Development of New Trastuzumab-Chelating Agent Complexes for Breast Cancer Treatment

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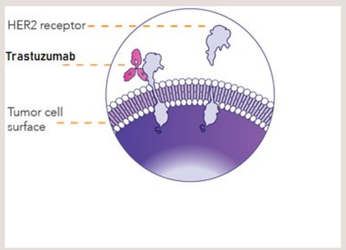
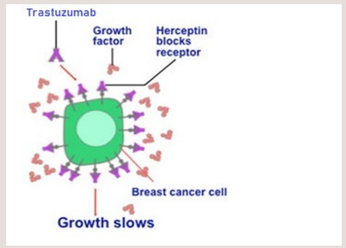
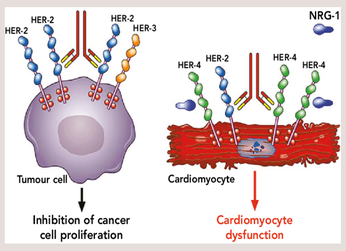
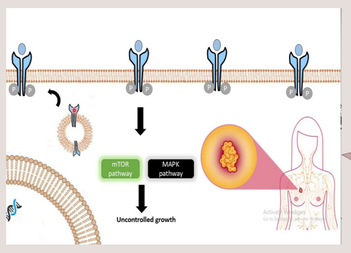
INTRODUCTION





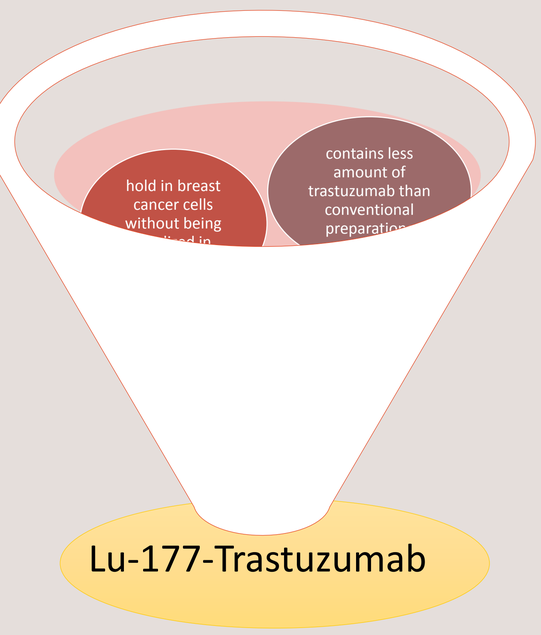
Trastuzumab is a monoclonal antibody used in the treatment of breast cancer.



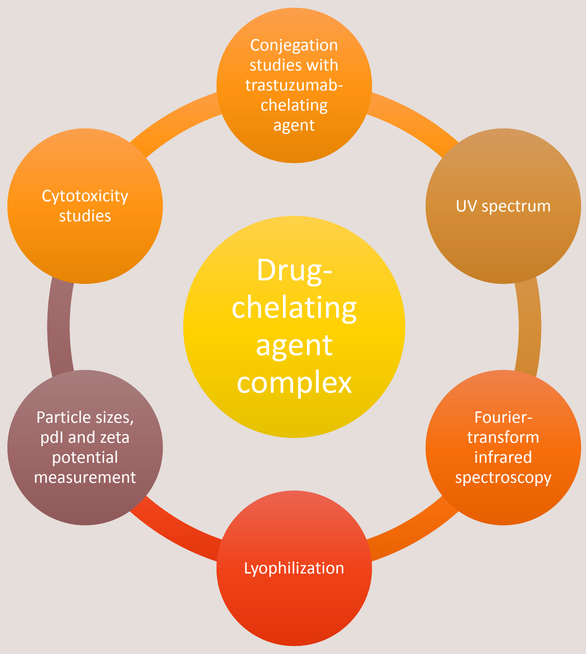


cytotoxicity causes negativities such as cardiotoxicity and development of resistance, which cause death

AIM



METHODS



Trastuzumab-chelating agent chelation

•1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA),
•Diethylenetriaminepentaacetic acid (DTPA),
•Ethylenediaminetetraacetic acid (EDTA),
•1,2-Dimethyl-3-hydroxypyridine

