

SUPPLEMENTARY MATERIAL

Intelligent delivery of antitumor drugs mediated by polymeric nanomicelles: a review

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Table 1S. Recent systems used in the synthesis of nanocarriers based on polymeric micelles

Year	Polymer	Drug	Targeting	Binder	Size (nm)	Cancer cell	Type of cancer	Release stimulus	Ref.
2016	Poly (lysine-N, N'-bis (acryloyl) diamino hexane)	Doxorubicin	Passive	-	≈145	Hela	Cervical cancer	pH	1S
2016	Phenyl boric acid and chitosan hydrochloride	Doxorubicin	Active	Folic acid	≈190	4T1	Breast cancer	pH and glucose	2S
2016	Methoxy-poly (ethylene glycol) and poly (D, L-lactide)	Curcumin	Passive	-	≈110	B16F10 and MDA-MB-231	Melanoma and Triple-Negative Human Breast Cancer	-	3S
2016	Hyaluronic acid, glycyrrhetic acid and histidine	Doxorubicin	Passive	-	≈150	HepG2	Liver carcinoma	pH	4S
2016	Dextran	Camptothecin and doxorubicin	Passive	-	≈180	4T1	Breast cancer	pH and redox	5S
2016	Methoxy poly (ethylene glycol), poly (ε-caprolactone and di (1-hydroxyethylene) diselenide	Doxorubicin	Passive	-	≈108	HN30	oral squamous cell carcinoma	Redox	6S
2017	Methoxy polyethylene glycol and hexamethylene	Doxorubicin	Passive	-	≈175	A549	Adenocarcinoma	Redox	7S

	diacrylate								
2017	Poly (ethylene glycol) and poly (2- (diisopropylamino) ethyl methacrylate	Doxorubicin	Passive	-	≈43	Hela	Cervical cancer	pH	8S
2017	Poly (2-hydroxymethylmethacrylate) and poly (N - isopropylacrylamide	Doxorubicin	Passive	-	≈100	MCF-7	Breast cancer	pH and temperature	9S
2018	Poly (2-methoxyethoxyethyl phosphorylcholine), poly(ε-caprolactone) and poly(β-aminoester)	-	Passive	-	≈130	HepG2 and 293T	Liver carcinoma	pH	10S
2018	Poly (2-methoxyethoxyethyl phosphorylcholine) and poly (L-Lysine)	Doxorubicin	Passive	-	≈88	4T1	Breast cancer	pH	11S
2018	Poly (L-glutamic acid) and poly methoxy (ethylene glycol)	Doxorubicin and camptothecin	Passive	-	≈80	MCF-7	Breast cancer	Redox	12S
2018	Poly (N-propargildietanolamine 4,4'-dithiodibutyronate) and monomethoxy poly (ethylene glycol)	Doxorubicin	Passive	-	≈40	Hela	Cervical cancer	pH and redox	13S

2018	Poly (ethylene glycol) and poly (2- (metacrililoiloxi) ethyl 5- (1,2-dithiolan-3-il) pentanoate)	Doxorubicin	Passive	-	≈100	MDA-MB-231	Triple-negative human breast cancer	Redox	14S
2018	Hyaluronic acid-hydrazone	Doxorubicin	Active	Hyaluronic acid	≈200	Hela	Cervical cancer	pH	15S
2018	1,2-distearoil-sn-glycero-3-phosphoethanolamine-N-[aldehyde (polyethylene glycol) -2000]	Methotrexate	Active	-	≈30	MCF-7 and Hela	Breast cancer and cervical cancer	pH	16S
2018	Pluronic and linoleic acid	Brusatol	Passive	-	≈100	MCF-7	Breast cancer	Redox	17S
2018	Maltoheptaose and acetylated maltoheptaose	Doxorubicin	Passive	-	≈20	Hela	Cervical cancer	pH and redox	18S
2018	Poly (ethylene glycol) and vitamin E	Curcumin	Active	Transferrin	≈114	Hela and HepG2	Cervical Cancer and Liver Carcinoma	-	19S
2018	Poly (ethylene glycol) and poly (lactide)	Docetaxel	Passive	-	≈150	-	-	-	20S
2018	Poly (ethylene glycol), poly (b-benzyl L-aspartate) and poly (ethylene)	Doxorubicin	Passive	-	≈81	MCF-7 and SMMC-7721	Breast cancer and liver carcinoma	pH	21S
2018	Poly (bis (carboxyphenoxy) phosphazene) and poly	Paclitaxel	Active	Cholic acid	≈218	MCF-7	Breast cancer	pH	22S

