Indonesian Journal of Pharmaceutics
IdJP
ISSN : 2597-8748

Vol 4, Issue 1, 2022 (189-198)
http://journal.unpad.ac.id/idjp

Utilization of 1-(3-aminopropyl)-imidazole in development of pH-sensitive nanocarrier for anticancer drug delivery

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Submitted : 13/07/ 2022, Revised : 27/07/ 2022,, Accepted : 02/08/ 2022, Published : 09/08/2022

Abstract

pH-sensitive nanocarriers have demonstrated as successful drug carriers due to the higher drug accumulation at the tumor site by pH-dependent release at acidic tumor microenvironment. Imidazole can be utilized to obtain pH-sensitive nanocarriers. One of the imidazole-based compounds used by researchers in development of pH-responsive carriers is 1-(3-Aminopropyl)-imidazole. This review is focused on utilization of 1-(3-aminopropyl)-imidazole to develop pH-sensitive nanocarrier especially for delivery of anticancer drug. In addition, this review also shows research performed by researchers to develop pH-sensitive nanocarrier for anticancer drug delivery using 1-(3-aminopropyl)-imidazole to prepare imidazole-based pH-sensitive nanocarriers. The data were collected from published journals with 15 and 20 journals as primary and supporting literatures, respectively. Properties of imidazole groups to deprotonate at pH 7.4 and protonate at pH ≤ 6.5 implies that the drug release was pH-dependent, leading to a limited release of drug from carriers under physiological pH conditions and diminishing the drug's effect in blood circulation before reaching the tumor site, resulting in more effective anticancer activity.

Keywords: pH-sensitive, imidazole, poly (β-Benzyl-L-Aspartate), polymer, nanocarrier

1. Introduction

Delivery systems of drug using pH-sensitive carrier have shown improved anticancer activity in comparison with pH-insensitive carrier (1, 2). pH-sensitive nanocarriers have shown great interest because of their advanced functionality (3-6). Different characteristics were shown by the pH-responsive nanocarriers under an acidic, basic, or neutral environment (7, 8). In the case of anticancer drug delivery, pH-sensitive carriers have been reported as competent drug carrier as pH-dependent release of anticancer agents triggered by tumor microenvironments (tumor extracellular pH (pHex = ~ 6.5 to 7.2) or endosomal pH (pHen ≤ 6.5) (3-6).

Imidazole is a typical pH-sensitive compound, which was used to obtain the pH-sensitive and sustained drug release ability of nanoparticles (9). 1-(3-aminopropyl)-imidazole has been used in development of pH-sensitive nanocarrier. Imidazole can protonate resulted in a

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https://doi.org/10.24198/idjp.v4i1.40691

positive charge under acidic pH condition (10). Deprotonation at physiological pH (pH 7.4) and protonation at pH ≤ 6.5 of imidazole groups provided pH triggered drug release and tumor pH targeted drug delivery. Some methods can be used to synthesize pH-sensitive nanocarrier using 1-(3-aminopropyl)-imidazole either by grafting or by directly substitution/modulation of functional side groups of a polymer (11, 12).

This review is aimed to depict utilization of 1-(3-aminopropyl)-imidazole in development of pH-sensitive nanocarrier including properties of imidazole group as pH-sensitive moiety and synthesis methods to prepare pH-sensitive nanocarrier using 1-(3-aminopropyl)-imidazole. In addition, this review also shows several studies performed by researchers that use 1-(3-aminopropyl)-imidazole in development of pH-responsive nanocarrier to deliver anticancer drug. Urgency of this review paper is to introduce the use 1-(3-aminopropyl)-imidazole in preparation of pH-sensitivity carrier using easy and simple method.

2. Methodology

By using specific keywords "imidazole, 1-(3-aminopropyl)-imidazole pH-sensitive nanocarrier for cancer", this review was prepared. Inclusions criteria (related to specific keywords) and exclusions criteria (opinions and unrelated topics) were also determined. Finally, 15 and 20 journals published in 2011-2022 were collected as primary and supporting literatures, respectively. Figure 1 depicts the flowchart of the methodology.

