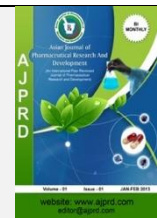


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Review Article

## A Comprehensive Review on Transdermal Delivery of Nanosponges

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### ABSTRACT

The field of innovative medication delivery has greatly benefited from nanotechnology and miniaturisation, which have also transformed the potential in the current healthcare industry. The design of nano-scale drug carriers using various nanotechnology-based approaches for the delivery of lipophilic drug molecules is the current trend in novel drug delivery-based research. Nanotechnology and miniaturisation, which have also changed the possibilities in the contemporary healthcare business, have tremendously helped the field of inventive medicine distribution. Targeting medication distribution in a regulated manner is made possible in large part by NSs. The use of NSs, its preparation, and assessment have all been covered in this review paper. The healthcare industry is seeing encouraging results from a variety of nanosponges formulations, including parenteral, topical, oral, and inhalation, which offer enormous promise for future development and study.

**Keywords:** Nanosponges, Transdermal, Nanotechnology, Targeting drug delivery system

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### INTRODUCTION:

The notion of "miniaturisation" is central to the research and innovation area of nanotechnology, which has significant implications for treatments, diagnostics, and healthcare-related research<sup>(1)</sup>. Drugs of the nanoscale size range are made possible by nanotechnology, which improves their effectiveness in a range of dosage forms. Reduced fed/fasted variability, reduced patient-to-patient variability, improved solubility, greater oral bioavailability, faster rate of dissolution, increased surface area, reduced dosage required, and quicker beginning of therapeutic action are just a few benefits of nanosizing.<sup>(2)</sup> Polymeric or solid lipid nanoparticles, lipid or albumin nanocapsules, liposomes and micelles, dendrimers, nanovesicles, nanogels, nano-emulsions, and nanosuspensions are a few examples of several forms of nanocarriers. Nanocarriers are crucial

elements in the creation of new drugs.<sup>(3)</sup> They improve bioavailability, safeguard and maintain more delicate substances (such proteins), reduce negative effects, and offer mechanisms for active targeting.<sup>(4)</sup> An exterior polymer shell and an interior core make up most nanocarriers for medications.<sup>(5)</sup> The outer core, which also provides stability and regulates particle circulation time, determines how the nanoparticle interacts with its surroundings and cell surfaces.<sup>(6)</sup> These are usually between 1 and 300 nm in size and contain a therapeutically effective substance. Many cutting-edge techniques, including as hydrophilic nanogels, solid lipid nanoparticles, and nanosponges, have just lately been used in the administration of poorly soluble medications. These techniques increase the residence duration, reduce adverse effects, and increase the drugs' bioavailability and therapeutic efficacy.<sup>(7)</sup>

