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QbD: Application in Nanosponges for Topical Drug Delivery System

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ABSTRACT

Quality by Design (QbD) is an approach to the design and development of the formulation by using different scientific strategies, tools and various nanoparticulate data available. QbD can assist the pharmaceutical industry and research scholars to satisfactorily move towards the more scientific, active, risk-based pharmaceutical development. Qbd, if applied, to the entire product cycle minimizes the end product testings and leaves one with safe, effective and quality product. In the present study, an attempt is made to apply the QbD to the Nanosponges for topical drug delivery system; a highly porous nanostructure. They can entrap drug molecules in their aqueous pore such as hydrophilic as well as lipophilic. Nanosponges to enhance the drug stability, to enhance the short half-life due to the shorter half-life. The nanosponges were prepared by the solvent emulsion diffusion method. Nanosponges can be used as a carrier for biocatalysts in the delivery and release of enzymes, proteins, vaccines, and antibodies. Nanosponges have various applications like enhancing bioavailability of drugs and delivery of drugs into oral, topical as well as parenteral routes.

INTRODUCTION[1-3]:

Nanosponges are porous polymeric delivery systems that are small spherical particles with large porous surfaces are tiny sponges with a size about virus (250nm-1µm). These are used for the passive targeting of cosmetic agents to the skin, thereby achieving major benefits such as reduction of total dose, retention of dosage form on the skin and avoidance of systemic absorption. These nanosponges can be effectively incorporated onto topical systems for prolonged release and skin retention thus reducing the variability in drug absorption, toxicity and improving Bioavailability. The active ingredient is added to vehicles in the entrapped form since the nanosponge particles have an open structure (they do not have continuous membrane surrounding them) the active substance is free to move in or out from the particles into the vehicle until equilibrium is reached when the vehicle become saturated. Once product is applied to skin, the active substance that is already in vehicle will become unsaturated, therefore disturbing the equilibrium. This will start the flow of active ingredient from nanosponges particles into vehicle, from it, to the skin until vehicle is either dried or absorbed. Even after that nanosponge particles are retained on the surface of stratum corneum, they will continue to gradually release active ingredient to skin providing prolonged release over time. Nanosponges are a new class of materials and made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water-soluble molecules. The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. By the method of associating with drugs, the nanoparticles can be classified into encapsulating nanoparticles, complexing nanoparticles and conjugating nanoparticles. The first type is represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are sponge-like nanoparticles containing many holes that carry the drug molecules. Nanosponges embraces nanotechnology which is applied to pharmacy as nanomaterials, diagnosing and focusing right place in the body and controlling release of the drug[5] . These tiny shape nanosponges can circulate in to the body until they encounter the specific target site and stick the surface on the organ in to the body and begin to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of systemic circulation in the body it will be more effective for a particular given dosage. Another important feature of these nanosponges is their aqueous solubility which allows the use of these systems effectively for drugs with poor solubility [6] .

The nanosponges are solid and sponge in nature[7]. They have been found to be safe for oral and invasive routes, and thus they could serve as a potential carrier for drug delivery [8,9]. For oral administration, the complexes may be dispersed in a matrix of excipients, diluents, lubricants and anti-caking agents suitable for the preparation of capsules or tablets. For parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions. For topical administration they can be effectively incorporated into topical hydrogel [10,11]. Nanosponges are encapsulating type of nanoparticles which encapsulate the drug molecules within its core .[12]

The major [2] challenges in the preparation of nanosponges are manufacturing variability, due to lack of understanding of the effect of critical material attributes (CMAs) and critical processing parameters (CPPs) to attain small size, narrow polydispersity index (PDI), and so on. This lack of understanding and manufacturing variability increase the cost of nanosponges drug delivery system. Nanosponges drug delivery system is also known for its toxicities due to the fast onset of action increase in solubility, permeability, and bioavailability, high diffusion rate.

FACTORS AFFECTING DRUG RELEASE FROM NANOSPONGES[2,4]:

1) Physical and chemical properties of entrapped actives.

2) Physical properties of sponge system such as pore diameter, pore volume, and resiliency.

3) Properties of the vehicle, in which the sponges are finally dispersed.

4) Particle size, pore characteristics, and compositions can be considered as imperative parameters.