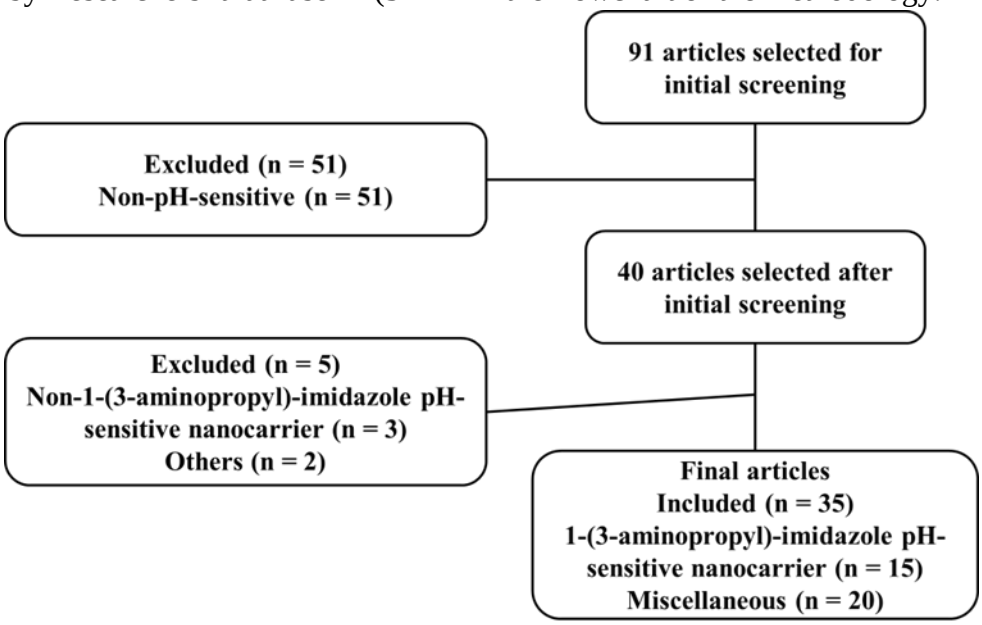

Figure 1. Flowchart of methodology

2.1 Properties of imidazole group as pH-sensitive moiety

Acidic microenvironment is abnormality of tumor tissue (10). Intracellular pH (pH_i) of normal cells in healthy tissues is 7.2 and a slightly higher extracellular pH (pH_{ex}) of 7.4. However, a pH_i of 7.2 and pH_{en} of 6.2–7.0 are found in tumor cells (13-16). The lower pH_{en} in the tumor interstitium is caused by lactate accumulation. Elevated anaerobic metabolism by the cancer cells produces an acidic by-product called lactate in the hypoxic tumor microenvironment (17-19). Therefore, pH in tumor microenvironment or inside cancer cells is one of the internal stimuli for cancer targeting (7, 14). pH-responsive nanocarriers containing weakly acidic or basic ionizable groups (pKa values 3 - 10) can either donate or accept protons in response to changes in environmental pH, resulting in change in

structural and other properties (surface activity, solubility, chain conformation, etc.) (7, 8, 20). Thus, pH activation of nanoparticle by tumor microenvironment can be used to release of drug (Figure 2) (21-25).

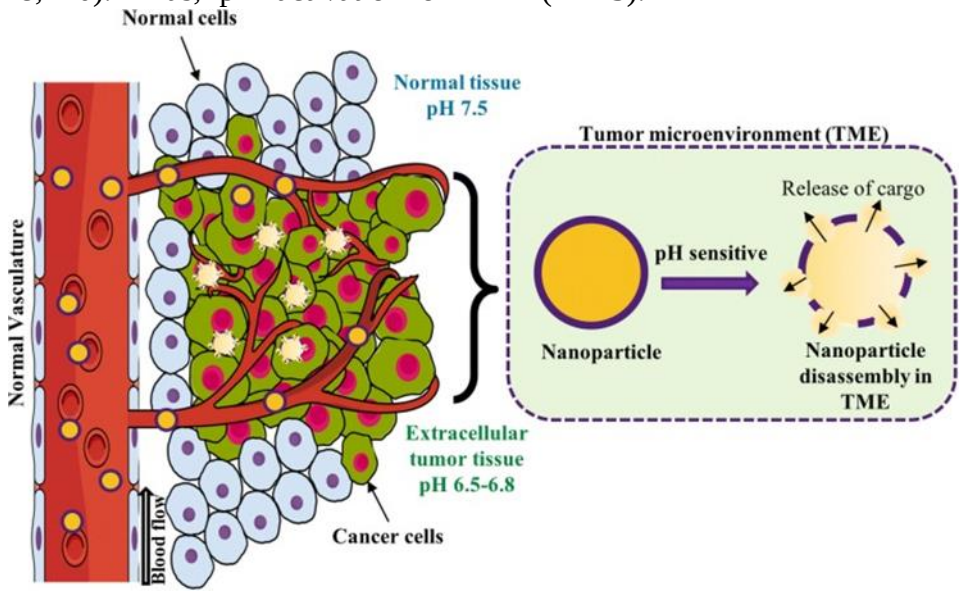

Figure 2. Schematic illustration of pH activation of nanoparticle by tumor microenvironment (21)

One of the imidazole-based compounds used by researchers in development of pH-responsive carriers is 1-(3-Aminopropyl)imidazole (Figure 3) which is used in the synthesis of pH-responsive polyaspartamide derivatives and the preparation of pH-sensitive amphiphilic polymers (26). Imidazole exhibits a prominent pH-sensitive functional group in pharmaceutical sciences. pKa value of imidazole is 5.0–6.5, leading to protonate under acidic pH, resulting in a positive charge (Figure 4) (10-12, 27).

