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NANOSPONGES: AN INNOVATIVE STRATEGY FOR TARGETED DRUG DELIVERY- A REVIEW

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RUNNING TITLE: A REVIEW ON NANOSPONGES

Abstract:

Targeted drug delivery to specific sites is the important problem which is being faced by the researchers. The invention of nanosponges become a significant step towards overcoming the problems. However, the most important appilication of targeted drug delivery system is to treat cancer.

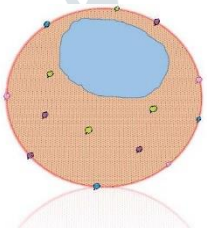
Nanosponges are tiny in size with a three dimensional network and nanometric cavity. Nanosponges are highly porous and having unique ability to entrap active molecules and offer programmable release. They are prepared by reacting cyclodextrins with appropriate cross linking agents in a specified ratio. Nanosponges circulate throughout the body until they reach the specific target site, stick on the surface and release the drug in a predictable manner. They posses higher drug loading capacities compared to other nanocarriers

This review focuses on the methods of preparation, nanosponge applications, factors effecting drug delivery area, characterization of nanosponges. It helps to understand the adavantages of this new medication method over conventional medication system.

Key words - Nanosponge, Cyclodextrins , Cross linking agents , Controlled release, Poor Solubility, Targeted Drug Delivery,

Introduction:

Nanosponge is a unaccustomed technique which delivers controlled/ systematic drug delivery for topical use[1]. nanosponges are microsponges with a size of about a virus with an average diameter under 1um .These microsponges can diffuse / spread over the body until they meet the particular target site and stick on the surface and began to release the drug in a disciplined and expectable manner . As the drug can be released at the particular target site in place of spreading across the body .it will be more effective for a peculiar given dosage[2-3].The sponges acts as a three dimensional network or scaffold. The backbone is long length polyester.The polyester is biodegradable,so it breaksdown,it releases its drug payload in a expectable model ,it is blended in solution with cross linkers to build the polymer[4]. Nanoparticles are available in different forms like polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, nanosponges, carbon nanotubes, micellar systems, dedrimers etc[5]. Nanosponges are compact in nature they are found to be safe for oral and invasive routes Hence they can serve as an constitutional carrier for drug delivery. Nanosponges have a high power of enmeshing wide ranges of active ingredients and they can bind poorly soluble drugs within its matrix and enhance their bioavailability.



Advantages[(6-14)]:

1. Targeted site peculiar drug delivery
2. This technique provides entrapment of different types of ingredients and dimish the side effects
3. Nanosponges offers ceaseless action upto 12 hrs that is enlarge release
4. Amend stability, enlarged elegance and enriched formulation flexibility
5. Offers enlarge release upto 12 hrs
6. Delivers industrious ingredient from degradation

7. Cost efficient, simple to scale up
8. Immscible liquids can be integrated
9. Masks distasteful flavours

Compounds worned for the amalgamate of nanosponges:

(Or)

Components coaxing nanosponges evolution of nanosponges:

A) Polymer:

Kind of polymer worned can impact the evolution binds the accomplishment of nanosponges[15]. should be adequate to capture a drug molecule of a notably size into it for complexation/ targeted[16]. For the baited drug discharge the polymer should have the equity to adhere with the peculiar lligands[17].

B) Cross-linking agent:

Picking of cross linking agent lean on the assemble of polymers and the drug to be detailed/formulated leaning upon the quality of cross linkers,water soluble/water resolvable or unresolvable nanosponges are evoluted/ assembled[18].