	(diallyldimethylammonium chloride)								
2018	Cholesterol, α -tocoferil succinate and poly (ethylene glycol)	Curcumin	Passive	-	≈ 170	MDA-MB-231 and B16F10	Breast cancer and murine melanoma	-	23S
2018	Sodium alginate	Doxorubicin	Passive	-	≈ 83	4T1	Breast cancer	-	24S
2019	Poli (N- vinylcaprolactam) and chitosan	Doxorubicin	Passive	-	≈ 200	MCF-7	Triple-negative human breast cancer	pH and temperature	25S
2019	Poly (lactide) and poly (2-ethyl-2-oxazolin)	Paclitaxel	Active	Spermine	≈ 110	MDA-MB-231 and KCC853	Triple-negative human breast cancer and kidney cancer	pH	26S
2019	Dimethyl L- cystinate, poly (caprolactone) and poly (ethylene glycol)	Paclitaxel	Passive	-	≈ 100	4T1	Breast cancer	pH and redox	27S
2019	Poly (AMA-co-IMMA) and poly (OEGMA)	Paclitaxel and Cisplatin	Passive	-	≈ 131	Hela and Skov-3	Cervical cancer and ovarian cancer	pH and redox	28S
2019	N- proparyldietanolamine 3,3'-dithiopropionate), poly (ethylene glycol) methyl ether and Camptothecin	Doxorubicin and camptothecin	Passive	-	≈ 31	HepG2 and 293T	Liver carcinoma	pH and redox	29S

2019	Cyclodextrin	Doxorubicin	Active	RGD	≈25	A2780, A549, MDA-MB-231 and SH-SY5Y	Ovarian adenocarcinoma, lung carcinoma, breast carcinoma and neuroblastoma	-	30S
2019	Poly (ε-caprolactone) and poly (ethylene glycol)	Camptothecin	Passive	-	≈60	HepG2	Liver carcinoma	Redox	31S
2019	Pluronic	Salinomycin	Passive	-	≈50	A549	Lung carcinoma	-	32S
2019	Poly(β-hydroxyamine)	Doxorubicin	Passive	-	≈56	MCF-7	Breast cancer	pH and redox	33S
2019	Dimethyl L- cystinate and poly(ε-caprolactone) ε	Paclitaxel	Passive	-	≈100	4T1	Breast cancer	pH and redox	27S
2020	Poly(ε-caprolactone) and polycarboxybetaine methacrylate	Doxorubicin	Active	Galactosamine	≈75	HepG2	Liver carcinoma	Redox	34S
2020	Poly (lactic-co-glycolic acid) and albumin	Doxorubicin-triphenylphosphonium	Active	ATRAM	≈130	MCF-7	Breast cancer	pH	35S
2020	Vitamin E succinate	Paclitaxel	Active	Folic acid and hyaluronic acid	≈148	MCF-7	Breast cancer	Redox	36S

2020	Spider Silk Proteins	Doxorubicin	Active	Peptide H2.1	≈400	Her2-positive	Triple-positive human breast cancer	pH	37S
2020	Poly (propylene glycol) and adenine	Magnolol	Passive	-	≈24-52	Hela	Cervical cancer	pH and temperature	38S
2020	Aminopyridinyl amide (DAP) and poly (ethylene glycol)	Doxorubicin	Passive	-	≈80-110	Hela	Cervical cancer	pH	39S
2021	Poly(oligo(ethylene glycol) monomethyl ether methacrylate)-co-poly(2-(dimethylamino)ethyl methacrylate) (p(OEGMA-DMAEMA)) e poly(2-diisopropylaminoethyl methacrylate)-co-poly(pyridyl disulfide ethyl methacrylate) (p(DIPAMA-PDSEMA))	Mellitin	Passive	-	≈32	CT26 e 4T1	Breast cancer And colon cancer	pH	40S
2021	Poly(lactide-co-glycolide)-g-polyethylenimine	Camptothecin	Ative	5-boronopico linic acid	≈150	4T1 e MCF-7	Breast cancer	pH	41S
2021	Poly (propylene glycol) and	Trapoxin A and	Passive	-	≈70	MCF-7	Breast cancer	pH	42S

	Poly(lactide-co-glycolide)	methotrexate							
2022	Chitosan and stearic acid	Doxorubicin and curcumin	Passive	-	≈87	HCT116	Colon cancer	Redox	43S
2022	N-isopropylacrylamide; sodium bicarbonate; N,N'-methylenebisacrylamide; sodium dodecyl sulfate; tetramethylethylenediamine and ammonium persulfate	Cisplatin	Passive	-	≈250	A549	Lung cancer	pH and temperature	44S
2022	Poly (ethylene glycol), poly(caprolactone) and palladium	Doxorubicin	Passive	-	≈13-20	4T1	Breast cancer	pH	45S