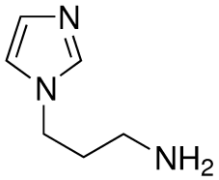

Figure 3. Chemical structure of 1-(3-Aminopropyl)imidazole (26)

If the imidazole groups are grafted to a polymer or substituted /modulated of functional side groups of a polymer for a drug carrier, the disintegration of carrier is induced by pH change (11, 12). At pH 7.4, the imidazole groups are deprotonated. However, at pH ≤ 6.5, imidazole groups protonate, leading to change in structure of carrier, resulting in release drug from its destabilized cores of the carrier (Figure 4) (11, 12, 28).

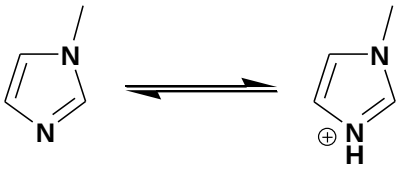

Figure 4. Illustration of protonation of imidazole groups under different pH conditions (pH 7.4 and 6.0)

2.2 Synthesis methods to prepare pH-sensitive nanocarrier using 1-(3-aminopropyl)-imidazole

Either by grafting or direct substitution/modulation of functional side groups method can be used for synthesis pH-sensitive nanocarrier using 1-(3-aminopropyl)-imidazole (11, 12, 29-31). For the grafting method, Kim et al. develop a pH-sensitive polymer by grafting the

imidazole groups to poly(aspartic acid)-*block*-poly(ethylene glycol) (P(Asp)-PEG), resulting in P(Asp-*g*-Im)-PEG to target acidic pH (Figure 5) Briefly, poly(ethylene glycol)-poly(β-benzyl-L-aspartate) (PEG-PBLA) was prepared by coupling PBLA with monocarboxylated PEG. Next, the benzyl groups were removed from PBLA by dissolving the PBLA-PEG in a solution of dimethylformamide/methanol (DMF/MeOH) mix and Pd/C catalyst. To graft the imidazole groups, the preactivated of deprotected P(Asp)-PEG was dissolved in DMF in the presence of 1-(3-aminopropyl)-imidazole and stirred for 24 h at 30 °C (11). Other researchers, Cheng et al. also developed pH-sensitive carboxymethyl chitosan nanoparticles by grafting *N*-(3-Aminopropyl)-imidazole onto carboxymethyl chitosan and showed pH-triggered drug release at acidic environment (29). In addition, Han et al. synthesized a pH-responsive nanocarrier using hyaluronic acid (HA)-*graft*-imidazole-dodecylamine (HID) for anticancer drugs delivery (32).

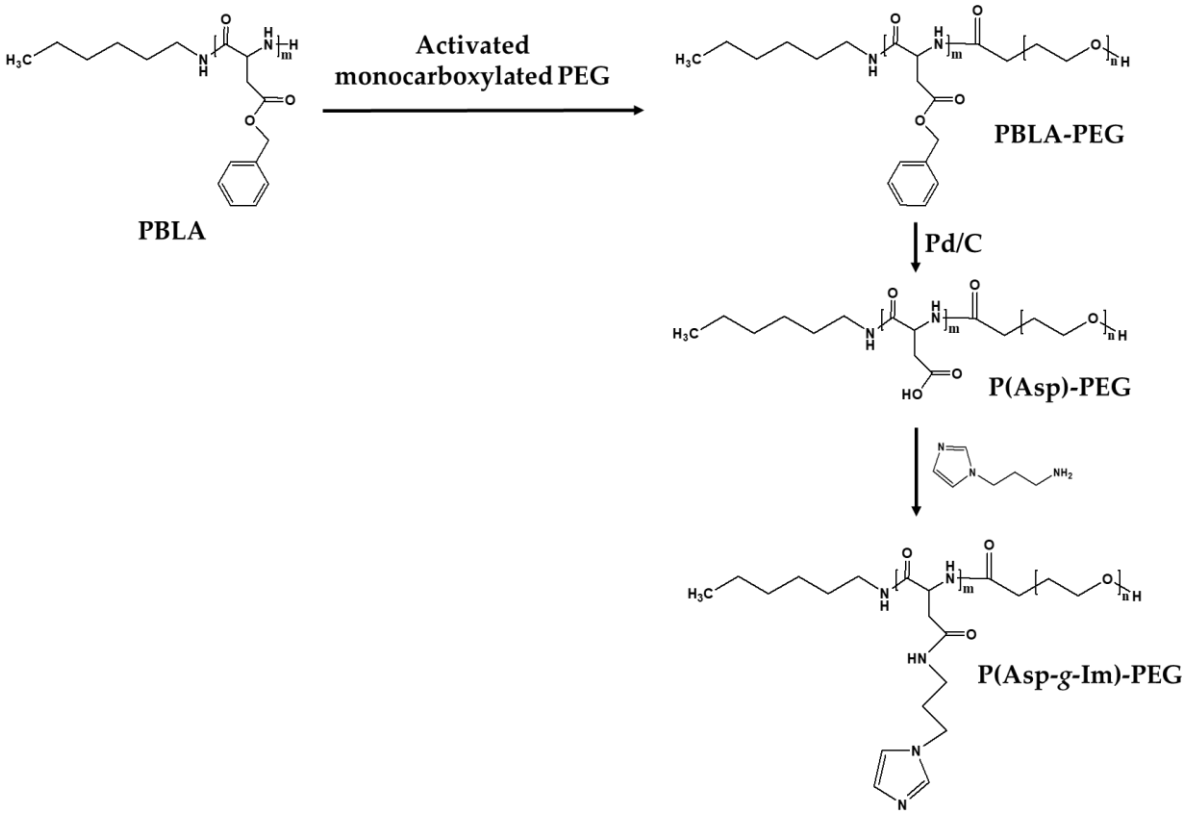

Figure 5. Synthetic route of grafting the imidazole group to P(Asp)-PEG (11)