5) External triggers such as pressure, temperature, and solubility of actives

6) Pressure: Pressure or rubbing can release active ingredient from microsponges onto the skin.

7) Temperature: Some entrapped actives can be too viscous at room temperature to flow spontaneously from sponges onto the skin but increased skin or environment temperature can result in increased flow rate and ultimately drug release[13].

8) Solubility: Sponges loaded with water-soluble ingredients such as antiperspirants and antiseptics release the ingredient in the presence of water.

CHARACTERISTIC FEATURES OF NANOSPONGES

1) Nanosponges exhibit a range of dimensions (1µm or less) with the tuneable polarity of the cavities.

2) They could be either Para-crystalline or in crystalline form, depending on the process conditions.

3) Crystal structure of Nanosponges plays a very important role in their complexation with drugs. The drug loading capacity of Nanosponges mainly depends on the degree of crystallization.

4) They are nontoxic, porous particles insoluble in most organic solvents and stable at high temperatures up to 300 °C.

5) Nanosponges as formulations are stable over the pH range of 1 to 11 and temperature up to 130 °C.

6) They form clear and opalescent suspensions in water and can be regenerated by simple thermal desorption, extraction with solvents, by the use of microwaves and ultrasounds.

7) They can be targeted to different sites due to their ability to be linked with different functional groups. Chemical linkers enable NSs to bind preferentially to the target site.

APPLICATION OF NANOSPONGES

Due to their biocompatibility and versatility, nanosponges have many applications in the pharmaceutical field. They can be used as excipients in preparing tablets, capsules, pellets, granules, suspensions, solid dispersions or topical dosage forms. They can encapsulate a variety of drugs as shown in Table 1. Nanosponges can act as multifunctional carriers for enhanced product performance and elegance, extended release, reduced irritation, improved thermal, the physical and chemical stability of the product. Following are the application of nanosponges which shows the versatility of nanosponges.

- In cancer treatment
- Insolubility enhancement
- In topical drug delivery
- For protein delivery
- In enzyme immobilization
- As a carrier for delivery of gases
- As a protective agent from light or degradation. They form inclusion and non-inclusion complex

THE CONCEPT OF QUALITY BY DESIGN

1) Pharmaceutical Quality by Design:

ICH Q8 defines quality as[3] "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. "ICH Q8 guideline states that Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".[1]

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are the foundation of QbD.

"Product testing alone is not sufficient to assure that a process consistently produces a product with predetermined specifications. Adequate process design; knowledge and control of factors that produce process variability and successful validation studies, in conjunction with product testing, provide assurance that the process will produce a product with the required quality characteristics".

Understanding and controlling formulation and manufacturing process variables affecting the quality of a drug product.

➢ Where Does Design for Quality Begin?

- Target product quality profile – Beginning drug development with the end in mind – What performance is needed to get the clinical benefit and meet consumer expectation.

- Pharmaceutical Quality = *ƒ* (drug substance, excipients.

➢ What Does QbD Constitute?

- Define target product quality profile – The performance needed to get the clinical benefit and meet consumer expectation.

- Design and develop product and manufacturing process to meet target product quality profile.

- Identify and control critical raw material attributes, process parameters, and sources of variability.

- The process is monitored and adapted to produce consistent quality over time.

2) Historical Background:

In 2007, the FDA received a total of 5000 proposals for new drug applications (NDAs) and biological license applications and abbreviated new drug applications (ANDAs). „Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" was launched by the FDA in August 2002. A further guidance on process analytical technology (PAT) was released as part of the „cGMPs for the 21st Century" initiative, which hoped to encourage the adoption of more modern and flexible manufacturing technology in the pharmaceutical industry [7, 8]. In March 2004, the FDA launched The Critical Path Initiative (CPI) to address the steep decline in the number of innovative pharmaceutical products submitted for approval. The national strategy was to modernize the pharmaceutical sciences through which FDA-regulated products are developed, evaluated, manufactured and used [9]. This prompted to the publishing of a guideline to aid manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency"s current thinking for cGMP regulations. The impetus is to have quality in-built. Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial

manufacturing processes and for post-development changes and optimization [10]. Good manufacturing practices for the 21st century have been continually evolving as the ICH quality initiatives have been adopted. The move from empirical assessment based on performance to the concept of "building quality in" based on critical attributes has gained traction as new guidance documents have been published. The ICH published a series of guidance documents supporting QbD approaches that are highlighted in:

(1) ICH Q8 Pharmaceutical Development.