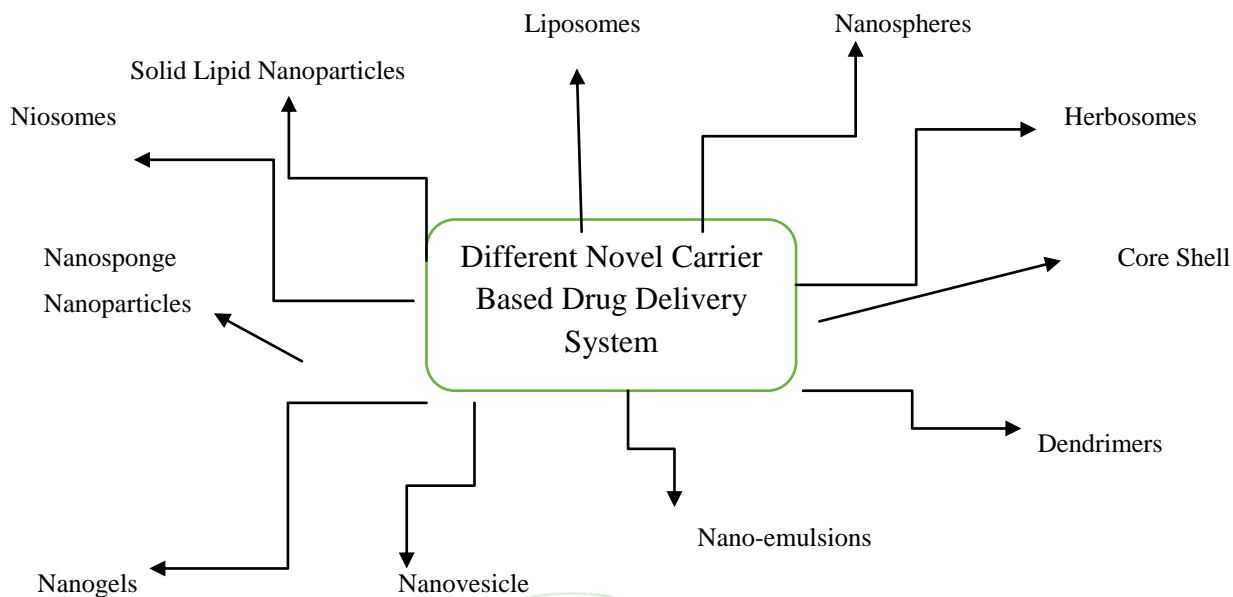


Figure 1: Different Novel Carrier Based Drug Delivery System

**Nanosponges Are Novel Class of Drug Delivery System:**

Injecting nanosponges into the body after loading them with a medication and adding unique chemical "linkers" that preferentially adhere to a characteristic found only on the surface of growth cells is a replacement category of tiny sponges around the size of a virus. These tiny sponges move through the body until they reach a growth cell's surface, where they attach to it (or are drawn inside the cell) and release their powerful medicine in a predictable and controlled manner. The backbone of nanosponges, which resemble a three-dimensional network or scaffold, is long

polyester fibres. Cross-linkers mix with solution with small molecules that act like tiny grappling hooks. Cavities filled with spherically shaped particle which produced net effect, where drug molecules can be stored. Because the polyester is biodegradable, it degrades over time in the body. By adjusting the ratio of cross-linkers to polymer, it is also feasible to alter the size of the nanosponges particles, which will rely on the structure of the nanosponges. Nanosponges are tiny mesh-like structures that will revolutionise the way numerous diseases are treated. This technology makes it five times easier to distribute cancer medication than conventional methods two.<sup>(8)</sup>

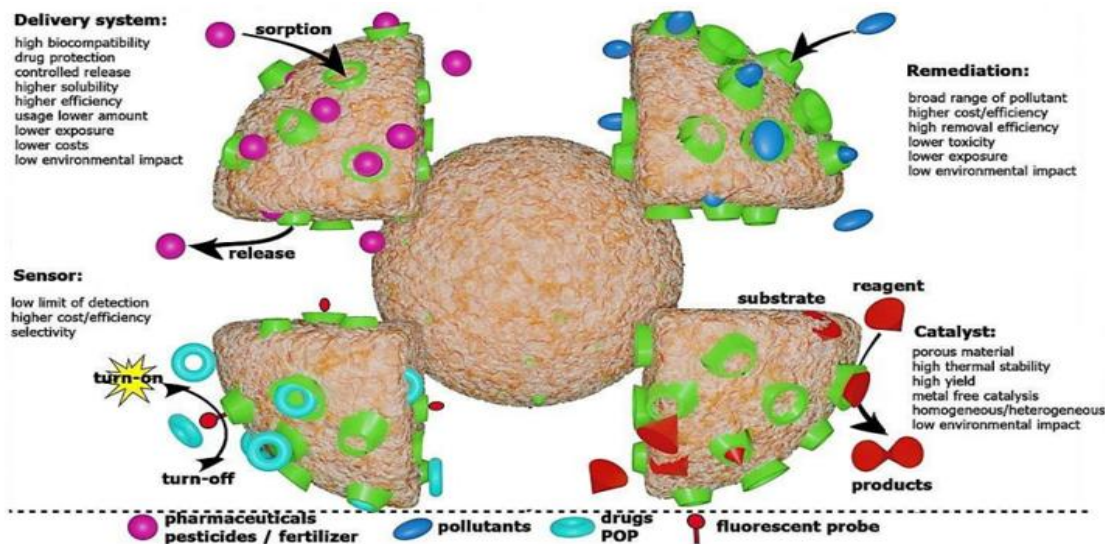


Figure 2: Structure of Nanosponges

**Advantages:**<sup>(9,10,11,12,13)</sup>

1. Forms non-toxic complexes.
2. Protective shielding of the drug.
3. Wide PH range stability.
4. Surface functionalization property.
5. Possess formulation flexibility.
6. Easy to handle and store.
7. Stable and compact.
8. Versatile nanocarriers.
9. Forms Non-mutagenic.
10. Non- irritating.
11. Biodegradable.
12. The drug profiles can be very from fast, medium to slow release in case dosing therapy.