For substitution/modulation of functional side groups method, Chu et al. prepared pH and reduction micelles using methyloxy-poly(ethylene glycol)-*b*-poly[(benzyl-L-aspartate)-*co*-(N-(3-aminopropyl) imidazole-L-aspartamide)] (mPEG-SS-P(BLA-*co*-APILA). These researchers introduced imidazole groups in the side chain of the block copolymer for pH sensitivity moiety by substitution reaction from mPEG-SS-PBLA, resulting in mPEG-SS-P(BLA-*co*-APILA (Figure 6). The block copolymer and 1-(3-aminopropyl)-imidazole was mixed in DMF under stirring at 40 °C for 5 h (33).

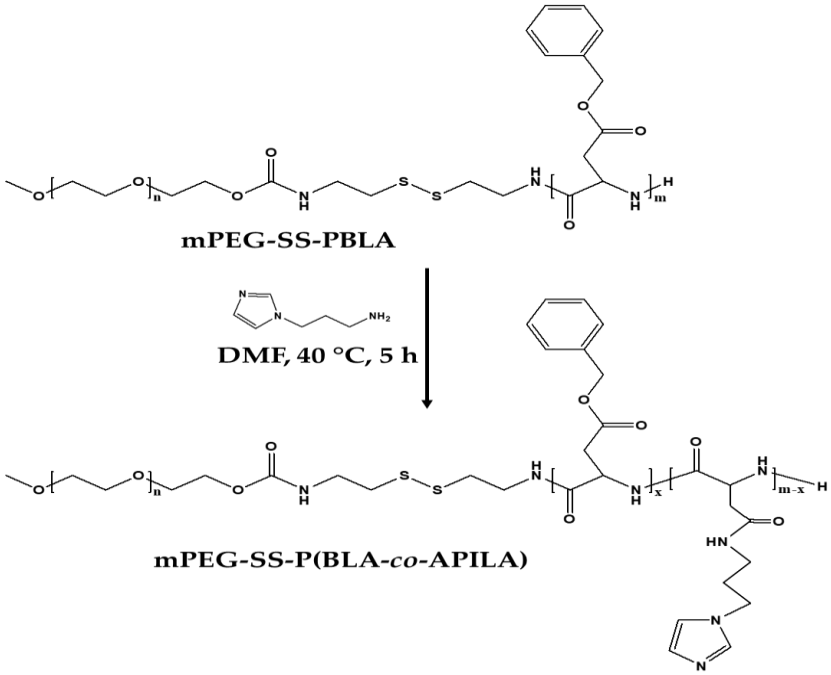

Figure 6. Substitution reaction of mPEG-SS-PBLA to prepare mPEG-SS-P(BLA-*co*-APILA) (33)

Recent study by Sim et al. also developed a pH-sensitive polymer prepared by partly modulation of benzyl groups of the hydrophobic PBLA block of PBLA-PEG. Dissolving PBLA-PEG in DCM containing 1-(3-aminopropyl)-imidazole and triethylamine (TEA) at 35 °C under stirring for 24 h would result in poly[(benzyl-L-aspartate)-*co*-(N-(3-aminopropyl) imidazole-L-aspartamide)]-poly(ethylene glycol) (PABI-PEG) (Figure 7) (12).

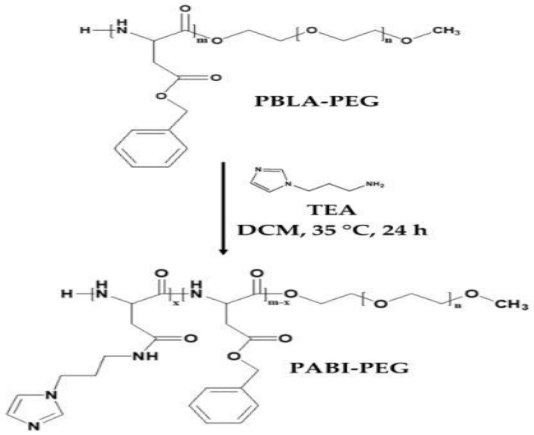

Figure 7. Modulation of functional side groups of PEG-PBLA to form PEG-PABI (12)

2.3 Utilization of 1-(3-aminopropyl)-imidazole in development of pH-sensitive nanocarrier for anticancer drug delivery

A number of studies have used 1-(3-aminopropyl)-imidazole to develop pH-responsive nanocarrier for delivery of an anticancer drug (28-31, 33-35). For example, Chu et al. prepared dual sensitive (pH and reduction) micelles. Doxorubicin (DOX) was loaded into the micelles. DOX release from micelles showed retarded

release in pH 7.4 and fast release at acidic or reductive environment. These researchers reported DOX was found rapid internalization and fast release inside cells. The cytotoxicity study using HeLa cells showed that the DOX-encapsulated micelles could kill cancer cells (33). Cheng et al. developed nanoparticles of surface-fluorinated and pH-sensitive carboxymethyl chitosan (CMCS). To prepare pH-responsive nanoparticles, *N*-(3-aminopropyl)-imidazole (API) was grafted to CMCS. At acidic condition, the swelling of nanoparticles containing imidazole was obtained, resulting in the accelerated release of DOX (29).