(2) ICH Q9 Quality Risk Management.

(3) ICH Q10 Pharmaceutical Quality System.

- Benefits of Qbd:

➢ For Industry:

1) A better understanding of the process.

2) Less Batch failure.

3) Ensure better design of products with fewer problems in manufacture.

4) Allows for continuous improvement in products & manufacturing process.

➢ For FDA:

1) Enhance scientific base for analysis.

2) Provide better consistency.

3) Ensures decision made on science & not on observed information.

3) Developing A Quality Target Product Profile:

Quality target product profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." QTP forms the basis of QbD, which is in relation to the predefined objective criteria mentioned in the definition of QbD. As per ICH guideline Q8 R2, the Quality Target Product Profile forms the basis for design and the

development of the product. Considerations for the Quality Target Product Profile could include:

- Intended for use in a clinical setting, route of administration, dosage form, suitable delivery Systems. Dosage strength(s), container and closure system.

- Therapeutic moiety release or delivery and attributes affecting, Pharmacokinetic parameters (e.g., dissolution, aerodynamic performance). Drug product quality criteria like sterility, purity, stability and drug release as appropriate for dosage form the intended for marketing.

QbD requires a Target Product Profile; it may be called as Quality Target Product Profile (QTPP) which defines the expectations in the final product. In case of analytical method development, it is called an analytical target profile, it is also called as Target Product Profile. The TPP can play a pivotal role in the entire drug discovery and development processes like optimization, planning and decision making, and designing of clinical research strategies. The Target Product Profile can be used to design the clinical trials, safety, and ADME studies, as well as to design the drug product. The TPP will help to identify critically.

4) Defining a Preclinical Plan to Support the QTPP:

Because of the complexity of nanosponges' products and the biological systems in which they are designed to operate, the preclinical development and evaluation of nanosponges' products necessarily rely on in vitro and in vivo models to assess biological performance versus the QTPP and to understand how performance is impacted by drug product characteristics. Key biological performance attributes of a nanosponges drug product typically relate to the interaction of particles with target cells and tissues, the PK and biodistribution of the drug product and its payload, the toxicological properties of the drug product and its constituents, and the efficacy of the drug product in disease models. No single biological model is likely to satisfactorily inform all of the key attributes, and so multiple models are selected on the basis of discriminating power, throughput, cost, and clinical relevance and can be deployed in a staged manner with certain models used to define and optimize the drug product characteristics and others used to evaluate one or more lead candidates versus success criteria. Product attributes addressable with in vitro models include, for example, binding, uptake and intracellular trafficking of actively targeted nanoparticles by target cells,

QTPP of prepared nanosponges is depicted in the table below:

Table no 1

QTPP Element	Target	Justification
The dosage form	Product Specific	Pharmaceutical Equivalent.
Route of administration		
Strength		
Pk		
Stability		
Drug product, quality attributes, Container, closure system		

5) Defining Product Critical Quality Attributes:

According to ICH Q8 R2 "A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality".

To use a risk-based approach to identifying and classifying product attributes (and ultimately process parameters), it is important not only to identify ways to effectively characterize the product but also to define which of those characterizations are critical to quality and acceptable ranges for each attribute. While attributes correlating with biological performance are generally well understood for conventional dosage forms, for newer technologies, this correlation must be established through biological studies. As described, it is important that the biological models used are relevant to the target indication in order to be confident that the results will translate into the clinic. Increasing non-clinical and clinical experience will over time build in vitro/in vivo correlations relationships between physicochemical properties and biological performance and in vivo, biological studies will not be required as frequently for product optimization and continual improvement. With a new technology such as ACCURINS®, the types of attributes to measure may be fairly obvious, but to determine which specific tests to use and what their target values require a good deal of performance testing. For example, one can presume that particle size is important for a nanosponges

delivery system. However, whether the mean size, polydispersity, maximum size, tailing factor, morphology, or some combination of these size-related variables is important for product quality is not clear until the performance impact of each variable is studied in a systematic manner. Sustained-release products are designed to provide an advantageous drug exposure profile for the patient compared to a conventional delivery, but the combination of release profile and dosing schedule to achieve optimal exposure is also uncertain and must be evaluated non clinically and clinically. For complex formulations, it is important to develop an understanding of the relationship between product attributes and in vivo performance at an early stage in the product development process. Nanosponges based delivery based targeting and consequent improvement in payload biodistribution. Alteration of the physicochemical properties of the particle surface, however, may lead inadvertently to enhanced particle opsonization. Consequently, the capability to precise control both the identity and the expression level of the targeting ligand is of critical importance to ensure optimal biological performance.