**Disadvantage:**

1. Dose dumping may occur occasionally.
2. May retard the release of drug.
3. Depend only upon loading capacities.

**Preparation of Nanosponges**<sup>(14-16)</sup>

The nanosponges are prepared by various method as follows,

1. Hypercrossed linked  $\beta$ -CD method:
  - a) Melt method
  - b) Solvent method
2. Quasi emulsion diffusion method
3. Emulsion solvent diffusion method
4. Ultrasound assisted synthesis nanosponges

**1. Hypercrossed linked  $\beta$ -CD method:**

$\beta$ -cyclodextrin which act as Nanos porous materials was used to prepare nanosponge perform their work as carriers for drug delivery. As a result, 3-D networks are created, which may resemble a protein-sized, approximately spherical structure with interior channels and pores. Cross-linkers include 2, 2-bis (acryl amido) acetic corrosive, di-isocyanates, di-aryl carbonates, carbonyl diimidazoles, and carboxylic corrosive dianhydrides. Cyclodextrin was used in response, and so forth. Depending on the expert used as a crosslinker, nanosponges can be included in neutral or acidic structures. The surface charge, density, and pore size of the nanosponges may be adjusted to attach various molecules. Depending on the agent utilised as a crosslinker, nanosponges can be created in either neutral or acidic forms. Fractions Although a diameter lower 500 nm can be used, the typical NS diameter is less than 1  $\mu$ m. Nanosponges may encapsulate a variety of compounds by creating inclusion and non-inclusion complexes. Hypercrossed linked  $\beta$ -CD nanosponges can be further divide as follows www.wjpr.net Vol 9, Issue 12, 2020. Agrawal et al. World Journal of Pharmaceutical Research 276

**A) Melt method:**

In the melt method, the crosslinker is melted along with  $\beta$ -CDs. The remaining components are finely homogenised and added to a 250 ml jar that has been preheated to 100 °C. The reaction is then performed for 5 hours while attractive

magnetic mixing is used. The reaction mixture is allowed to cool and the obtained product is broken down followed by repeated washing with suitable solvents to remove unreacted excipients and byproducts<sup>[7]</sup>

**B) Solvent method:**

This approach eliminates the melting stage by solubilizing the crosslinker in solvents like dimethylformamide or dimethyl sulfoxide (DMF/DMSO). It is customary to combine the polymer with a polar aprotic solvent before adding the resulting combination to an excessive amount of crosslinker. Optimization of the process is performed by varying the crosslinker/polymer molar ratio. The reaction is carried out at temperatures ranging from 10 °C to the reflux temperature of the solvent, for 1 to 48 hrs. The carbonyl compounds such as diphenyl carbonate (DPC), dimethyl carbonate (DMC) or carbonyldiimidazole (CDI) are the cross-linker required for the reaction. The product is acquired by adding the cooled answer for an expansive overabundance of distilled water. The item is recovered using vacuum filtering, and it is also washed down by delayed Soxhlet extraction<sup>[8]</sup>

**2. Quasi emulsion diffusion method:**

Various quantities of the polymer were used to make the nanosponges. To prepare the inner phase, Eudragit RS 100 is mixed with the appropriate solvent. The drug was given a solution and was dissolved by ultrasonication at 35°C. This inner phase serves as an emulsifying agent when added to the PVA-containing exterior phase. The mixture is agitated for 3 hours at 1000–2000 rpm at room temperature, and it is then dried for 12 hours in an air-heated oven at 40 °C.

**3. Emulsion solvent method:**

Ethyl cellulose and polyvinyl alcohol, two phases employed in this process, are used in various ratios of organic and aqueous materials. Dichloromethane (20 ml) containing ethyl cellulose, medication, and a certain quantity of polyvinyl alcohol should be added to 150 ml of an aqueous continuous phase before the dispersed phase is dissolved. Then, the mixture is stirred properly at 1000 rpm for 2hr. The necessary nanosponges were gathered during the filtration procedure and stored for drying in an oven at 40°C for 24 hours. In order to ensure that there is no remaining solvent in the dried nanosponges, they were kept in a desiccator. www.wjpr.net Vol 9, Issue 12, 2020. Agrawal et al. World Journal of Pharmaceutical Research 277

**4. Ultrasound assisted synthesis of nanosponges:**

In this method, in the absence of solvent, the polymers with cross-linker are sonicated and are used to formulate nanosponges. The nanosponges obtained by this method will be uniform in size and spherical in shape. In a flask, combine the cross-linker and the polymer in a certain molar ratio. Heat the flask to 90°C by submerging it in a water-filled ultrasonic bath. Sonicate the mixture for five hours, then let it cool and coarsely break the product. The product should be washed in water to eliminate any non-reacted

polymers before being purified using a lengthy ethanol Soxhlet extraction. Dry the final product under vacuum and store at 25°C until further use.

