Current Organic Chemistry, 2023, *27*, 1111-1113

EDITORIAL

Click Chemistry as an Efficient Strategy to Improve Nanoparticle Performances in Drug Delivery

Fabio Pizzetti[1], Arianna Rossetti[1], Alessandro Sacchetti[1] and Filippo Rossi[1,*]

[1]*Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133, Milan, Italy*

ARTICLE HISTORY

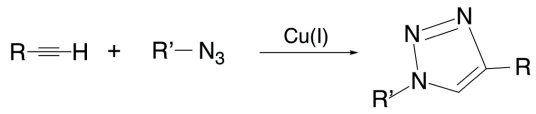
Received: June 13, 2023
Revised: September 06, 2023
Accepted: September 11, 2023

DOI:
10.2174/0113852728263162231004042237

1. INTRODUCTION

1.1. A Place that Click Chemistry Deserves…

This editorial aims to emphasize the key role of click chemistry in improving nanoparticles performances as drug delivery systems, starting from the generic press release issued by the Royal Swedish Academy of Sciences that awarded this discovery with the Nobel Prize in Chemistry on 5th October 2022: *"The Royal Swedish Academy of Sciences has decided to award Carolyn R. Bertozzi, Morten Meldal, and K. Barry Sharpless the Nobel Prize in Chemistry 2022, for the development of click chemistry and bioorthogonal chemistry"*. Historically the term click chemistry was used for the first time by Prof. Sharpless in 2001, then in 2002, he focused his attention on a specific reaction that considers the copper(I)-catalyzed regioselective ligation of azides and terminal alkynes forming a triazole (Scheme **1**) [1].



Scheme 1. Copper catalyzed alkyne azide reaction.

Nowadays many other reactions are known under the name of click chemistry like: Michael type addition, Diels-Alder reaction, Schiff-base crosslinking, thiol-disulfide exchange, oxime reactions, and selective activations (active esters, ketones, aldehydes, epoxides, anhydrides, oxazolines or isocyanates) [2] (Fig. **1**). The main characteristics of these reactions are *i*) simple reaction conditions; *ii*) the possibility to use water as solvent; *iii*) very high yield and stereospecificity and *iv*) inoffensive by-products. In the last decades, these reactions have been used in many different fields, from biology to small molecule synthesis and macromolecule generation [3, 4].

2. POLYMERIC NANOPARTICLES AND DRUG/GENE DELIVERY

Here we focused our attention on polymeric nanoparticles (NPs), tools for controlled drug or gene delivery that have attracted a lot of interest since the 2000s, thanks to their capability to localize and sustain the release of active species *in situ* [5]. Polymeric NPs are generally defined as colloidal dispersions in the range of 1 to 100 nm that are suitable to synopsize or adsorb active composites within or onto their structure. The high surface-to-volume ratio, biocompatibility, and biodegradability represent polymeric NPs main characteristics and, together with their versatility in terms of size and hydrophilic or lipophilic characteristics, has made them suitable as delivery systems. In addition, the possibility of targeting a specific biological site (cell selectivity) working as a Trojan horse is a key point and probably represents the biggest advantage of nanomedicine over classic medical treatments [6].

Filippo Rossi

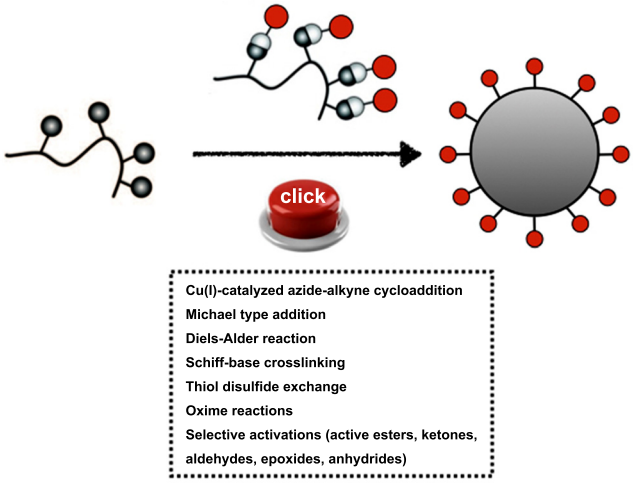


Fig. (1). Schematic representation of nanoparticle functionalization using click chemistry. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

The main reason for this is the prolongation of the release period localized specifically within the targets in the human body. In detail, nanoparticles can be engineered to release drug molecules in a controlled manner, prolonging their presence at the target site. This sustained release profile offers several advantages.