Summarize the CQAs on the basis of quality attributes identified as a target along with justification for being CQA (Critical quality attributes).

Table no 2;

QA Of DP	Target	Is It CQA	Justification
It Should Include Product And Process Specific Quality Attributes	Desired Quality	Based On Impact Of Attributes On QTPP	Statement Should Clarify Justify

Drug product CQAs;

Physical attribute, assay, drug content, drug release, degradation products etc.

Pharmaceutical unit operation	Dosage form	Model of drug	Design of experiment	Critical material attributes	Critical process parameters	Critical quality attributes
Spray drying	Solid nanosponges crystalline powder	Indomethacin	Full factorial design	NA	Inlet temperature, flow rate, aspiration rate	Particle size, moisture content,% drug release
Emulsion solvent diffusion method	Nanosponges	Cyclosporine-A	Plackett Burman design	Type of solvent organic to aqueous phase ratio, drug concentration, polymer concentration, surfactant concentration	Stirring rate	Encapsulation efficiency, particle size, zeta potential burst release, Dissolution efficiency
Physical mixture, solvent evaporation	Solid nanosponges	Felodipine	Box Behnken design	Amount of polymer HPMC, amount of polymers of surfactant	Preparation technique	Maximum solubility after 24 hr, dissolution efficiency
Hot melt extrusion	Solid lipid nanoparticles	Fenofibrate	Plackett-Burman screening design	Lipid concentration, surfactant concentration	Screw speed, barrel temperature, zone of liquid addition	Particle size, polydispersibility index, zeta potential, entrapment efficiency

Steps for pharmaceutical implementation:[4]

1. Identification of the CQA

2. Identification of possible CMAs and CPP

3. Identify and control the sources of variability from the raw materials and the manufacturing process.

4. To improve the manufacturing process to assure consistent product, So pharmaceutical unit operation process can be optimized by applying the concept of QbD, Each unit operation has its own output material attributes, process parameters and quality attributes such as emulsion solvent diffusion method, spray drying, hot melt extruder.

Factors to be considered to achieve CQA:

1) Selection of polymer in nanosponges:

Type of polymer used can influence the formation as well as the performance of Nanosponges. For complexation, the cavity size of nanosponges should be suitable to

accommodate a drug molecule of a particular size. Such as cyclodextrin and its derivatives like Methyl β- Cyclodextrin, Diphenyl Carbonate, Ethylcellulose, chitosan, 2-Hydroxy Propyl β-Cyclodextrin Diisocyanates.

2) Co-polymers used in nanosponges:

When two or more different monomers unite together to polymerize, the product is called a copolymer and the process is called copolymerization. Copolymerization is used to modify the properties of manufactured plastics to meet specific needs, for example, to reduce crystallinity, modify glass transition temperature, and control wetting properties or to improve solubility. It is a way of improving mechanical properties, like Poly (valerolactone allyl valerolactone) Pyromellitic anhydride, Epichloridrine, Glutaraldehyde Poly (valerolactone allyl valerolactone oxepane dione) Carboxylic acid dianhydrides, Ethyl Cellulose, 2, 2-bis (acrylamide) Acetic acid, PVA

3) Selection of crosslinkers in nanosponges:

The amount of Crosslinker used for biomedical applications like polymer formulations in drug delivery is very less and could be regarded as almost safe. The use of cross-linker depends on the biopolymer you are using such as Dichloromethane, ethanol, glutaraldehyde, dimethyl carbonate.

4) Selection of Drug in nanosponges formulation:

Drug molecules to be complexed with nanosponges should have certain characteristics:

- Molecular weight between 100 and 400
- Drug molecule consists of less than five condensed rings
- Solubility in water is less than 10mg/ml.
- The melting point of the substance is below 250°C.