### Factors affecting drug release from nanosponges<sup>(17)</sup>

1. The physical and chemical characteristics of activities captured.
2. Sponge system characteristics such as pore size, pore volume, and resilience.
3. Vehicle characteristics that affect how the sponges are ultimately distributed
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 skin
7. Temperature: Some entrapped actives may be too viscous to flow spontaneously from sponges onto skin at ambient temperature, but rising skin or environment temperatures may cause flow rates to rise and ultimately lead to drug release.
8. Solubility: Sponges loaded with water-soluble ingredients such as antiperspirants and antiseptics release the ingredient in the presence of water.

### Characterization of nanosponges:

Sr. no.	Evaluation parameter	purpose	Conclusion from different research work	References
1.	Particle size	To identify mean particle size of nanosponges	The mean particle size of nanosponges were up to 400-800nm, particle size was increased with decrease in polymer amount.	18
2.	Scanning electron microscopy(SEM)	For the determination of surface characteristics	It was operated at an accelerated voltage of 15Kv; the processed images confirmed nanosponges are uniform and spherical in nature.	19
3.	Zeta potential	Average hydrodynamic diameter was measured	It was performed with dynamic light scattering measurements using zeta sizer.	20
4.	Production yield	To known the obtained yield of nanosponges	Production yield is calculated by dividing practical mass of nanosponges obtained by theoretical mass (polymer and drug) *100.	21
5.	Entrapment efficiency	To known the amount of drug entrapped in nanosponges	The amount of drug entrapped in particular nanosponge formulation is calculated by subtracting total amount of drug from drug in supernatant, which is divide with total amount of drug. Generally, 9000 rpm for 30 min is considered for ultracentrifugation. Entrapment efficiency (%EE) depends on internal and external phase volume, it was observed that change in phase volume changed %EE.	18
6.	Drug content uniformity	To know the amount of drug contained in specific formulation	The drug content in formulation was calculated on the basics of absorbance values of known standard solution.	22
7.	In vitro diffusion studies	To study release profiles of the formulated nanosponges	It was observed that release of drug from nanosponges had decrease with the increase in polymer contents.	23
8.	Thermo analytical studies	Used to estimate thermal characteristics of a substance	Methods used are differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA) by heating from RT to 300°C providing heat at the rate of 10°C/min, under nitrogen. DSC curve of nanosponge formulation showing the absence of drug melting peak indicates the successful encapsulation of drug in nanosponge.	20
9.	X- ray diffraction analysis	Used to analyse drug polymer complexation	It was carried out in x-ray diffractometer with Cu K $\alpha$ radiation with the speed of 100/min at an angle of 10-800. Masking of crystalline peaks indicates the successful encapsulation of drug in nanosponge core.	20

### List of drug molecules encapsulated with transdermal nanosponges:

Sr. no.	Drugs	Author name	Nanosponge vehicle	Indication	Transdermal Nanosponge	Application	References
1.	Econazole nitrate	Renuka Sharma	Ethyl cellulose, poly vinyl alcohol	Fungal skin infection	Cream	Fungal skin infections such as athlete's foot, jock itch and ringworm.	24
2.	Itraconazole	Shankar S.	$\beta$ cyclodextrin, copolyvidonum	Fungal infection	Cream, gel, hydrogel powder	Used to treat a variety of fungal infections	25
3.	Voriconazole	Prathima S.	Ethyl cellulose, polymethylmethacrylate, PVA	Fungal infection	Cream, gel, powder	To treat serious fungal or yeast infection, such as aspergillosis, candidemia	26
4.	Clotrimazole		$\beta$ cyclodextrin	Tinea corporis,	Cream, powder,	Used to treat	27