Above all, it is able to maintain therapeutic drug levels over an extended period, ensuring continuous efficacy, while reducing the drug dose required, minimizing potential toxicity and side effects. In the next section, we will discuss how click strategy can be used in nanoparticles and how it can improve their delivery performances.

*Address correspondence to this author at the Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133, Milan, Italy;
E-mail: filippo.rossi@polimi.it

1875-5348/23

3. BIOCONJUGATION AND CLICK CHEMISTRY: A PROMISING STRATEGY TO IMPROVE NANOPARTICLE DELIVERY PERFORMANCES

The first help that click chemistry can provide to drug delivery systems is represented by a smart strategy to bioconjugate peptides, aptamers, or antibodies onto the surface of already formed nano-objects [7]. This would allow their active uptake to a specific target (selective therapies) like organs or cells. Moreover, the proper click of synthetic macromolecules is a very widely known strategy to improve colloid stability and interaction with the body (pharmacokinetics).

In order to preserve their integrity, both from functional and structural sides, it is fundamental that these processes take place very quickly (rapid kinetics) in very mild conditions and aqueous solvents. In this framework, classic click reaction (Cu(I)-catalyzed azide-alkyne cycloaddition) can cause the formation of undesired reactions, like homocoupling of alkynes *via* copper-catalyzed reactions. The drawbacks correlated to the use of copper, a standard catalyst in Cu(I)-catalyzed azide-alkyne cycloaddition, can be overcome using copper chelating ligands. The main aim of these ligands is to stabilize the Cu(I) oxidation state, preventing the formation of byproducts sequestering copper ions. This causes the reduction of biomolecule's structural damage and helps the separation of down-processes. In this direction, bathophenanthroline disulphonated disodium salt, tris(hydroxypropyltriazolylmethyl) amine, and tris(benzyltriazolylmethyl)amine can be efficiently used [8, 9]. As an alternative, the group of Prof. Bertozzi discovered many alternative catalytic systems for bioconjugation avoiding the use of copper. Among them, cyclooctyne, biarylazacyclooctynone, difluorocyclooctyne, bicyclononyne, and dibenzoazacyclooctyne derivatives were developed for this purpose [10, 11].

4. CLICK STRATEGIES AND ORGANIC OR INORGANIC DELIVERY COLLOIDS

Considering organic nanoparticles many different click reactions have been used either to prepare co-polymers that can assemble forming nanoparticles or to functionalize already formed colloids. An example of the first one is represented by the work of Sumerlin who used click reaction to synthesize T-responsive block copolymers functionalized with folic acid [12]. The resulting co-polymer was able to self-assemble forming polymeric nanoparticles with a diameter of 46 nm that can be used as selective drug delivery systems for cancer treatment. Similarly, the group of Li [13] developed a library of degradable poly(ε-caprolactone)-based glycopolymers. These polymers were prepared using ring-opening polymerization followed by functionalization with saccharides *via* Cu(I)-catalyzed azide-alkyne cycloaddition to obtain amphiphilic co-polymers that can self-assemble in nanoparticles that can be used as selective delivery systems. An example of the second use of click chemistry in organic nanoparticles (functionalization of already formed nanoparticles) is described by the Shoichet group that used click reaction (here Diels-Alder cycloaddition) to produce immune-polymeric nanoparticles. They successfully prepared an amphiphilic polymer with furan as a terminal diene that can then be self-assembled [14]. Furan groups present on the surface of nanoparticles can react with maleimide-modified anti-HER2, a therapeutic antibody used for breast cancer treatment. The key advantages of using click reaction in this synthesis are that, due to the mild reaction conditions, the activity and efficiency of the antibody are preserved. Then the subsequent coordination with doxorubicin (well known chemotherapeutic agent) allowed us to build an efficient codelivery system for both chemotherapeutics and antibodies. Functionalization after nanoparticle formation can also be widely used also onto inorganic nanoparticles made of gold, silver, platinum, or iron. They are demonstrated to be very promising tools in biomedical applications due to the fact that they can work as theranostic agents. However, even if the preparation of monodisperse inorganic nanoparticles is generally quite easy and scalable they suffer from reduced chemical stability in liquid state with consequent aggregation. This drawback can be solved using click chemistry and so introducing onto the surface molecules that can avoid the interpenetration between them (polymers, tensides, or biomolecules). This is widely known as steric stabilization which can be also associated with electrostatic stabilization if the coating added presents electric charges at the pH typical of their biomedical target (Fig. **2**) [15].