5) Selection of Temperature:

Temperature changes can affect Drug/Nanosponges complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the

Drug/Nanosponge complex may be due to a result of the possible reduction of drug/nanosponge interaction forces, such as Vander Waals' forces and hydrophobic forces with rising of temperature.

6) Method of preparation:

The method of loading the drug into the nanosponge can affect Drug/Nanosponge complexation. However, the effectiveness of a method depends on the nature of the drug and polymer, in many cases, freeze-drying has been found to be most effective for drug complexation.

7) The degree of substitution:

The complexation ability of the nanosponge may be greatly affected by type, number, and position of the substituent on the parent molecule.

Selections of suitable method form the nanosponges and enhance solubility properties:

Solubility assessment is also another important critical factor for adhesive, additive, penetration enhancer solvent, plasticizer, the solvent of the investigative formulation. The adhesives are exposed to different drug concentration. Stability of Nanosponges is determined at room temperature and elevated temperature (50°C). Identification test is performed to monitor drug loaded nanosponges growth over a few weeks. Crystal seeding studies are performed by preparing drug adhesive mixture with various drug concentrations and by seeding drug crystals of all polymorphs onto the surface. Observed growth or dissolution of seeded drug crystals can be predictors of porous nanosponges during storage. Selection of crosslinker, polymer component, and functional groups, molecular weight, cross-linked to polymer ratio. Addition of cohesive strengthening agents: non-ionic surfactants, fatty acid esters of glycerol. For topical nanosponges a Once product is applied to the skin, the active substance that is already in the vehicle will become unsaturated, therefore disturbing the equilibrium This will start the flow of active ingredient from nanosponges particles into the vehicle, from it to the skin until the vehicle is either dried or absorbed.

Approaches of Qbd in Nanosponges formulation: as shown in

Table no:3

Independent variables	Dependent variables
Amount of Drug	Particle size
Amount of polymer	% cumulative drug release
Amount of plasticizers	Permeation rate
Amount of Surfactant	Zeta potential
Stirring time	Viscosity
Rotation speed	Drug content
Effect of Temperature	Stability
Nature of substitution	% drug entrapment efficiency
Nature of solvent	Moisture content

Method of preparation of nanosponges:

1) Emulsion solvent diffusion method
2) Hyper cross-linked beta-cyclodextrin
3) Quasi-emulsion diffusion method
4) Solvent Evaporation method

1) Emulsion solvent diffusion method:

In this method, two phases are used in a different proportion of organic and aqueous (ethyl cellulose and polyvinyl alcohol). The dispersed phase has ethyl cellulose and drug gets dissolved in dichloromethane (20 ml) and a definite amount of polyvinyl alcohol added to 150 ml of aqueous continuous phase. Then, the mixture is stirred properly at 1000 rpm for 2hr. The nanosponges were collected by the process of filtration by using Whatman filter paper(.45µm) and kept for drying in an oven at 40ºC for 24hr. Nanosponges are dried were stored in desiccator sand residual solvent removal.