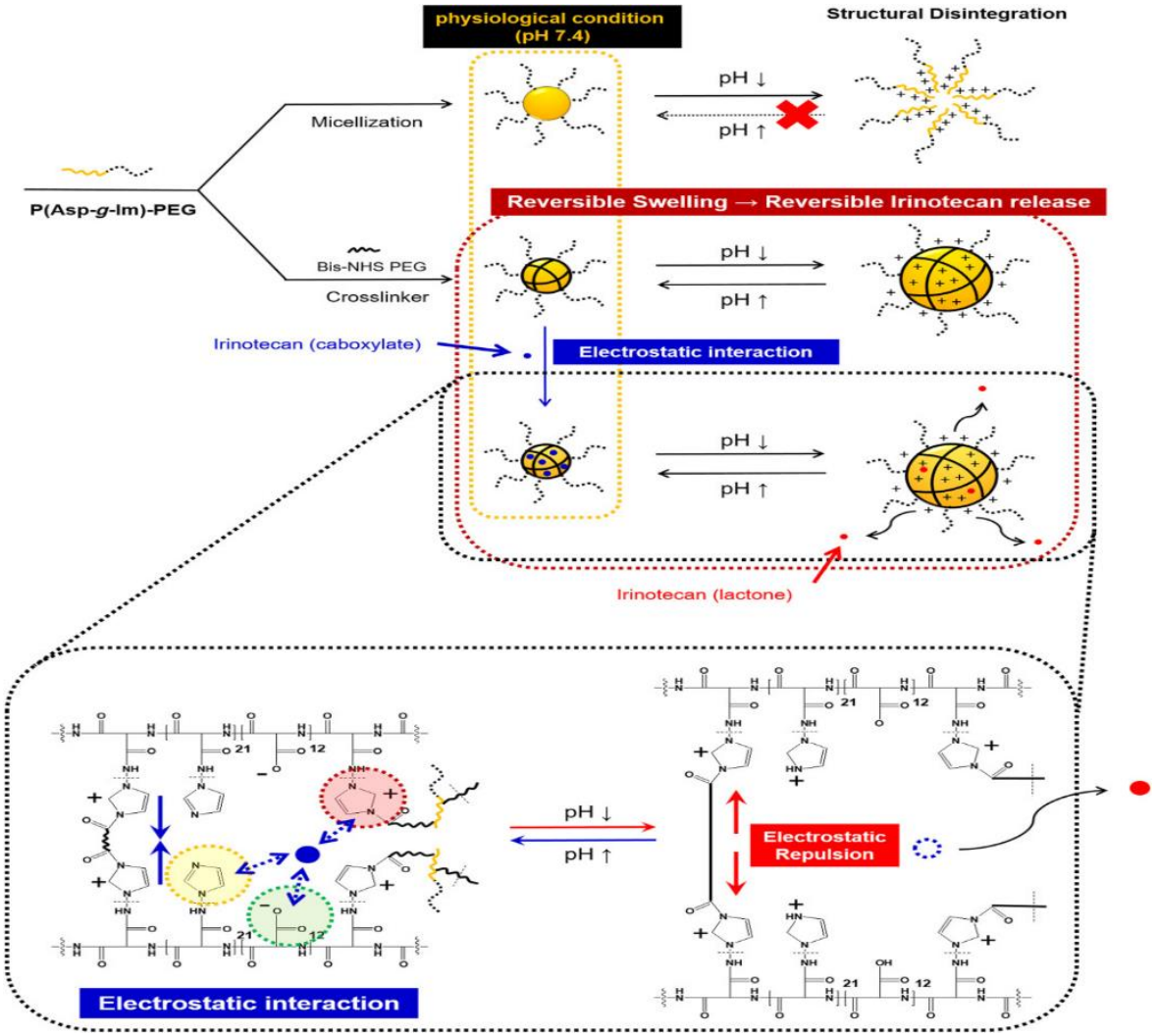

Figure 8. Schematic diagram of irinotecan-loaded pH-sensitive nanogels. Reproduced with permission of Sim T, Lim C, Cho YH, Lee ES, Youn YS, Oh KT., Development of pH-Sensitive Nanogels for Cancer Treatment using Crosslinked Poly(Aspartic Acid-*graft*-Imidazole)-*block*-Poly(Ethylene Glycol); published by John Wiley and Sons, 2018.