Chemicals used for the preparation of nanosponges

Polymers	Hyper crosslinked Polystyrens, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxy-carbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and copolymer like poly (valerolactone allylvalerolactone) and Poly (valerolactone – oxepanedione) and Ethyl Cellulose and Poly Vinyl acetate.
Cross linkers	Diphenyl Carbonate, Di-aryl carbonates, Di-isocyanates, Pyromellitic anhydride, Carbonyldi- imidazoles, Epi-chloridrine, glutaraldehyde, Carboxylic acid di- anhydrides, 2,2 – bis (acrylamido), Acetic acid and Dicholomethane

C) Kinds of drugs and medium worned for reciprocal action:

Drug molecules to be tangled with nanosponge should have peculiar attributes for flourishing capture into Nano dents[19]. The molecular weight of the drug molecule should be in differing from 100 -400 daltons. The structure/ assemble of molecules should carry out more than five condensed/ compact rings[20].when the drug brimfuled / loaded into the nanosponges, the drug molecules should have minor melting/ liquifying points. Resolvability in water should be below 10 mg/ ml. The reciprocal action amid nanosponge dents and baited compounds dynamically leans on the Medium; Namely,a hydrophilic intermediate will move the organic guest molecules into hydrophobic dents .these dynamic reciprocal actions amid host and guest molecules lean on collaborative matching of size , hydrophobic ambient and armature equities.

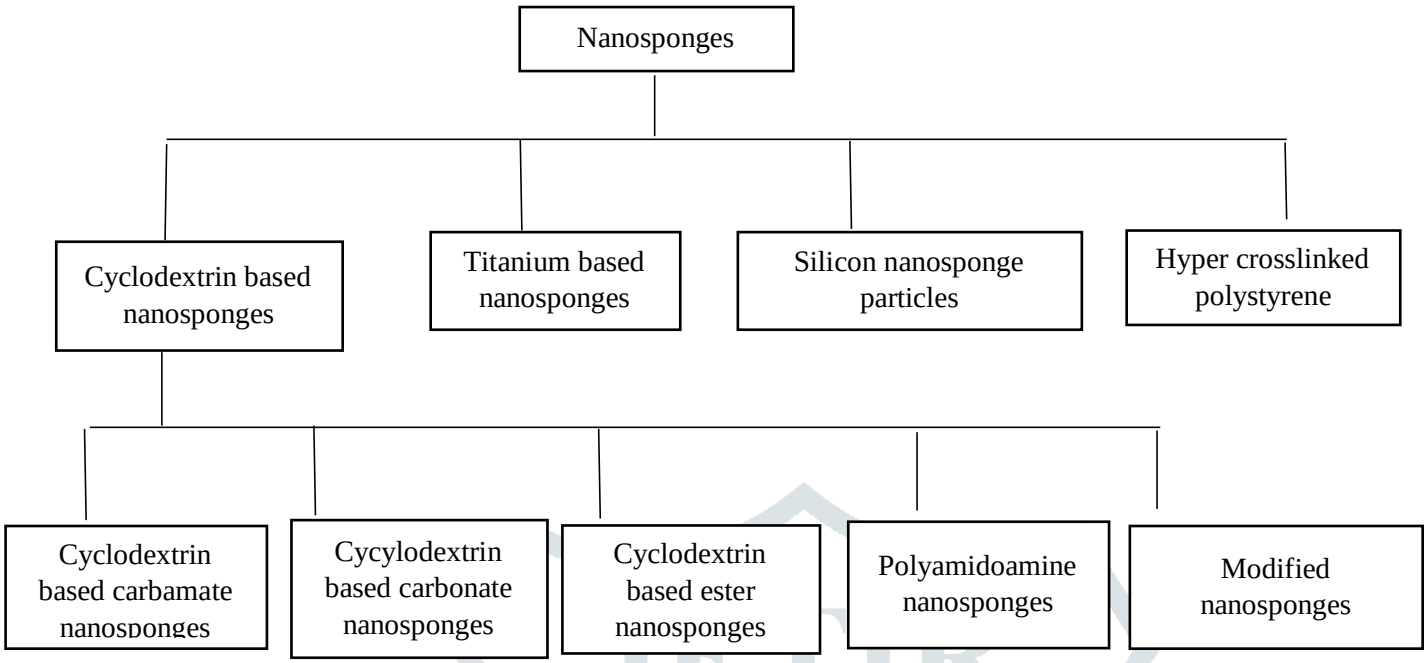
D)Tangled/ complexation temperature:

The immatability constant of a complex is reliant on temperature alters / changes with a rise in temperature[21], the momentousness of distinct immutability constant or stability constant diminishes due to decrement in drug or nanosponge reciprocal action[22]. Which may be resulting from vanderwaal forces and hydrophobic forces with rise of temperature[23].