Table 2S. Glossary

Antigenicity	Consists of the ability of a substance to be recognized by the body's immune system.
Immunogenicity	Consists of inducing the activation of an organism's immune system.
Opsonization	It is the fixation of flags on a system, indicating that it must be phagocytosed.
Endocytosis	It is the process by which extracellular material is transported into cells.
Endosome	They are vesicles formed from the process of endocytosis.
Critical Micelle Concentration	It is the minimum concentration of polymer required for micelle formation.
Pharmacokinetics	It is the segment that studies the activity of a drug in the body, considering its rate of absorption, distribution and clearance.
Amphiphilic	It is a chemical species that has a polar and a nonpolar part in its structure, promoting the interaction between media with different polarities.

REFERENCES

- 1S. Wu, L.; Ni, C.; Zhang, L.; Shi, G.; *J. Biomater. Sci., Polym. Ed.* **2016**, 27, 643.
[<https://doi.org/10.1080/09205063.2016.1147797>]
- 2S. Zhao, L.; Zhang, Y.; Shao, J.; Liang, H.; Na, H.; Zhu, J.; *RSC Adv.* **2016**, 6, 35658.
[<https://doi.org/10.1039/c6ra01885h>]
- 3S. Kumari, P.; Swami, M. O.; Nadipalli, S. K.; Myneni, S.; Ghosh, B.; Biswas, S.; *Pharm. Res.* **2016**, 33, 826. [<https://doi.org/10.1007/s11095-015-1830-z>]
- 4S. Wu, J. L.; Tian, G. X.; Yu, W. J.; Jia, G. T.; Sun, T. Y.; Gao, Z. Q.; *Int. J. Mol. Sci.* **2016**, 17.
[<https://doi.org/10.3390/ijms17040364>]
- 5S. Cao, D.; He, J.; Xu, J.; Zhang, M.; Zhao, L.; Duan, G.; Cao, Y.; Zhou, R.; Ni, P.; *Polym. Chem.* **2016**, 7, 4198. [<https://doi.org/10.1039/c6py00701e>]
- 6S. Wei, C.; Zhang, Y.; Xu, H.; Xu, Y.; Xu, Y.; Lang, M.; *J. Mater. Chem. B* **2016**, 4, 5059.
[<https://doi.org/10.1039/c6tb01040g>]
- 7S. Duan, X.; Bai, T.; Du, J.; Kong, J.; *J. Mater. Chem. B* **2017**, 6, 39.
[<https://doi.org/10.1039/c7tb02817b>]
- 8S. Xu, Z.; Xue, P.; Gao, Y.-E.; Liu, S.; Shi, X.; Hou, M.; Kang, Y.; *J. Colloid Interface Sci.* **2017**, 490, 511. [<https://doi.org/10.1016/j.jcis.2016.11.091>]
- 9S. Massoumi, B.; Ghamkhari, A.; Agbolaghi, S.; *Int. J. Polym. Mater. Polym. Biomater.* **2017**, 1.
[<https://doi.org/10.1080/00914037.2017.1300901>]
- 10S. Ou, H.; Cheng, T.; Zhang, Y.; Liu, J.; Ding, Y.; Zhen, J.; Shen, W.; Xu, Y.; Yang, W.; Niu, P.; Liu, J.; An, Y.; Liu, Y.; Shi, L.; *Acta Biomater.* **2018**, 65, 339.
[<https://doi.org/10.1016/j.actbio.2017.10.034>]
- 11S. Ma, B.; Zhuang, W.; Wang, Y.; Luo, R.; Wang, Y.; *Acta Biomater.* **2018**, 70, 186.
[<https://doi.org/10.1016/j.actbio.2018.02.008>]
- 12S. Li, Y.; Yang, H.; Yao, J.; Yu, H.; Chen, X.; Zhang, P.; Xiao, C.; *Colloids Surf., B* **2018**, 169, 273. [<https://doi.org/10.1016/j.colsurfb.2018.05.025>]
- 13S. Li, J.; Yang, X. L.; Liu, Y. H.; Wu, W. X.; Liu, B. Y.; Wang, N.; Yu, X. Q.; *J. Mater. Chem. B* **2018**, 6, 6993. [<https://doi.org/10.1039/c8tb01973h>]
- 14S. Maiti, C.; Parida, S.; Kayal, S.; Maiti, S.; Mandal, M.; Dhara, D.; *ACS Appl. Mater. Interfaces* **2018**, 10, 5318. [<https://doi.org/10.1021/acsami.7b18245>]
- 15S. Liao, J.; Zheng, H.; Fei, Z.; Lu, B.; Zheng, H.; Li, D.; Xiong, X.; Yi, Y.; *Int. J. Biol. Macromol.* **2018**, 113, 737. [<https://doi.org/10.1016/j.ijbiomac.2018.03.004>]