Oh's group developed pH-responsive nanogels using crosslinked P(Asp-*g*-Im)-PEG for cancer treatment (Figure 8). Irinotecan (IRI), an anticancer drug, was used as a model drug that was loaded into nanogels (ILNs). Study results indicated that IRI release was higher under pH 6.5 than pH 7.4 condition. Further, the effect of ILNs on cell viability was also tested against colorectal cancer. Cytotoxic effect of the ILNs was higher at pH 6.5 than at pH 7.4 (34).

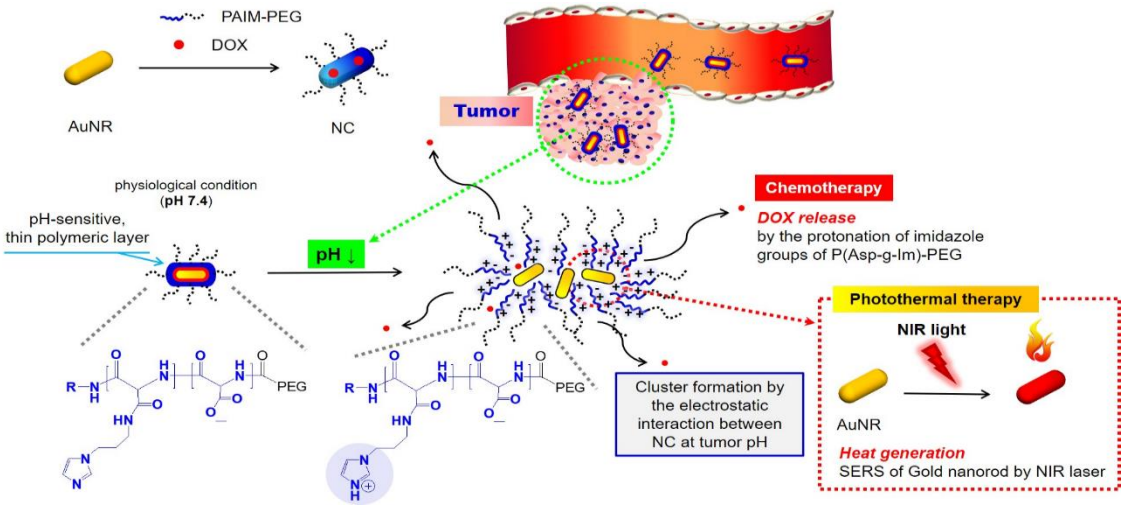

Figure 9. Illustration of pH-sensitive nanocluster (NC) system using a pH-sensitive polymer, P(Asp-g-Im)-PEG, for encapsulation of gold nanorods and DOX for cancer treatment (28).

In other studies, Oh's group prepared pH-responsive nanocluster (NC) using a pH-responsive polymer. Gold nanorods and DOX were encapsulated by P(Asp-*g*-Im)-PEG for cancer treatment (Figure 9). These researchers reported not only a stable and structured but also low systemic toxicity at pH 7.4 of NC systems resulted. In contrast, aggregated structures of the NC systems were occurred at pH 6.5, leading to high drug release. Furthermore, the NC systems also resulted an increased accumulation and high DOX release at the tumor site at pH_{ex} and pH_{en} with application of near-infrared light locally, leading to increase antitumor efficacy (Figure 10) (28).