E) Degree of substitution:

The tangled capacity of the nanosponges may be highly impacted by type, number and position of substituent on the parent molecule[24]. The kind of replacement is essential due to beta cyclodextrine derivatives are accessible in different forms varing in functional groups display on the surface of the cyclodextrine derivative. Higher the number of replacements higher the cross-linking capacity. Accelerate in the degree of cross-linking tends to evolution of highly because of many concentrations amid polymers assembling a mesh kind of network or chain structure[25].

Types of Nanosponges

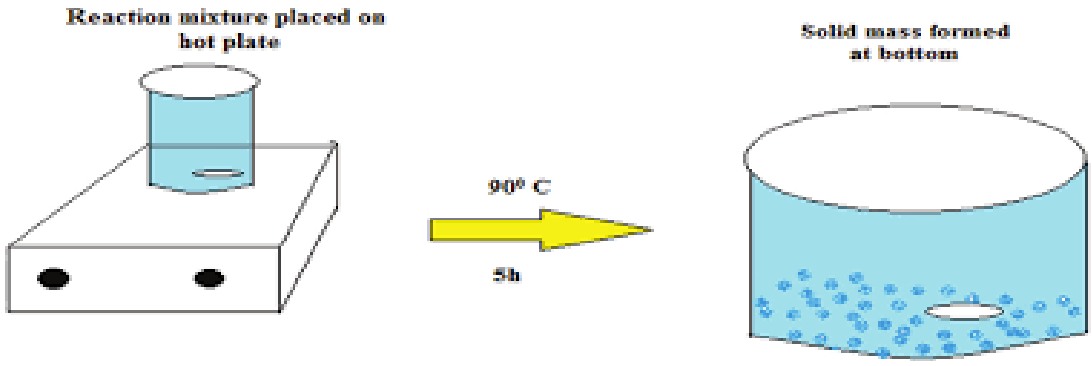


Forms formation of nanosponges

Nanosponges are formed reliant on the kind of consignment networks. Nanosponges can be formed by advance formulation parameters such as drug, polymer ratio, polymer, crosslinking agent ratio and agitation or stirring speed.

1. **Melt technique\demateralise approach :**

In melt technique cyclodextrin is proceed with appropriate crosslinkers like diphenyl carbonate, carboxylic acid an hydrides; all ingredients are cautiously integrated or amalgamated and put in a 250ml flask warmth at 100°c and the approach is allow out for 5h warming magnetic stirrer. the combination is ratified to cool and the arranged output is bust down and to abolish curesponsive excipients the output is washed with a befitting solvents[27].



