Cyclodextrin-based nanosponges (CD NSs) are innovative polymers deriving from starch and are exploited in numerous fields, such as agroscience, pharmaceutical, biomedical and biotechnological sectors.

It is important to analyze the key points of their historical development to understand how they progressed from relatively simple crosslinked networks to today’s multifunctional polymers.

The name “nanosponge” appeared for the first time in the 1990s due to their nanoporous, sponge-like structure and responded to the need to overcome the limitations of native cyclodextrins (CDs), particularly their water solubility and inability to encapsulate charged and large molecules efficiently. Since CD NSs were introduced, efforts have been made over the years to understand their mechanism of action and their capability to host molecules with low or high molecular weight, charged, hydrophobic or hydrophilic by changing the type of cyclodextrin, crosslinker and degree of crosslinking used. Since the ‘60s many advances have been made as emerges from the growing number of studies carried out, which suggests that NS research is far from reaching its conclusion.

Cyclodextrins (CDs) are natural oligosaccharides widely used in numerous fields, including biomedicine, cosmetics, food industry, wastewater remediation and catalysis. The popularity of CDs is mainly attributable to their inclusion capacity and ability to improve desired physico-chemical properties of guest molecules, such as apparent solubility and stability.

However, native CDs have some limitations, among all solubility. Time-consuming and expensive separation techniques would be necessary to recover the CDs from an aqueous environment. When CD polymers came on the scene, this limit was overcome and their solubility could be tuned by changing the degree of crosslinking. Nowadays, CD insoluble polymers are usually called “nanosponges” (NS), referring to their sponge-like structure, which has high porosity and capacity of entrapping various kinds of molecules into the matrix [1].

Figure 1. Schematic representation of nanosponge formation.

Being insoluble is not the only advantage of CD NSs. In fact, while internal cavities of CDs can host hydrophobic molecules, the interstitial pores present between crosslinker units and the external walls of CDs make NSs capable of also entrapping hydrophilic molecules [2]. This ability has triggered extensive research, and CD NSs have emerged as a promising material in various fields such as environmental, enzymological, agricultural, biomedical, catalytical and pharmaceutical applications, as well as in gas storage, flame retardants, etc.

Their saccharide composition has made them particularly promising in the pharmaceutical field. In fact the advantages of using polysaccharides are that they can be easily modified chemically due to the presence of derivable groups on the molecular chains, and they are safe, non-toxic, hydrophilic, biodegradable and
are low cost as they are readily available in nature. In addition, the hydrophilic groups contained in most natural polysaccharides, such as hydroxyl, carboxyl and amino groups, which may form non-covalent bonds with biological tissues (mainly epithelia and mucous membranes), thus giving rise to bioadhesion, prolong the residence time of the encapsulated drug and solve the bioavailability problems. These properties combined with the capability of NSs to carry a wide variety of drugs make NSs the therapeutic nanocarriers of choice.

A comprehensive overview of the various kinds of NSs used in drug delivery has been provided in the review conducted by Caldera et al. [3], in which they were classified into generations.

NS history (Figure 2) began in the 1960s when simple network polymers made up of crosslinked CDs were introduced for the first time [4]. Their binding properties tested on organic compounds suggested a possible application in separation techniques, which was further developed in the 1970s with the production of stationary phases for nucleic acids, etc.

In the 1980s, research explored new polymers and made efforts to understand their properties alongside their binding ability. The influence of the crosslinker and the degree of crosslinking on guest binding properties of CDs were investigated for the first time [5].

In the 1990s, CD polymers found application as debittering agents and food component carriers (e.g., caffeine, vanillin and theobromine). Moreover, in the water remediation field, they overcame the limits of purification methods used up to then due to their high adsorption capacity, tenability and low cost. At the end of this decade they were called “nanosponges” for their nanoporous spongelike structure [6].

In the new millennium, new opportunities for nanosponges were studied without neglecting the known applications, such as water purification, with efforts made to improve NS trapping potential by functionalizing them or by replacing potentially toxic crosslinking agents with carbonate compounds, improving the removal of organic pollutants even at a few ppb.

For the first time, nanosponges were investigated as drug delivery systems [2]. Different kinds of drugs were successfully loaded, and a sustained release was achieved. In addition, their safety, negligible toxicity [2] and biodegradability became a matter of concern as they were intended for human use.

This field of application was extensively studied in the following years (2010–2015) lengthening the list of drugs delivered, e.g., anticancer drugs, polyphenols, L-Dopa, NSAIDs and gases of pharmaceutical interest (i.e., oxygen and carbon dioxide) [8].

The period 2016–2019 has seen pharmaceutics as the main field of application. All NS generations are present, including innovative smart nanosponges capable of releasing drugs triggered by external stimuli (i.e., pH and GSH) [9] and the most recent ones having natural ligands grafted on the surface able to perform active targeting [10], thus being capable of keeping up with the advances in nanomedicine.

In these years, alongside the pharmaceutical field, the great versatility of NSs has been confirmed by studies conducted in the food industry identifying new applications, such as active/intelligent packaging [11]. Other applications have been found in the environmental field, the textile industry, solid-phase extraction and catalysis.

Much attention is being paid to fully characterize NSs in terms of structure and mechanism of action with a view to selecting the most appropriate polymer also with the aid of mathematical tools, such as a design approach to rationalize experimentation and improve the product quality [12].
Conclusions

Today’s NSs are the result of intense research conducted over the years. They have progressed from the relatively simple crosslinked networks of the 1960s to today’s multifunctional polymers.

The success of cyclodextrin-based nanosponges certainly is due to their ability to keep up with the times while retaining their initial features, i.e., low cost, environmental compatibility, non-toxicity and the ability to host various kinds of molecules. Their synthesis has evolved in the direction of greener processes culminating in the most recent solvent-free synthesis. All of these advantages would make NSs suitable for future industrial scale up.

For the reasons discussed above, NS research has not yet reached its conclusion. On the contrary, the potential advantages that could be obtained from their use certainly justify further studies aimed, on the one hand, at investigating in greater depth their existing fields of application in which appropriately optimized NSs are useful as carriers and, on the other, at exploring new fields in which their potential could be exploited to the full as a promising, safe innovation for human health and activities.

The history of nanosponges is important to better understand the present and possibly have a glimpse of the future opportunities of such innovative and promising polymers.

As Winston Churchill said, “The farther backward you can look, the farther forward you are likely to see”.

References

3. Fabrizio Caldera; Maria Tannous; Roberta Cavalli; Marco Zanetti; Francesco Trotta; Evolution of Cyclodextrin Nanosponges. *International Journal of Pharmaceutics* **2017**, 531, 470-479, 10.1016/j.ijpharm.2017.06.072.
7. Pravin Shende; Yogesh A. Kulkarni; R. S. Gaud; Kiran Deshmukh; Roberta Cavalli; Francesco Trotta; Fabrizio Caldera;


9. Monica Argenziano; Chiara Lombardi; Benedetta Ferrara; Francesco Trotta; Fabrizio Caldera; Marco Blangetti; Hinanit Koltai; Yoram Kapulnik; Ronit Yarden; Casimiro Gigliotti; et al. Umberto Dianzani; Chiara Dianzani; Cristina Prandi; Roberta Cavalli; Glutathione/pH-responsive nanosponges enhance strigolactone delivery to prostate cancer cells. *Oncotarget* **2018**, *9*, 35813-35829, [10.18632/oncotarget.26287](https://doi.org/10.18632/oncotarget.26287).


**Keywords**

history; cyclodextrin nanosponge; crosslinked polymer

Retrieved from https://encyclopedia.pub/1486