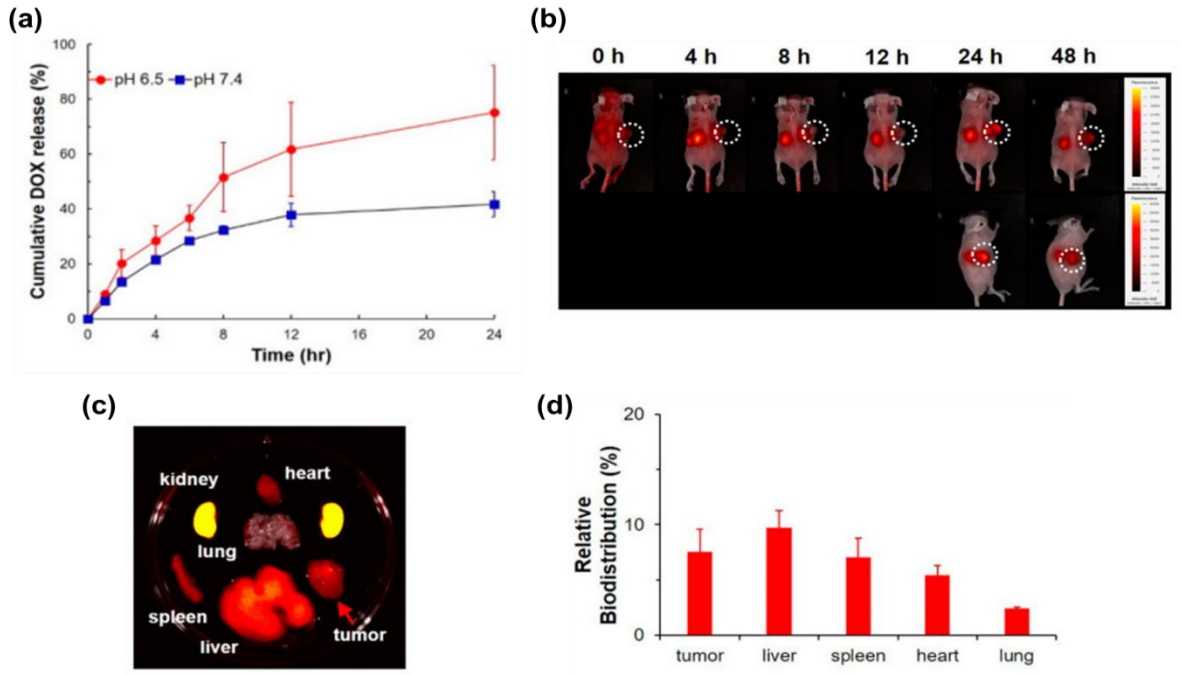

Figure 10. (a) DOX release at different pH conditions (pH 7.4 and pH 6.5). (b) whole body imaging after i.v. injection. (c) EX vivo optical and fluorescent imaging of tumor and organs obtained 24 h post-injection. (d) relative biodistribution by quantitative fluorescence intensity (FI) of tumors and main organs. Modified from (28).

3. Conclusion

1-(3-aminopropyl)-imidazole has been used in development of pH-sensitive nanocarrier. pH activation of nanocarrier by tumor microenvironment can be used for anticancer drug delivery. Deprotonation at physiological pH (pH 7.4) and protonation at pH ≤ 6.5 of imidazole groups implies that the drug release was pH-dependent, leading to minimal drug effect in the bloodstream before the drug-loaded carrier reach the tumor site. The tumor pH_{ex} and pH_{en} would trigger release of drug from its carrier, resulting in effective antitumor activity.

References

1. He X, Li J, An S, Jiang C. pH-sensitive drug-delivery systems for tumor targeting. Ther Deliv. 2013;4(12):1499-510.
2. Liu J, Huang Y, Kumar A, Tan A, Jin S, Mozhi A, et al. pH-sensitive nano-systems for drug delivery in cancer therapy. Biotechnol Adv. 2014;32(4):693-710.
3. Gao GH, Li Y, Lee DS. Environmental pH-sensitive polymeric micelles for cancer diagnosis and targeted therapy. Journal of Controlled Release. 2013;169(3):180-4.
4. Kao SH, Huang KY, Li HJ, Tseng SJ, Liao ZX, Kempson I. Environmental pH-sensitive polymeric nano-carriers for targeted tumor delivery (vol 213, pg e46, 2015). Journal of Controlled Release. 2015;218:1-.
5. Yin HQ, Kang HC, Huh KM, Bae YH. Biocompatible, pH-sensitive AB(2) miktoarm polymer-based polymersomes: preparation, characterization, and acidic pH-activated nanostructural transformation. Journal of Materials Chemistry. 2012;22(36):19168-78.
6. Wu LL, Zou Y, Deng C, Cheng R, Meng FH, Zhong ZY. Intracellular release of doxorubicin from core-crosslinked polypeptide micelles triggered by both pH and reduction conditions. Biomaterials. 2013;34(21):5262-72.
7. Husni P, Ghifari MA, Putriana NA. Potential of Stimuli-Responsive Star Polymer for Cancer Targeting. Indonesian Journal of Pharmaceutics. 2020;2(3):124-31.
8. Alsuraifi A, Curtis A, Lamprou DA, Hoskins C. Stimuli Responsive Polymeric Systems for Cancer Therapy. Pharmaceutics. 2018;10(3).
9. Xu ZL, Yang D, Long T, Yuan L, Qiu S, Li DF, et al. pH-Sensitive nanoparticles based on amphiphilic imidazole/cholesterol modified hydroxyethyl starch for tumor chemotherapy. Carbohyd Polym. 2022;277.
10. Huang R, Gyanani V, Zhao S, Lu Y, Guo X. Imidazole-Based pH-Sensitive Convertible Liposomes for Anticancer Drug Delivery. Pharmaceuticals (Basel). 2022;15(3).
11. Kim JH, Oh YT, Lee KS, Yun JM, Park BT, Oh KT. Development of a pH-sensitive polymer using poly(aspartic acid-graft-imidazole)-block-poly(ethylene glycol) for acidic pH targeting systems. Macromol Res. 2011;19(5):453-60.
12. Sim T, Han SM, Lim C, Won WR, Lee ES, Youn YS, et al. A pH-Sensitive Polymer for Cancer Targeting Prepared by One-Step Modulation of Functional Side Groups. Macromol Res. 2019;27(8):795-802.
13. Reshetnyak YK. Imaging Tumor Acidity: pH-Low Insertion Peptide Probe for Optoacoustic Tomography. Clin Cancer Res. 2015;21(20):4502-4.
14. Ning J, Zhang G, Balash M, Li H, Zhu L. Current nano-strategies to target tumor microenvironment to improve anti-tumor efficiency. OpenNano. 2022;7:100042.
15. Neri D, Supuran CT. Interfering with pH regulation in tumours as a