2. Emulsion solvent dispersal technique :

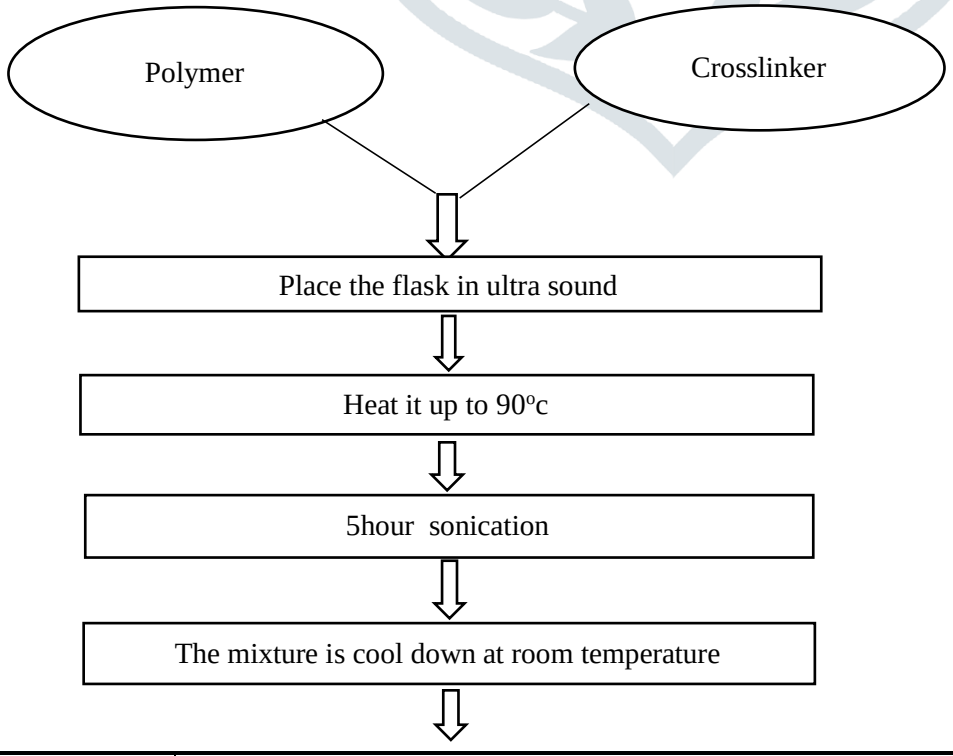
In this approach two different confines of organic and aqueous phases are worned in organic stage, drug and polymer are amalgamated and in aqueous stage ,polyvinyl alcohol [PVA] is worned after melting drug and polymer to the right organic solvent ,This stage is slowly combined to the aqueous stage and agitates for two or more hours at 1000 rpm worning magnetic stirrer. Then the ready nanosponges are collected by filtration washed and then dried in air at room temperature or in vaccum over 40^0c for 24hrs[28].

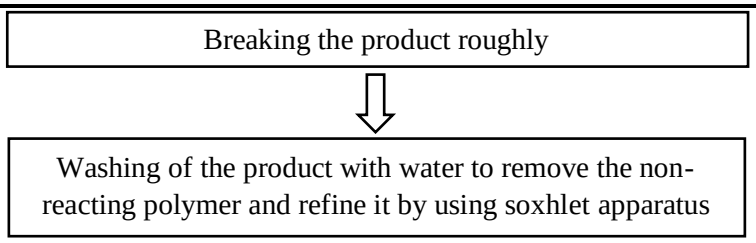
3. Quasi emulsion solvent dispersal method:

The nanosponges can also be processed by quasi- emulsion solvent dispersal approach worning the distant polymer amounts. To processed the inner stage ,edragit R_{s100} was dematerialize in appropriate solvent. Then drug can be joined to solution and dematerialized under ultrasonication at 35^0c, the innerstage was spouted into the polyvinyl alcohol solution in water [outer stage]. Following 60mins of stirring the compound is filterated to discrete the nanosponges, the nanosponges are dried in an air or heated over at 40^0c for 12hrs[29].

4. Ultrasound abetted synthesis/consolidate:

Polymers are made to counter with crosslinkers in a flask without the solvent. The flask is planted in an ultrasound bath which is filled with water and heated upto 90^0c and the compound is sonicated for 5hrs[30].





5. Solvent approach:

The polymer is combined with a appropriate solvent like dimethyl formamide, dimethyl sulfoxide etc. this compound is combined to extra amount of cross linkers faine act in crosslinker polymer ratio of mostly worned crosslinkers are carbonyl mixtures like diphenyl carbonate, dimethyl carbonate and carbonayl diimidazole[31]. The reaction is coveyed at temperature differing from 10^0c to the reflux temperature of the solvent for 1-48hrs after completion of the reaction the solution is endorsed to cool at room temperature and the extra amount of distilled water is combined the output is redeemed by filtration under vaccum and refined by prolong Soxhlet extraction with ethanol output is dried under vaccum and base in a mechanical mill to a homogenous powder[32].