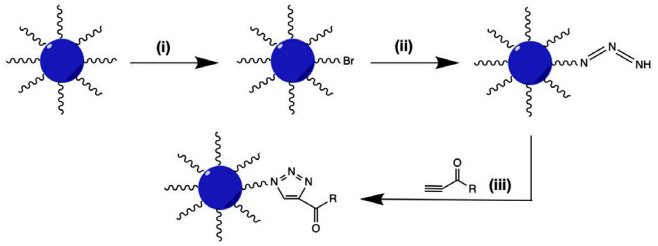


Fig. (2). "Click" functionalization of Au nanoparticle surfaces. Reprinted with permission from [15] Copyright 2006 American Chemical Society. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

5. WHAT ABOUT THE FUTURE?

In recent times numerous pre-clinical studies demonstrated the importance of the use of click-functionalized NPs for drug delivery, but several challenges need to be addressed before achieving clinical results [16]. First, mechanisms behind intracellular uptake and the fate of nano-objects in the human body should be deeply understood. This knowledge would help to develop a better design for nanocarriers. Technical and health issues should also be taken into account not only during medical treatment but also during the manufacturing process, which alone represents another big challenge. It is indeed generally known that colloid manufacturing is easier at a laboratory scale, while increasing the production scale, bulk properties act against the formation of new surfaces and consequently, the nanoparticle formation is disfavored. Moreover, further functionalization using click chemistry would add additional steps in the production process that should be studied and analyzed in order to guarantee their reproducible and consistent production. In addition, economic and financial barriers represent an obstacle to the use of functionalized NPs for drug delivery. Only a real advancement in the treatment of serious pathologies would allow and justify their use in the clinic.

CONCLUSION

Even if polymeric colloids represent a strong reality for the efficient delivery of therapeutic molecules, the simple combination of synthetic and natural polymers does not always satisfy the criteria for clinical applications. For these reasons, click chemistry can be efficiently used to functionalize nanoparticles with specific and selective chemical groups able to guarantee the improvement of the final design: drugs, gene materials, peptides, and proteins can be loaded and released in the targeted region, in a desired intracellular area, preventing unwanted loss of the therapeutic cargo.

ABBREVIATION

NPs = Nanoparticles

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Rostovtsev, V.V.; Green, L.G.; Fokin, V.V.; Sharpless, K.B. A stepwise huisgen cycloaddition process: copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem. Int. Ed.,* **2002**, *41*(14), 2596-2599. http://dx.doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4 PMID: 12203546

[2] Tornøe, C.W.; Christensen, C.; Meldal, M. Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(i)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J. Org. Chem.,* **2002**, *67*(9), 3057-3064. http://dx.doi.org/10.1021/jo011148j PMID: 11975567

[3] Jewett, J.C.; Bertozzi, C.R. Cu-free click cycloaddition reactions in chemical biology. *Chem. Soc. Rev.,* **2010**, *39*(4), 1272-1279. http://dx.doi.org/10.1039/b901970g PMID: 20349533

[4] Leyva, E.; Rubén Rodríguez-Gutiérrez, I.; Moctezuma, E.; Noriega, S. Mechanisms, copper catalysts, and ligands involved in the synthesis of 1,2,3-triazoles using click chemistry. *Curr. Org. Chem.,* **2023**, *26*(23), 2098-2121. http://dx.doi.org/10.2174/1385272827666230201103825