		P. Suresh Kumar		skin infection	gel	pityriasis, fungal infection	
5.	Miconazole Nitrate	Kumar P.S.	$\beta$ cyclodextrin, Diphenyl carbonate	Fungal skin infection	Cream, gel	Used to treat pityriasis, fungal infection	28
6.	Ketoconazole	Jyoti Pandey	Ethyl cellulose, PVA	Fungal infection	Cream, shampoo, soap, powder gel	To treat skin infection	29
7.	Fluconazole	Nasir Abbas	Ethyl cellulose, PVA	Vaginal candidiasis	Gel, cream, hydrogel	To treat vaginal yeast infection	30
8.	Tamoxifen	Wiliam K.	$\beta$ cyclodextrin	Breast cancer	Gel, hydrogel	To reduce the risk of breast cancer	31
9.	Dexamethasone	Thorat A.	$\beta$ cyclodextrin	Relieves inflammation, certain forms of arthritis, certain types of cancer	Eye drops, cream	Used to treat conditions such as arthritis, blood disorders	32
10	Lansoprazole	Subhash Chandra Bose penjuri	Ethyl cellulose, PVA, Pluronic F- 68	Indigestion, heartburn, acid reflux, gastroesophageal reflux disease (GORD)	Cream	Used to treat certain stomach, oesophagus problems	33
11.	Paclitaxel	Ansari K.A.	$\beta$ cyclodextrin	Breast, ovarian, bladder, lung, prostatic, melanoma, oesophageal, Kaposi sarcoma, and other solid tumours	gel	To treat breast cancer, ovarian cancer and non-small cell lung cancer	34

### Marketed preparation of nanosponges: <sup>(35)</sup>

Drug	Administration route	Marketed formulation
Dexamethasone	I.V., Dermal	Dexamethasone sodium phosphate
Alprostadil	I.V.	Alprostadil injection IP
Iodine	Topical	Povidone Iodine
Tamoxifen	Oral	Nolvadex

### Application:

#### As topical agents:

Nanosponge drug delivery system is a unique technology for sustained delivery of topical agents into the skin and retention of drug on the skin. Local anaesthetics, antifungal and antibiotics are commonly formulated drugs as topical nanosponges. Generally, side effects like rashes, allergy can be seen in general topical formulations but this technology allows sustained rate of release, reducing irritation and maintaining efficiency of the drug.

A wide variety of substances can be incorporated into final formulations like gel, lotion, cream, ointment, liquid, or powder <sup>(36)</sup>. Clotrimazole is a topical,azole group of synthetic fungistatic agents with a broad spectrum of activity against the division and growing of fungi. It is used in the topical treatment of tinea infection like ringworm, effective in skin infection caused by co bacteria. In order to improve its solubility, dissolution and sustain the release it was formulated into nanosponges which is further incorporated in a suitable gel base for sustained action. <sup>(37)</sup>

#### In antiviral therapy:

The selective delivery of antiviral drugs to nasal epithelia & lungs can be accomplished by nanocarriers in order to target viruses that infect the RTI (Respiratory tract infection such as respiratory syncytial virus, influenza virus & rhinovirus etc. Zidovudine, saquinavir, interferon-  $\alpha$ , acyclovir are some of the drugs used as nano delivery systems. These kind of nano delivery systems can also be used for HIV (Human Immuno Virus), and HSV (Herpes Simplex Virus). <sup>(38)</sup>

#### In cancer therapy:

Nanosponges can be used as anticancer drug delivery system for tumours. The tiny sponges on the surface of nanosponge are filled with drug and expose a targeting peptide which will bind to radiation induced cell surface receptor on tumour. When the sponge encounter tumour cell they stick to surface and triggered to release cargo. Studies have been carried out in animals with paclitaxel as the sponge load, paclitaxel is the one of the important drugs which is formulated as nanosponge. Camptothecin which is a plant alkaloid and has a potent antitumor activity is reported to have limited therapeutic utility because of its

poor aqueous solubility nature, instability and side effects. Cyclodextrin-based nanosponges are reported to combat this problem by formulating complexes of camptothecin with  $\beta$ -cyclodextrin based nanosponges and increase the solubility of poorly soluble drug moieties.<sup>(39,40)</sup>

### More effective than direct injection:

Recent studies shown that nanosponges could be five times more effective than direct injection at reducing tumour growth. The drug delivery system has invented a new technology of filling virus-sized sponges with anti-cancer drug, and attaching chemical linkers which will bond to a receptor on the surface of tumour cells, then the sponge is injected into the body. When the sponges come in touch with a cancer cell, they either stick to the surface or are drawn inside, where they release their lethal contents in a regulated and predictable manner<sup>(41, 42, 43).</sup>

### CONCLUSION:

With demand for innovative and highly efficient pharmaceutical and cosmetic products, the market holds considerable potential for NS 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. NSs are versatile drug carrier system as they carry both hydrophilic and hydrophobic drugs by forming inclusion and non-inclusion complexes. Nanosponges enable the insoluble drugs and protect the active moieties from physicochemical degradation and controlled release. Because of their small size and spherical shape nanosponges can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules.

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