6. Loading of drugs into nanosponges :

Nanosponges for drug dispatch should be prearranged to acquire a callous particle size below 500nm. Defer the nanosponges in water and sonicate to duck the contiguity of aggregates and then centrifuge the suspension to acquire the colloidal fraction. Defached the supernant and dry the specimen by freeze drying[33]. Fix the aqeous suspension of nanosponge and disperse the extra amount of the drug and preserve the suspension or holding pattern under stable stiring for peculiar time necessary for complexation. After complexation, detach the umcomplexed (undissolved) drug from complexed drug by centrifugation. Then acquire the solid crystals of nanosponges by solvent evaporation or by freeze drying. Crystral construct of nanosponge disport a very vital function in complexation with drug[34]. A examination disclosed that paracrystaline nanosponges displayed dismilar loading capabilities when contrast to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one. In deficiently crystalline nanosponges, the drug loading appear like mechanical compound rather than inclusion complex[35].

Characteristics/Diagnostics of Nanosponges[37]:

- Nanosponges delivered a variety **o**f proportions [1um or less than that] dent with coordinate duality.
- By modifying cross linker to polymer ratio nanosponges of a peculiar size can be amalgamated.
- They display paracrystalline or crystalline configuration, reckoning on the procedure case. Crystal arrangement of nanosponges recreate a pivotal role throughout complexation with drugs.
- Drug burden capability lean on the amount of crystallization.
- Different drug burden capabilities can be displayed by paracrystalline nanosponges.
- They are non-toxic/disarmed, porous/penetrable particles, unsolvable in most organic solvents & firm up to 300^{o}c.
- They are firm at the PH scope of 1-11.
- They assemble crystal clear and polychromatic moratorium in water.
- They can be replicated by simple thermal desorption/ elementary scorching fractionation, eradication with solvents, by operating microwaves & ultrasounds.
- Nanosponges can crunch willingly to the destinated site across chemical linkers.
- Utilizing a different of drugs to configuration complexes can be assembled by nanosponges.
- Nanosponges can attain magnetic landscape when magnetic particles are combined to the reaction blend.

Applications:

Nanosponges have multiple applications in the pharmaceutical field because-of their biocompatibility and versatility. Due to their nano parous arrangement, nanosponges can beneficent haul water unsolvable drugs [Bio pharmaceutical classification systems class-II drugs]. These complexes can be worn to accelerate the dissolution rate, solubility & solubility of drugs, to camouflage distasteful flavours & to transform liquid materials to solids. In the pharmaceutical industry, Nanosponges can be worn as an excipient for the articulation of tablets , capsules ,granules, pellets, suspensions, solid dispersions & topical dosage configuration. Nanosponges can perform like multifunctional shipper for enrich product enactment and gracefulness. Elongated release, diminish irritation, better thermal, physical and chemical cohesion of product[38].

Following are the applications of nanosponges which displays skillfulness of nanosponges.

- **Nanosponges like confirmed delivery system:**

Acyclovir is one of extensively worn antiviral agents for the medication of herpes simplex virus infection[39]. Its consumption in the GIT is dull and deficient & greatly variable. The invitro release profile of the acyclovir from various types of nanosponges displayed ceaseless discharge of the drug. The percentage discharge of acyclovir from carbo-nanosponges and nanosponges after the 3hrs of regime were about 22% & 70%. The drug was not captivated on the nanosponge facial since no basic burst effect was not detected[40].