[5] Dilliard, S.A.; Siegwart, D.J. Passive, active and endogenous organ-targeted lipid and polymer nanoparticles for delivery of genetic drugs. *Nat. Rev. Mater.,* **2023**, *8*(4), 282-300. http://dx.doi.org/10.1038/s41578-022-00529-7 PMID: 36691401

[6] Duan, F.; Jin, W.; Zhang, T.; Sun, Y.; Deng, X.; Gao, W. Thermo-pH-sensitive polymer conjugated glucose oxidase for tumor-selective starvation-oxidation-immune therapy. *Adv. Mater.,* **2023**, *35*(17), 2209765. http://dx.doi.org/10.1002/adma.202209765 PMID: 36773963

[7] Kaur, J.; Saxena, M.; Rishi, N. An overview of recent advances in biomedical applications of click chemistry. *Bioconjug. Chem.,* **2021**, *32*(8), 1455-1471. http://dx.doi.org/10.1021/acs.bioconjchem.1c00247 PMID: 34319077

[8] Chan, T.R.; Hilgraf, R.; Sharpless, K.B.; Fokin, V.V. Polytriazoles as copper(I)-stabilizing ligands in catalysis. *Org. Lett.,* **2004**, *6*(17), 2853-2855. http://dx.doi.org/10.1021/ol0493094 PMID: 15330631

[9] Lewis, W.G.; Magallon, F.G.; Fokin, V.V.; Finn, M.G. Discovery and characterization of catalysts for azide-alkyne cycloaddition by fluorescence quenching. *J. Am. Chem. Soc.,* **2004**, *126*(30), 9152-9153. http://dx.doi.org/10.1021/ja048425z PMID: 15281783

[10] Baskin, J.M.; Prescher, J.A.; Laughlin, S.T.; Agard, N.J.; Chang, P.V.; Miller, I.A.; Lo, A.; Codelli, J.A.; Bertozzi, C.R. Copper-free click chemistry for dynamic *in vivo* imaging. *Proc. Natl. Acad. Sci. USA,* **2007**, *104*(43), 16793-16797. http://dx.doi.org/10.1073/pnas.0707090104 PMID: 17942682

[11] Codelli, J.A.; Baskin, J.M.; Agard, N.J.; Bertozzi, C.R. Second-generation difluorinated cyclooctynes for copper-free click chemistry. *J. Am. Chem. Soc.,* **2008**, *130*(34), 11486-11493. http://dx.doi.org/10.1021/ja803086r PMID: 18680289

[12] De, P.; Gondi, S.R.; Sumerlin, B.S. Folate-conjugated thermoresponsive block copolymers: highly efficient conjugation and solution self-assembly. *Biomacromolecules,* **2008**, *9*(3), 1064-1070. http://dx.doi.org/10.1021/bm701255v PMID: 18288803

[13] Xu, N.; Wang, R.; Du, F.S.; Li, Z.C. Synthesis of amphiphilic biodegradable glycocopolymers based on poly(ε-caprolactone) by ring-opening polymerization and click chemistry. *J. Polym. Sci. A Polym. Chem.,* **2009**, *47*(14), 3583-3594. http://dx.doi.org/10.1002/pola.23443

[14] Shi, M.; Ho, K.; Keating, A.; Shoichet, M.S. Doxorubicin-conjugated immuno-nanoparticles for intracellular anticancer drug delivery. *Adv. Funct. Mater.,* **2009**, *19*(11), 1689-1696. http://dx.doi.org/10.1002/adfm.200801271

[15] Fleming, D.A.; Thode, C.J.; Williams, M.E. Triazole cycloaddition as a general route for functionalization of Au nanoparticles. *Chem. Mater.,* **2006**, *18*(9), 2327-2334. http://dx.doi.org/10.1021/cm060157b

[16] Pinelli, F.; Sacchetti, A.; Perale, G.; Rossi, F. Is nanoparticle functionalization a versatile approach to meet the challenges of drug and gene delivery? *Ther. Deliv.,* **2020**, *11*(7), 401-404. http://dx.doi.org/10.4155/tde-2020-0030 PMID: 32372721