therapeutic strategy. Nat Rev Drug Discov. 2011;10(10):767-77.
16. Webb BA, Chimenti M, Jacobson MP, Barber DL. Dysregulated pH: a perfect storm for cancer progression. Nat Rev Cancer. 2011;11(9):671-7.
17. Lee SH, Griffiths JR. How and Why Are Cancers Acidic? Carbonic Anhydrase IX and the Homeostatic Control of Tumour Extracellular pH. Cancers. 2020;12(6).
18. Parks SK, Pouyssegur J. Targeting pH regulating proteins for cancer therapy-Progress and limitations. Semin Cancer Biol. 2017;43:66-73.
19. Bhatnagar S, Venuganti VVK. Cancer Targeting: Responsive Polymers for Stimuli-Sensitive Drug Delivery. J Nanosci Nanotechno. 2015;15(3):1925-45.
20. AlSawaftah NM, Awad NS, Pitt WG, Husseini GA. pH-Responsive Nanocarriers in Cancer Therapy. Polymers-Basel. 2022;14(5).
21. Uthaman S, Huh KM, Park IK. Tumor microenvironment-responsive nanoparticles for cancer theragnostic applications. Biomater Res. 2018;22:22.
22. Shinn J, Kwon N, Lee SA, Lee Y. Smart pH-responsive nanomedicines for disease therapy. J Pharm Invest. 2022.
23. Park S, Lee WJ, Park S, Choi D, Kim S, Park N. Reversibly pH-responsive gold nanoparticles and their applications for photothermal cancer therapy. Scientific Reports. 2019;9.
24. Chu SL, Shi XL, Tian Y, Gao FX. pH-Responsive Polymer Nanomaterials for Tumor Therapy. Frontiers in Oncology. 2022;12.
25. Jin MJ, Hou Y, Quan XQ, Chen LQ, Gao ZG, Huang W. Smart Polymeric Nanoparticles with pH-Responsive and PEG-Detachable Properties (II): Co-Delivery of Paclitaxel and VEGF siRNA for Synergistic Breast Cancer Therapy in Mice. International Journal of Nanomedicine. 2021;16:5479-94.
26. Sigma-Aldrich. 1-(3-Aminopropyl)imidazole 2022 [updated 2022 July 1. Available from: https://www.sigmaaldrich.com/KR/en/product/aldrich/272264.
27. Lee ES, Kim JH, Sim T, Youn YS, Lee BJ, Oh YT, et al. A feasibility study of a pH sensitive nanomedicine using doxorubicin loaded poly(aspartic acid-graft-imidazole)-block-poly(ethylene glycol) micelles. J Mater Chem B. 2014;2(9):1152-9.
28. Sim T, Lim C, Ha Hoang N, Shin Y, Kim JC, Park JY, et al. An On-Demand pH-Sensitive Nanocluster for Cancer Treatment by Combining Photothermal Therapy and Chemotherapy. Pharmaceutics. 2020;12(9).
29. Cheng X, Zeng XL, Zheng Y, Wang X, Tang RP. Surface-fluorinated and pH-sensitive carboxymethyl chitosan nanoparticles to overcome biological barriers for improved drug delivery in vivo. Carbohyd Polym. 2019;208:59-69.
30. Sim T, Lim C, Hoang NH, Kim JE, Lee ES, Youn YS, et al. Synergistic photodynamic therapeutic effect of indole-3-acetic acid using a pH sensitive nano-carrier based on poly(aspartic acid-graft-imidazole)-poly(ethylene glycol) (vol 5, pg 8498, 2017). J Mater Chem B. 2018;6(2):337-.
31. Yu SF, Wu GL, Gu X, Wang JJ, Wang YN, Gao H, et al. Magnetic and pH-sensitive nanoparticles for antitumor drug delivery. Colloid Surface B. 2013;103:15-22.
32. Han SM, Kim JC, Shin Y, Lee D, Sim T, Lim C, et al. Development of a pH-Responsive Polymer Based on Hyaluronic Acid Conjugated with Imidazole and Dodecylamine for Nanomedicine Delivery. Macromol Res. 2022.
33. Chu YF, Yu H, Ma YY, Zhang YT, Chen WH, Zhang GY, et al. Synthesis and characterization of biodegradable

pH and reduction dual-sensitive polymeric micelles for doxorubicin delivery. J Polym Sci Pol Chem. 2014;52(13):1771-80.
34. Sim T, Lim C, Cho YH, Lee ES, Youn YS, Oh KT. Development of pH-sensitive nanogels for cancer treatment using crosslinked poly(aspartic acid-graft-imidazole)-block-poly(ethylene glycol). J Appl Polym Sci. 2018;135(20).
35. Bai J, Wang J, Feng YC, Yao YF, Zhao XB. Stability-tunable core-crosslinked polymeric micelles based on an imidazole-bearing block polymer for pH-responsive drug delivery. Colloid Surface A. 2022;639.