- **Solubility enhancement**:

Nanosponges have been also used for developing the resolvability and dissolution rate of inadequately resolvable drugs besides delivering organized release profile. However the molecular dimensions/magnitude and confirmation are crucial dimensions clouting inclusion complexation within nanosponges & thus may not be universally applicable to all molecules. Nanosponges of cefpodoxime proxetil [cp] have been arranged to developed dissolution ratio of cp[41]. Formulation of cross linked B-cyclodextrins grounded nanosponges of Itraconazole has been addressed to appreciate the resolvability of the deficiently soluble drugs. It was encountered that the solubility of Itraconazole was revised more than 50- folds with a terarry solid dispersion system. Worn copolyvidonum in conjunctionwith nanosponges abetted to accelerate the solubilization ability of nanosponges[42].

- **Nanosponges in Drug delivery:**

Nanosponges have spherical shape and nanomeric in size accomplishing them ideal in arranging different dosage configuration alike topical parenteral, aerosol, tablets and capsules. commanding to their versatile, biocompatible and nano parous nature, nanosponges have different of applications in pharmaceuticals, cosmetics, agriculture, environment, food and polymer industry[43].

Telmisartan [TEL] is a BCS class-II drug having dissolution rate bounded bioavailability. Beta-cyclodextrin [B-CD] grounded nanosponges were assembled by cross-linking B-CD with carbonate bonds. Telmisartan was assimilated into the nanosponges. Saturation solubility and in

vitro dissolution study of B-CD complex of TEL was contrasted with plain TEL and nanosponges complexes of TEL. It was encountered that resolvability of TEL was developed by 8.53 fold in distilled water, 3.35 fold in 1 mol HCL and 4.66fold in phosphate buffer PH 6.8 by assimilating $NaHco_3$ in drug nanosponges complicated than TEL, the highest resolvability and in vitro drug delivery was noticed in inclusion complex arranged from nanosponges and $NaHco_3$. Because of nanoporous nature they are worn like carrier for water-resolvable/soluble drugs [BCS class-II drugs]. These complexes can be used to enhance the dissolution rate, solubility/resolvability and stability/cohesion of drugs along with to mask. The distasteful flavor. Beta-cyclodextrin grounded NSS are disclosed to bear the drug to the destination site 3-5 times more flourishing than command injection[44].

- **Nanosponges for delivery of protein**:

The key bump/difficulty in protein formulation development is the alimentation of the native protein arrangement both throughout the formulation procedure and upon the deep-rooted repository/storage[45]. However, proteins can reversibly/undoable [or sometimes even irreversibly] denature upon lyophilization and accordingly embrace acceptance noticeably non identical from the native ones. This, a key obstacle in protein formulation development is the alimentation of the native protein arrangement both throughout the formulation procedure and upon the deep-rooted repository[46] .

To research the encapsulating ability of B-cyclodextrin grounded nanosponges , Bovine serum albumin[BSA] was worn like a classic protein[47].

- **Nanosponges in enzyme immobilization:**

The enzyme immobilization is specifically applicable for lipases, because it advances their reliability and adapts equity related enantio particularly and reaction/response rates[48]. As a fall out the necessitate for fresh solid reinforces appropriate for this kind of enzymes is consistently developing . For this boscolo etal disclosed high catalytic achievement of fluorescens lipase captivated on a fresh kind of cyclodextrin grounded nanosponges[49].

- **Nanosponges as a carrier for delivery of gases**:

Gases perform an vital role in medicine. Either for diagnostic or medication objectives. The glitch of abundant oxygen supply, named hypoxia, is associated to different pathologies, from inflammation to cancer. It is

occasionally challenging to emancipate oxygen in suitable configuration and dosage in clinical dry run/rehearsal. Cavallietal advanced nanosponges compositions like oxygen delivery systems for topical functions which have the capability to keepand to discharge oxygen gently one time[50].

