained	Calculating production yield involves dividing the actual mass of obtained nanosponges by the total mass (polymer and drug)*100.	52, 53
8.	Uniformity of drug content	To determine the amount of drug in a certain formulation	Based on known standard solution absorbance values, the drug content in the formulation was determined.	54
9.	In Vitro study	To analyze the formulated nanosponges' release profiles	It was shown that when the amount of polymer in nanosponges increased, the amount of drug released from pores decreased.	55
10.	Solubility studies	Higuchi and Connors' phase solubility approach, which studies how nanosponges affect a drug's solubility,	Solubility has significantly impacted by the amounts of the drug, the polymer, sonication, and PVA. Ref:	56

Table 3: Nanosponges' evaluation parameters and their specifications

❖ **Benefits of full factorial design in NSs:**

An experimenter can simultaneously control several independent variables using a factorial design. The impacts of independent variables can be examined both separately and collectively in this design. Compared to single-factor designs, factorial designs are more efficient. The independent or main effect of independent variables as well as the combined effect of two or more independent variables can be determined using factorial design. Due to the simultaneous manipulation of numerous independent factors, factorial experiments offer more comprehensive results and are more generalizable.[57]

2. Discussion

A group of statistical and mathematical techniques known as Response Surface Methodology (RSM) are helpful for creating, enhancing, and optimising processes. The greatest use of RSM is in circumstances when a number of input factors may have an impact on a single performance metric or the process's quality feature. The approximate representation of experimental and numerical responses can be achieved using RSM. The determining an approximate function and the development of an experimental strategy are two procedures that are required. A good experimental design should distribute the points around the area of interest, i.e., offer as much data on the issue as possible.

3. Conclusion:

The research comes to the conclusion that water solubility is crucial for drugs with a limited therapeutic window and is necessary to achieve targeted/controlled delivery. Nanosponges and other cutting-edge drug delivery methods were developed to address this. Using a factorial design, data from the previous decade regarding drug delivery methods for nanosponge were examined. The

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factor design method, according to study researchers, is crucial for maximising the dosage form for drug delivery.

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