- 16S. Xie, J. J.; Fan, Z. X.; Li, Y.; Zhang, Y. Y.; Yu, F.; Su, G. H.; Xie, L. Y.; Hou, Z. Q.; *Int. J. Nanomed.* **2018**, *13*, 1381. [<https://doi.org/10.2147/IJN.S152312>]
- 17S. Zhang, J.; Fang, X.; Li, Z.; Chan, H. F.; Lin, Z. X.; Wang, Y.; Chen, M.; *Int. J. Nanomed.* **2018**, *13*, 939. [<https://doi.org/10.2147/IJN.S130696>]
- 18S. Cheng, L.; Luan, T.; Liu, D.; Cheng, J.; Li, H.; Wei, H.; Zhang, L.; Lan, J.; Liu, Y.; Zhao, G.; *Polym. Chem.* **2018**, *9*, 1337. [<https://doi.org/10.1039/c7py01601h>]
- 19S. Muddineti, O. S.; Kumari, P.; Ghosh, B.; Biswas, S.; *Pharm. Res.* **2018**, *35*, 1. [<https://doi.org/10.1007/s11095-018-2382-9>]
- 20S. Sim, T.; Kim, J. E.; Hoang, N. H.; Kang, J. K.; Lim, C.; Kim, D. S.; Lee, E. S.; Youn, Y. S.; Choi, H. G.; Han, H. K.; Weon, K. Y.; Oh, K. T.; *Drug Delivery* **2018**, *25*, 1371. [<https://doi.org/10.1080/10717544.2018.1477865>]
- 21S. Feng, H.; Chu, D.; Li, Z.; Guo, Z.; Jin, L.; Fan, B.; Zhang, J.; Li, J.; *RSC Adv.* **2018**, *8*, 25949. [<https://doi.org/10.1039/c8ra04089c>]
- 22S. Mehnath, S.; Arjama, M.; Rajan, M.; Jeyaraj, M.; *New J. Chem.* **2018**, *42*, 17021. [<https://doi.org/10.1039/c8nj03251c>]
- 23S. Muddineti, O. S.; Vanaparthi, A.; Rompicharla, S. V. K.; Kumari, P.; Ghosh, B.; Biswas, S.; *Artif. Cells, Nanomed., Biotechnol.* **2018**, *46*, 773. [<https://doi.org/10.1080/21691401.2018.1435551>]
- 24S. Rosch, J. G.; Brown, A. L.; DuRoss, A. N.; DuRoss, E. L.; Sahay, G.; Sun, C.; *Nanoscale Res. Lett.* **2018**, *13*, 350. [<https://doi.org/10.1186/s11671-018-2748-2>]
- 25S. Niu, S.; Williams, G. R.; Wu, J.; Wu, J.; Zhang, X.; Chen, X.; Li, S.; Jiao, J.; Zhu, L. M.; *J. Nanobiotechnol.* **2019**, *17*, 1. [<https://doi.org/10.1186/s12951-019-0529-4>]
- 26S. Chen, Y.; Yang, C.; Mao, J.; Li, H.; Ding, J.; Zhou, W.; *RSC Adv.* **2019**, *9*, 11026. [<https://doi.org/10.1039/C9RA00834A>]
- 27S. Zhang, X.; Kang, Y.; Liu, G. T.; Li, D. D.; Zhang, J. Y.; Gu, Z. P.; Wu, J.; *Biomater. Sci.* **2019**, *7*, 1962. [<https://doi.org/10.1039/c9bm00009g>]
- 28S. Liao, J.; Song, Y.; Liu, C.; Li, D.; Zheng, H.; Lu, B.; *Polym. Chem.* **2019**, *10*, 5879. [<https://doi.org/10.1039/c9py01105f>]
- 29S. Li, J.; Hu, Z. E.; Yang, X. L.; Wu, W. X.; Xing, X.; Gu, B.; Liu, Y. H.; Wang, N.; Yu, X. Q.; *Biomater. Sci.* **2019**, *7*, 3277. [<https://doi.org/10.1039/c9bm00425d>]
- 30S. Viale, M.; Tosto, R.; Giglio, V.; Pappalardo, G.; Oliveri, V.; Maric, I.; Mariggiò, M. A.; Vecchio, G.; *Invest. New Drugs* **2019**, *37*, 771. [<https://doi.org/10.1007/s10637-018-0711-9>]
- 31S. Yu, B.; Meng, Q.; Hu, H.; Xu, T.; Shen, Y.; Cong, H.; *Int. J. Mol. Sci.* **2019**, *20*, 1961. [<https://doi.org/10.3390/ijms20081961>]