Table 1: Prepared formulations

Formulations	Drug solution	Chelating agent	Incubation time (min)	Turbidity
F 1	25 mg TRZ/ 2 mL sodium bicarbonate solution (pH 8-9)	6 mg DTPA/ 2 mL sodium bicarbonate solution (pH 8-9)	10	+
F 2	25 mg TRZ/ 2 mL sodium bicarbonate solution (pH 8-9)	5 mg EDTA/ 2 mL sodium bicarbonate solution (pH 8-9)	10	+
F 3	5 mg TRZ/ 5 mL sodium bicarbonate solution (pH 8-9)	1 mg DTPA/ 1 mL sodium bicarbonate solution (pH 8-9)	15	+
F 4	5 mg TRZ/ 1 mL sodium bicarbonate solution (pH 8-9)	1 mg EDTA/ 1 mL sodium bicarbonate solution (pH 8-9)	15	+
F 5	5 mg TRZ/ 1 mL sodium bicarbonate solution (pH 8-9)	1 mg EDTA/ 1 mL sodium bicarbonate solution (pH 8-9)	10	+
F 6	5 mg TRZ/ 1 mL sodium bicarbonate solution (pH 8-9)	1 mg DTPA/ 1 mL sodium bicarbonate solution (pH 8-9)	15	+
F 7	10 mg TRZ / 2 mL sodium bicarbonate solution (pH 8-9)	0,8 mg DOTATATE/ 2 mL sodium bicarbonate solution (pH 8-9)	10	+
F 8	10 mg TRZ / 2 mL sodium bicarbonate solution (pH 8-9)	1 mg DOTATATE/ 2 mL saline solution	15	+
F 9	10 mg TRZ / 2 mL sodium bicarbonate solution (pH 8-9)	2 mg DOTATATE/ 2 mL saline solution	15	+
F 10	10 mg TRZ / 2 mL sodium bicarbonate solution (pH 8-9)	0,8 mg DOTATATE/ 0,8 mL saline solution	15	+
F 11	2.5 mg TRZ/ 1 mL sodium bicarbonate solution (pH 8-9)	5 mg DOTA/ 10 mL amonium acetate solution	10	+
F 12	5 mg TRZ/ 5 mL sodium bicarbonate solution (pH 8-9)	2 mg DTPA/ 10 mL pH sı 8-9 arasında olan sodyum bikarbonat tamponu	15	+
F 13	2 mg TRZ/ 1mL sodium bicarbonate solution (pH 8-9)	2 mg EDTA/ 5 mL sodium bicarbonate solution (pH 8-9)	10	+
F 14	2 mg TRZ/ 2 mL sodium bicarbonate solution (pH 8-9)	2 mg 1.2-dimethly 3-hydroksipyridin/ 5 mL sodium bicarbonate solution (pH 8-9)	10	+
F 15	5 mg TRZ/ 2 mL sodium bicarbonate solution (pH 8-9)	4 mg DTPA / 4 mL amonium acetate solution	10	+
F 16	5 mg TRZ/ 2 mL sodium bicarbonate solution (pH 8-9)	0,4 mg EDTA/ 0,4mL amonium acetate solution	15	+
F 17	5 mg TRZ/ 2 mL sodium bicarbonate solution (pH 8-9)	0,15 mg 1.2- dimethly 3-hydroksipyridin /0,15mL amonium acetate solution	15	+
F 18	10 mg TRZ /4 mL sodium bicarbonate solution (pH 8-9)	0,2 mg DTPA/ 0,2 mL amonium acetate solution	15	-
F 19	10 mg TRZ/ 4 mL sodium bicarbonate solution (pH 8-9)	0,2 mg EDTA/ 0,2 mL amonium acetate solution	10	+
F 20	10 mg TRZ/ 4 mL sodium bicarbonate solution (pH 8-9)	0,2 mg 1.2-dimethly 3-hydroksipyridin / 0,2 mL amonium acetate solution	15	-
F 21	10 mg TRZ/ 4 mL sodium bicarbonate solution (pH 8-9)	0,2 mg 1.2- dimethly 3-hydroksipyridin/ 0,1mL amonium acetate solution	10	-
F 22	10 mg TRZ/ 4 mL sodium bicarbonate solution (pH 8-9)	0,1 mg 1.2- dimethly 3-hydroksipyridin/ 0,1mL amonium acetate solution	10	-
F 23	10 mg TRZ/ 4 mL sodium bicarbonate solution (pH 8-9)	0,1 mg DOTA / 0,1mL amonium acetate solution	10	-

Trz: Trastuzumab
DTPA: Diethylenetriaminepentaacetic acid
EDTA: Ethylenediaminetetraacetic acid
DOTA: 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid

RESULTS

Table 2: Malvern Zetasizer results for solution formulations (diluted 1/400)