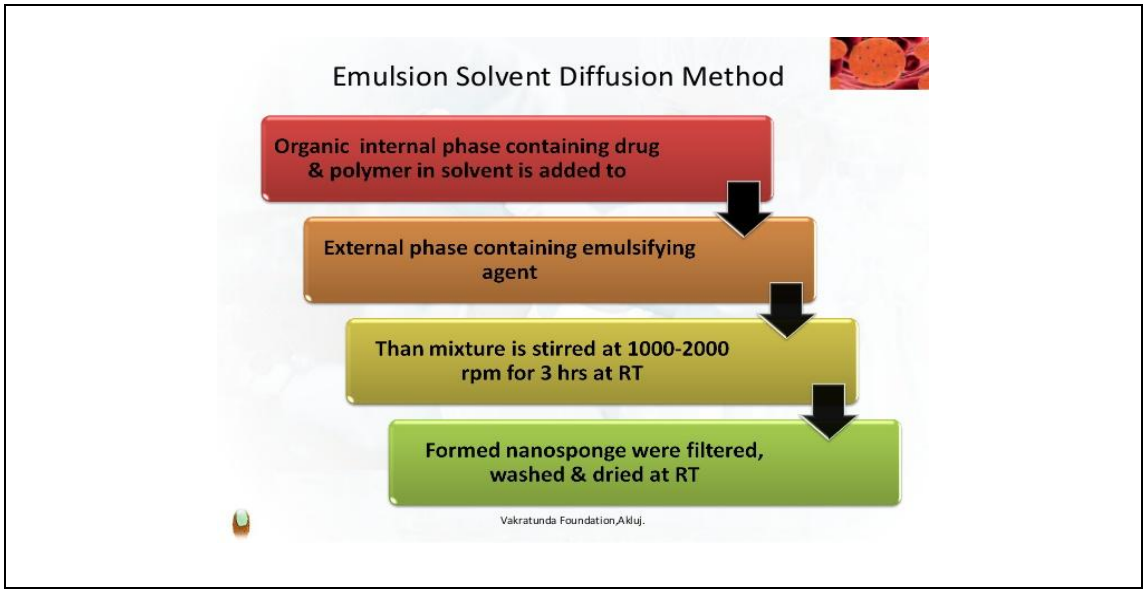

Figure no: 1

2) Hyper cross-linked beta-cyclodextrin:

Nanosponges can be obtained by cross-linking with different types of cyclodextrin with a carbonyl as a crosslinker. They are obtained by reacting cyclodextrin with cross-linkers such as biphenyl carbonate diisocyanates. The transparent block of hyper cross-linked cyclodextrin was roughly ground and excess of water is added remove solvent. The product obtained is purified using Soxhlet extraction with ethanol and product obtained is dried in an oven at 60˚C overnight [4].

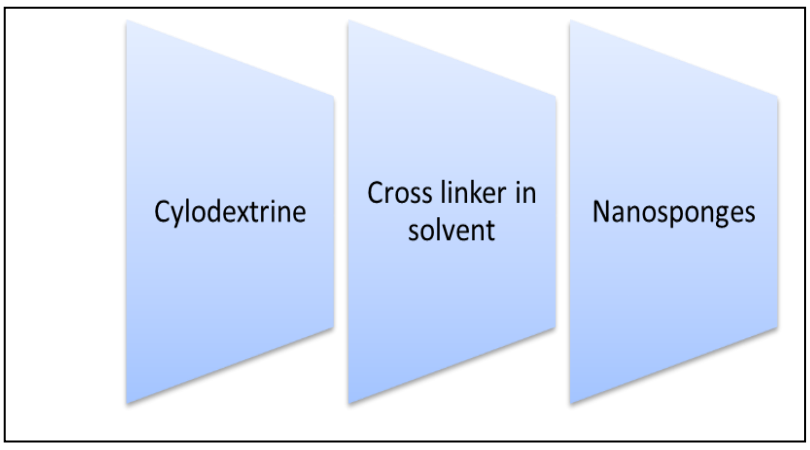

Figure no: 2

3) Quasi-emulsion diffusion method:

The nanosponges prepared using the polymer in different amounts. The inner phase is prepared using eudragit RS 100 and added to a suitable solvent. A drug used provided with a solution and dissolved under ultrasonication at 35ºC. This inner phase added to external phase containing PVA act as emulsifying agent. The mixture is stirred at 1000-2000 rpm for 3hr at room temperature and dried in an air-heated oven at 40ºc for 12hr.

4) Solvent Evaporation method

The solvent required is mixed with the polymer mainly in a polar aprotic solvent for example dimethylformamide, dimethylsulfoxide then this mixture is added to crosslinker in quantity excess, the ratio for crosslinker/ molar ratio is preferred as 4 to 16. The reaction proceeds with a solvent reflux temperature and time ranging from 1 to 48 hr. The preferred crosslinkers are carbonyl diimidazole and diphenyl carbonate. The reaction is completed and the solution is allowed to cool at room temperature then the product is added to an excess of bi-distilled water and product is recovered by filtration under vacuum and simultaneously purified by extraction with ethanol. Finally, the product is dried under vacuum and ground in a mechanical mill and subjected to prolong exhalation obtain a homogeneous powder.

Evaluation parameter of Nanosponges under QTPP:

1) Particle size and polydispersity index Determination:

- **Particle size** can be determined by laser light Diffractometry or zeta seizer. The cumulative percentage drug release from nanosponges of different particle size can be plotted against time to study the effect of particle size on drug release. Particle size range from 10-30µm can be preferred for topical drug delivery.