- 32S. Sousa, C.; Gouveia, L. F.; Kreutzer, B.; Silva-Lima, B.; Maphasa, R. E.; Dube, A.; Videira, M.; *Pharm. Res.* **2019**, *36*, 1. [<https://doi.org/10.1007/s11095-019-2615-6>]
- 33S. Sun, G.; Liu, J.; Wang, X.; Li, M.; Cui, X.; Zhang, L.; Wu, D.; Tang, P.; *Eur. Polym. J.* **2019**, *114*, 338. [<https://doi.org/10.1016/j.eurpolymj.2019.02.048>]
- 34S. Zhai, J.; Zhou, B.; An, Y.; Lu, B.; Fan, Y.; Li, J.; *J. Nanomater.* **2020**, 11. [<https://doi.org/10.1155/2020/7863709>]
- 35S. Palanikumar, L.; Al-Hosani, S.; Kalmouni, M.; Nguyen, V. P.; Ali, L.; Pasricha, R.; Barrera, F. N.; Magzoub, M.; *Commun. Biol.* **2020**, *3*, 1. [<https://doi.org/10.1038/s42003-020-0817-4>]
- 36S. Yang, Y.; Li, Y.; Chen, K.; Zhang, L.; Qiao, S.; Tan, G.; Chen, F.; Pan, W.; *Int. J. Nanomed.* **2020**, *15*, 2885. [<https://doi.org/10.2147/IJN.S249205>]
- 37S. Kucharczyk, K.; Florczak, A.; Deptuch, T.; Penderecka, K.; Jastrzebska, K.; Mackiewicz, A.; Dams-Kozłowska, H.; *J. Nanobiotechnol.* **2020**, *18*, 56. [<https://doi.org/10.1186/s12951-020-00609-2>]
- 38S. Bintang Ilhami, F.; Huang, S. Y.; Chen, J. K.; Kao, C. Y.; Cheng, C. C.; *Polym. Chem.* **2020**, *11*, 849. [<https://doi.org/10.1039/c9py01557d>]
- 39S. Cheng, C. C.; Sun, Y. T.; Lee, A. W.; Huang, S. Y.; Fan, W. L.; Chiao, Y. H.; Chiu, C. W.; Lai, J. Y.; *Polym. Chem.* **2020**, *11*, 2791. [<https://doi.org/10.1039/d0py00082e>]
- 40S. Lv, S.; Sylvestre, M.; Song, K.; Pun, S. H.; *Biomaterials* **2021**, 277, 121076. [<https://doi.org/10.1016/j.biomaterials.2021.121076>]
- 41S. Hao, X.; Gai, W.; Wang, L.; Zhao, J.; Sun, D.; Yang, F.; Jiang, H.; Feng, Y.; *Mater. Sci. Eng., C* **2021**, *119*, 111553. [<https://doi.org/10.1016/j.msec.2020.111553>]
- 42S. Akbari, E.; Mousazadeh, H.; Sabet, Z.; Fattahi, T.; Dehnad, A.; Akbarzadeh, A.; Alizadeh, E.; *J. Drug Delivery Sci. Technol.* **2021**, *61*, 102294. [<https://doi.org/10.1016/j.jddst.2020.102294>]
- 43S. Sood, A.; Gupta, A.; Bharadwaj, R.; Ranganath, P.; Silverman, N.; Agrawal, G.; *Carbohydr. Polym.* **2022**, *294*, 119833. [<https://doi.org/10.1016/j.carbpol.2022.119833>]
- 44S. Perera, K.; Dat, .; Nguyen, X.; Wang, D.; Kuriakose, A. E.; Yang, J.; Kytai, .; Nguyen, T.; Menon, J. U.; *Pharm. Res.* **2022**, *1*, 1. [[10.1007/s11095-022-03317-8](https://doi.org/10.1007/s11095-022-03317-8)]
- 45S. Wang, L.; Geng, Z.; Yannis, .; Ho, Y. L.; Zhou, J.; Judge, N.; Li, Y.; Wang, W.; Liu, J.; Wang, Y.; *ACS Appl. Mater. Interfaces* **2022**, *14*, 30546. [<https://doi.org/10.1021/acsami.2c06205>]