Formulation number	Size	PdI	Zeta Potential
1	1732±52,27	0,863±0,080	-5,61±2,06
2	908,3±89,02	0,737±0,068	-3,30±1,48
3	906,0±168,9	0,897±0,179	-11,7±0,723
4	1431±212,9	0,459±0,345	-6,80±1,67
5	1529±36,77	1,00	13,9±1,63
6	560,4±123,9	0,566±0,186	5,58±0,437
7	817,9±129,9	0,540±0,465	-6,29±0,609
8	783,3±163,4	0,428±0,281	-5,87±2,41
9	934,2±153,9	0,608±0,180	-10,1±1,13
10	1386±280,4	0,796±0,354	-7,41±1,45
11	1513±221,0	0,763±0,410	-10,6±0,856
12	834,2±171,0	0,674±0,117	-6,30±2,78
13	1363±246,9	1,00	-3,69±0,177
14	1126±124,5	0,870±0,213	0,798±0,178
15	469,2±139,8	0,601±0,197	-3,63±1,92
16	863,3±143,3	0,788±0,266	-3,45±1,80
17	568,3±72,74	0,458±0,151	-22,2±4,24
18	959,1±51,05	0,558±0,126	-12,9±2,66
19	486,0±122,8	0,467±0,092	-4,32±2,58
20	1011±142,3	0,789±0,298	-13,8±3,20
21	1760±289,0	0,848±0,151	-19,7±3,99
22	1070±234,2	0,569±0,447	-9,35±1,76
23	1134±353,6	0,123±0,083	-17,8±1,41

Table 3: Malvern Zetasizer results for kit formulations (diluted 1/400)

Formulation number	Size	PdI	Zeta Potansiyel
1	2548±72,83	1,00	-16,5±0,866
2	2464±456,9	0,932±0,118	-16,2±1,44
3	797,9±152,4	0,392±0,277	-18,5±1,35
4	457,5±85,64	0,635±0,131	-9,00±2,25
5	1607±271,5	1,00	-6,07±0,993
6	509,1±67,33	0,761±0,210	-13,0±1,48
7	1421±413,2	0,900±0,089	-3,81±2,67
8	692,8±76,53	0,783±0,175	-11,0±2,91
9	752,5±199,1	0,769±0,245	-14,9±2,95
10	1054±295,4	0,812±0,184	-2,15±1,23
11	1035±21,20	0,687±0,533	-11,8±1,50
12	904,4±86,12	0,672±0,305	-6,76±3,05
13	758,4±78,06	0,446±0,134	-9,40±1,25
14	787,4±107,1	0,653±0,053	-9,50±4,03
15	545,0±131,5	0,585±0,124	-3,35±0,221
16	693,1±59,22	0,900±0,080	-22,9±2,69
17	604,7±38,54	0,579±0,117	-8,48±1,59
18	457,5±62,15	0,669±0,296	-1,42±0,471
19	863,1±304,8	0,714±0,178	-16,2±1,86
20	966,8±121,9	0,901±0,081	-1,76±0,405
21	692,0±171,9	0,834±0,235	-11,9±0,757
22	537,5±20,76	0,583±0,262	-10,8±0,529
23	479,6±78,47	0,522±0,069	-17,3±1,31