- **The polydispersity index (PDI)** can also measure from dynamic light scattering Instruments.PDI is an index of width or variation with particle size distributes. Monodisperse samples have a lower PDI value, where a higher value of PDI indicates a wider particle size distribution and the polydisperse nature of the sample. PDI can be calculated by the following equations.

PDI=▲d/davg where. ▲d=width of distribution

The Range of Polydispersity index in the form of a table as below:

Table no: 4

Polydispersity index	Type of dispersion
0-0.05	Monodisperse standard
0.05-0.08	Nearly monodisperse
0.08-0.7	Mid-range polydispersity
> 0.7	Very polydisperse

2) Determination of production yield:

The production yield of the nanosponges was determined by calculating accurately the initial weight of the raw materials and the final weight of the nanosponges obtained. Normal Values of production yield of nanosponges is around 85%-98%.

$$\text{Production yield} = \frac{\text{Practical mass of nanosponges}}{\text{Theoretical mass}} \times 100$$

3) % Drug entrapment efficiency:

Drug entrapment efficiency was calculated by centrifugation method, about 5ml ornidazole loaded NS was taken in tube &further it was centrifuged in cooling centrifuge tube at 1300 rpm for 20 min. After centrifugation, the supernatant layer was removed &diluted with appropriate solvent

$$\%\ \text{drug Entrapment Eficiency} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

OR

$$\%\ \text{DEE} = \frac{\text{Wtinitial drug added into formulation} - \text{wt of the free drug into the formulation}}{\text{Winitial drug added into formulation}} \times 100$$

4) Saturation state interaction:

UV spectroscopy is used to carry out the saturated solution interaction study. Increasing the concentration of nanosponges' solution (1-80ppm) are added to fixed concentration of the drug. The samples are kept overnight for interaction and finally filtered solutions are scanned for λmax and absorbance is measured. Drug loading is interpreted by taking scans of the

formulation in the UV range and analyzing the shift of the absorbance maxima in the spectra compared to pure drug.

5) Zeta potential:

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment. Normal values of Nanosponges with Zeta Potential values greater than +25 mV or less than -25 mV typically have high degrees of stability.

6) Resiliency:

Viscoelastic properties of sponges are modified to produce beadlets which are softer and firmer when needed for final formulation. When cross-linking got increased and tends to slow down rate of release. Resiliency are studied according to requirement by releasing function of cross-linking with time.

7) Thermogravimetric analysis (TGA):

These studies are carried out to understand the melting point, thermostability and crystalline behavior of the particle.

8) SEM and TEM:

These tools are employed to evaluate the particle shape and size and to get morphological information related to the drug delivery system.

- **Case Study 1. Of Qbd Application in nanosponges:**

Khalid akhter Ansari et al have studied on **"**Cyclodextrin-Based Nanosponges for Delivery of Resveratrol: In Vitro Characterisation, Stability, Cytotoxicity and Permeation Study." [(10)]

Another major advantage is that the nanosponge particles are soluble in water. Encapsulating the anti-cancer drug in the nanosponge allows the use of hydrophobic drugs that do not dissolve readily in water. Currently, these drugs must be mixed with another chemical, called an adjuvant reagent that reduces the efficacy of the drug and can have adverse side-effects. The other major advantage of the nanosponge particles and for attaching the linkers, which are made from peptides, relatively small biological molecules built by linking amino acids.

The drug used for the animal studies was paclitaxel (the generic name of the drug Taxol) that is used in cancer chemotherapy. The researchers recorded the response of two different tumor types - slow-growing human breast cancer and fast-acting mouse glioma - to single injections. In both cases, they found that it increased the death of cancer cells and delayed tumor growth "in a manner superior to know chemotherapy approaches.

Objectives of this research work as:

1) Developing a novel Nanosponges based nanoformulation of the selected drug¬ at metronomic low dose applying a holistic QbD-based approach for developing the aforesaid¬ "optimized" drug Delivery system

2) Conversion of the optimized Nanosponges formulation into a patient¬ compliant oral dosage form.