- **Nanosponges as protective agent from light or degradation:**

Supino et.al announced that gamma –oryzanol [A ferulic acid ester mixture], an anti –oxidant and generally applied to balance food and pharmaceutical organic materials, Besides, worn like sunscreen in the cosmetics industry. Its functionis limited by its high unsteadiness and photo degradation. Gamma oryzanol has been encapsulated in nanosponges. Disclosing a strong photo degrading safety. The nanosponges medicated with gamma-oryzanol were classified with a gel and an o/w emulsion[51].

- **Nanosponges for cancer therapy:**

Ultimate demanding works now a days in the pharmaceutical field is the discharge of anticancer drug by reason of their enervated resolvability. In one article they affirm that nanosponges complex is 3 times higher competent to abate the growth of tumor then command injection. The Nanosponges complex amount with a drug and disclose a addressing peptide that fastens tightly with a radiation induced cell upper layer on the tumor receptor. When nanosponges encounters the tumor cell they firmly fixed on the facial of tumor cell and start to discharge the drug molecules. The pro of destinating drug discharde is to get a high compelling therapeutic effect of the similar dose and with deprecate side effect[52].

- **In antiviral therapy:**

They may be fruitful for eye, nasal, and pulmonary routes of administration. Nano hauler/carrier may undergo particular discharge of antiviral drugs to the nasal epithelia and lungs to encounter viruses that affect the RTI, like respiratory syncytial virus, influenza virus, and rhino virus; In nano discharge classifications, the drug articulated are zidovudine, saquinavir, interferon –alpha, acyclovir, Nelfinavir, etc[53].,

- **Oxygen delivery systems**:

Cyclodextrin nanosponges have also been evolved as oxygen delivery systems (oxygen discharge classification). For this intention, the 3 types of nanosponges made up of alpha, beta and gamma- cyclodextrin is append in water,

saturated with oxygen and in vitro characterized. Oxygen permeation across a silicone membrane can also be obtained worn a Beta-cyclodextrin / nanosponge/ hydrogel combo classification. Nanosponges could supply oxygen to the hypoxic tissues which are unveil in different diseases[54].

- **Modulating Drug release**:

The crucial defect of maximum of the current commercial/marketable obtainable drug delivery systems (drug discharge classification) is constant authority. However, a drug amounted into the nanosponge is retained and discharged gently over time. Hydrophilic cyclodextrin nanosponge can alter the rate of discharge of drugs, which can be worn to enlarge drug consumption across biological obstacles, performing as a potent drug cancer in compositions for instant release/discharge hydrophobic cyclodextrin nanosponge can deliver for water resolvable drugs, including peptide and protein drugs, like sustained discharge hauler. For example doxoriblin[an anticancer drug], and they can defend the medication when travel through the stomach. The drug is discharged very gently at PH1.1, whereas if the PH is boosted to 7.4 discharge is brisk/swift[55].

- **Topical drug delivery systems:**

Regional anesthetics, anti fungals and antibiotics are among the division of the drugs that can be easily articulated as topical nanosponges. In this ambience nanosponges can be processed by different types like emulsion solvent diffusion method etc,. The nanosponges of econazole nitrate were processed , which are streaming nanosized particles with crenelated/pierced with orange peel like morphology as visualized by SEM in the literature[56].

- **As absorbent in treating poision in blood**:

Nanosponges can clear away the harmful poisonous stuff from our blood by consuming the poison in place of worning antidotes, If we amalgamate nanosponges by injection/inoculation into blood nanosponge can absorb the toxins. In the blood flow, the nanosponges glimpse like red blood cell, tricks toxins into ambushing it and then consumes it; The number of toxin molecules in every nanosponge can consume lean on the toxin[57].

EVALUATION OF NANOSPONGES:

Inclusion complexes formed between the drug and nanosponges can be characterized by following methods.

Thermo-analytical methods

Thermo-analytical methods determine whether the drug substance undergoes some change before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. thermogram obtained by DTA and DSC can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes[58].

Solubility studies

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors ,which examines the effect of a nanosponge, on the solubility of drug . phase solubility diagrams indicate the degree of complexation[59].