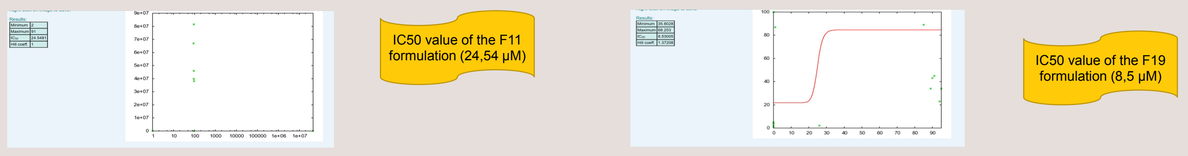


Figure 1: IC50 values of prepared formulations

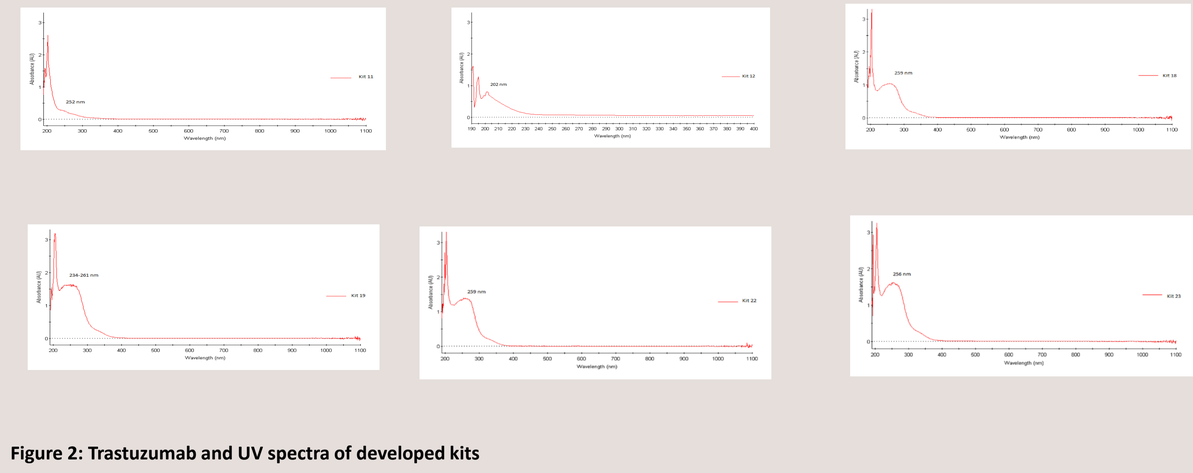


Figure 2: Trastuzumab and UV spectra of developed kits

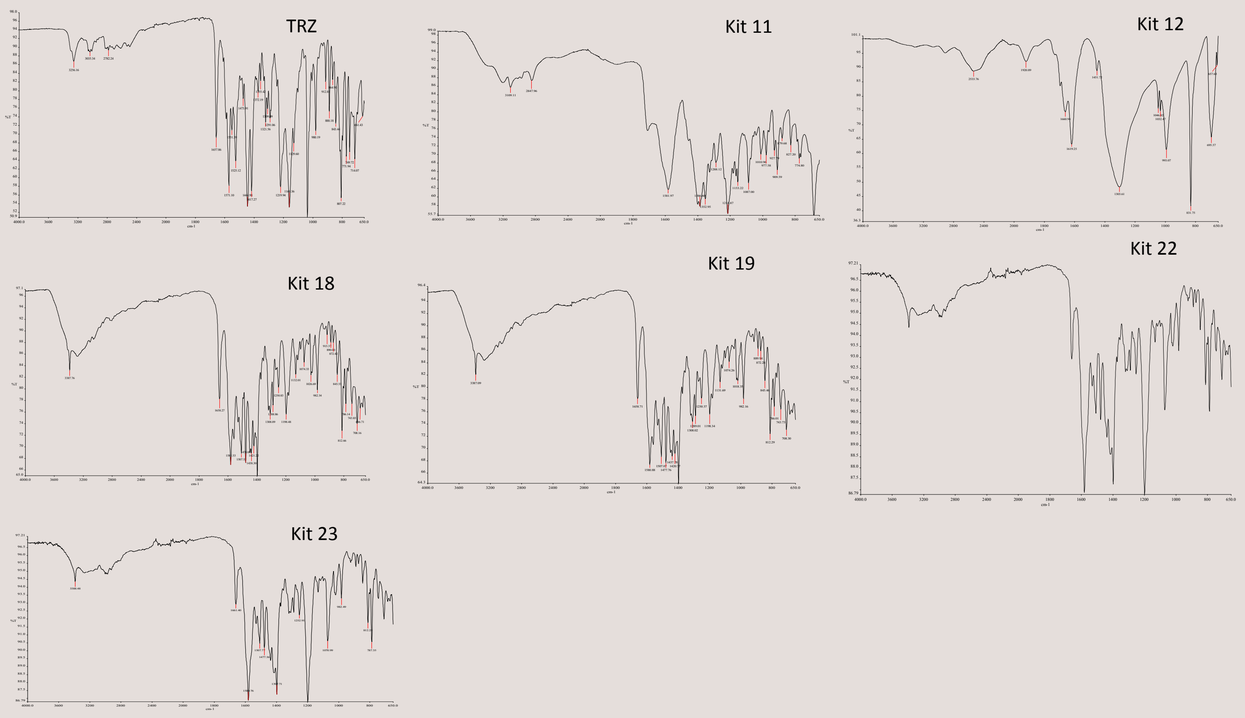


Figure 3: Trastuzumab and FTIR spectra of developed kits

CONCLUSION

23 of TRZ-different chelating agents were newly developed. The particle size and PDI of complexes were found approximately 1000 nm and 0,7, respectively. IC50 values were found to be between 8,5 and 24,54 µM. We plan to performed radiolabeling studies with Lutetium-177. The further studies will be continued with these 13 formulations.

REFERENCES

Mohan, N., Jiang, J., Dokmanovic, M. Wu, W. J. 2018. "Trastuzumab-mediated cardiotoxicity: Current understanding, challenges, and frontiers", Antibody therapeutics. NIH Public Access, 1(1), 13-17.

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