3) Studying the stability profile of the optimized formulation

It is also possible to control the size of nanosponge particles. By varying the proportion of cross-linker to the polymer, the nanosponge particles can be made larger or smaller. This is important because research has shown that drug delivery systems 100 nanometers, about the depth of the pits on the surface of a compact disc. The nanosponge particles used in the current study were 50 nanometers in size. "The relationship between particle size and the effectiveness of these drug delivery systems is the subject of active investigation,"

Quality Target product profile: slow release, Nanosponge based oral Nanoformulation of the Drug-loaded anticancer drug.Entrapment Efficiency Important for determining release characteristics, Zeta Potential Important for stability and determination of shelf life of the SLN formulation. Drug Release Characteristics Failure to meet the dissolution specifications may have an adverse impact on PKP, CQA Justification Particle Size significantly affects the physical stability of the formulation, release rate of the drug and the fate of the particles in-vivo. Polydispersity Index High PDI leads to particle agglomeration.

When Nanosponge loaded with an anticancer drug, a delivery system based on a novel material called nanosponge is three to five times more effective at reducing tumor growth than direct injection. Imagine making tiny sponges that are about the size of a virus, filling them with a drug and attaching special chemical "linkers" that bond preferentially to a feature

found only on the surface of tumor cells and then injecting them into the body. The tiny sponges circulate around the body until they encounter the surface of a tumor cell where they stick on the surface (or are sucked into the cell) and begin releasing their potent cargo in a controllable and predictable fashion. Targeted delivery systems of this type have several basic advantages: Because the drug is released at the tumor instead of circulating widely through the body, it should be more effective for a given dosage. It should also have fewer harmful side effects because smaller amounts of the drug come into contact with healthy tissue.

- **Case Study 2. Of Qbd Application in nanosponges[(12)]**

Emad B. Basalious et al have studied on "Application of Pharmaceutical QbD for Enhancement of the Solubility and Dissolution of a Class II BCS Drug using Polymeric Surfactants and Crystallization Inhibitors: Development of Controlled-Release formulation."

Applying a holistic QbD-based approach Drug solubility enhancement is one of the most important challenges in the field of pharmaceutics. Among the five key physicochemical parameters in early compound screening viz. dissociation constant, solubility, permeability, stability, and lipophilicity, poor solubility tops the list of critical compound property. One of the greatest limits to the development of various pharmaceuticals is the low water solubility of many drugs. About 40% of newly marketed drugs are poorly soluble in water, which hinders their clinical application. Nanosponge's formulation can improve the solubility of drug molecules with very poor solubility in water. The drugs can be molecularly dispersed within the nanosponge structure and then released as molecules, avoiding the dissolution step. Consequently, the apparent solubility of the drug can be increased. Drugs like Itraconazole, Tamoxifen, Paclitaxel, and ketoconazole are difficult to formulate due to their poor water solubility can be easily formulated as nanosponges by enhancing their solubility and attaining therapeutic efficacy.

CONCLUSION

With demand for innovative and highly efficient pharmaceutical and cosmetic products, the market holds considerable potential for nanosponge technology based formulations and the versatility they offer. As formulators consider new and creative ways to deliver actives, they can realize the full capabilities of these unique assets providing enhanced safety, improved stability, reduced side effects, enhanced multi-functionality and improved ingredient

compatibility. Complemented by novel development approaches and creative formulation techniques, nanosponge delivery systems can be a promising strategy for a new generation of pharmaceuticals and cosmeceuticals. Quality by design is an essential part of modern approach pharmaceutical quality. Identification of critical material attributes that provide a link to the product quality to the mfg. process. The role of control strategy as the mechanism for completion of QbD elements into practice [14]. It is an efficient path to the design space through the identification of noninteracting process variables. QbD also having wide scope in biotechnological products such as vaccines, enzymes, monoclonal antibody etc not only in dosage forms. Quality by Design acts as a regulatory shift, which facilitates manufacturing designs and product approvals for vaccines & other products.

Challenges:

The fast growth of interest in Qbd and its tool indicates that the approaches are not fashionable phenomena but responses to the demands of the modern manufacturing process. Qbd is a cost and time efficient approach to design and manufacturing process. This technology offers entrapment of ingredients and thus reduced side effects, improved stability. Nanosponges can be effectively incorporated into topical drug delivery system for retention of dosage form on the skin and also use for orally targeted on the colon.

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