X-ray diffraction studies

Powder X-ray diffractiometry can be used to detect inclusion complexation in the solid state. When the drug molecule is liquid since liquid have no diffraction pattern of their own, then the diffraction pattern of anewly formed substance clearly differs from that of uncomplexed nanosponge. This difference of diffraction pattern indicates the complex formation. When the drug compound is a solid substance, a comparison has to be made between the diffractogram of the assumed complex and that of the mechanical mixture of the drug andpolymer molecules.A diffraction pattern of a physical mixture is often the sum of those of each component, while the diffraction pattern of complexes are apparently different from each constituent and lead to a ―new solid phase with different diffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation. The complex formation of drug with nanosponges alters the diffraction patterns and also changes the crystalline nature of the drug. The complex formation leads to the sharpening of the existing peaks, appearance of a few new peaks and shifting of certain peaks[60].

Zeta potential

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment[61].

Photo degradation study:

The photo-degradation of drug loaded nanosponge complex is performed under UV lamp. The samples are kept at distance of 10cm from the lamp for 1hr. stirring under dark ; simultaneously the samples are quantitatively analyzed by HPLC[62].

Single crystal X-ray structure analysis:

It may be used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest molecules can be identified and the precise geometrical relationship can be established[63].

Entrapment efficiency

Weighed amount of drug loaded NSs are dispersed in methanol, centrifuged at 1000rpm for half an hour, the supernatant withdrawn, suitably diluted with methanol and are subjected to ultraviolet (UV) spectroscopy for taking absorbance of the sample against blank methanol . the percentage of drug entrapment is calculated by the following equation .the entrapment efficiency (%) of nanosponges can be resolute by[64]

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Polydispersibility index (PDI)

PDI is an index of width within the particle size allotment. PDI form scattered sample is lower, whereas PDI is superior for wider particle size allocation[65].

Microspcopic study:

To analyse microscopic aspects of medicine, nanosponge and system (Medicine / Nanosponge complex), Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) may be used. The disparity in the crystallization condition of the raw materials and the sample presented under an electron microscope indicates the structure of the inclusion complexes. The nanospongesand complex surfaces were examined using an electron scanning microscope (SEM; Quanta W (FEI Company). Double-sided adhesive tape was used to install the powdered pellets onto the stubs. The samples were sputter-coated in an argon atmosphere with platinum–palladium (80:20) and examined at a voltage acceleration of 15 kV. A Philips CM 10 transmission electron microscope was used to examine the suspension of complex to elucidate the shape and size of the particles. NIH(National Institutes of Health)picture analysis was used to calculate particle scale[66].

Particle size analysis:

Free-flowing powders With good graphical qualities can be produced by Manipulating the particle size during polymerisation. The measurement of particle size of loaded and unloaded nanosponges will be performedusing laser light diffractometry or Malvern Zeta sizer. The cumulative percentage of drug release from nanosponges of various particle sizes is measured to time to study the impact of particle size on the release of drug.The particles having size between 10 to 25 Åare preferred for the final formulation because particle size greater than 30Åcreat the gritty feel[67].

Dissolution studies

900ml of phosphate buffer pH6.8 was placed in vessel and the USP apparatus TypeII (paddle method) is assembled. The medium was allowed to equilibrate to a temperature of 37°C±0.5°C. Prepared NSs powder was placed in the vessel and operated for 12h at 75rpm. At definite time intervals, 5ml of the receptor fluid were withdrawn, filtered, diluted, and analyzed spectrophotometrically[68].

Conclusion

Nanoponges are the small sized particles having sponge like structures. Due to their tiny size, they can be incorporated into many formulations such as parenteral, aerosol, topical, tablets and capsules. They can effectively deliver the drug in a controlled manner at a targeted site. Drug deliver by nanosponges were proved

to be safe and effective and the pharmaceutical industries will be greatly benefited if clinical studies can prove their potential for human uses.

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