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**Mini Review**

## **Polymeric Nanoparticles and Their Novel Modifications for Targeted Delivery of Bortezomib**

Saeideh Allahyari<sup>1,2</sup>, Hadi Valizadeh<sup>3</sup>, Parvin Zakeri-Milani<sup>4</sup>

<sup>1</sup> Faculty of Pharmacy, Tabriz University of Medical Science, Tabriz, Iran

<sup>2</sup> Student Research Committee, Tabriz University of Medical Science, Tabriz, Iran

<sup>3</sup> Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Science, Tabriz, Iran

<sup>4</sup> Liver and Gastrointestinal Diseases Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

### **Running title:**

Polymeric Nanoparticles and BTZ delivery

### **Corresponding author:**

Parvin Zakeri-milani

Liver and Gastrointestinal Diseases Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

+98 9144157160

[pzakeri@tbzmed.ac.ir](mailto:pzakeri@tbzmed.ac.ir)

[parvinzm@gmail.com](mailto:parvinzm@gmail.com)

## Abstract

Bortezomib (BTZ) as a specific proteasome inhibitor is used to inhibit proliferation and migration of tumor cell in variety of cancers. Targeted delivery of this drug not only would minimize its unwanted side effects but also might improve its efficacy. This purpose could be gotten through different pathways but using efficient carriers may be the best one without using any additional ingredients/ materials. Some polymer based nanoparticles with specific functional groups have the ability to interact with boronic acid moiety in BTZ. This reaction might play an important role not only in cancer targeting therapy but also in loading and release properties of this drug. Novel modification such as making multifunctional or pH-sensitive nanocarriers, may also improve anticancer effect of BTZ.

This review might have remarkable effect on researchers' consideration about other possible interactions between BTZ and polymeric nanocarriers that might have great effect on its remedy pathway. It has the ability to brought bright ideas to their minds for novel amendments about other drugs and delivery systems.

**Key words:** Polymer; Nanoparticle; Bortezomib; Interaction

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## 1. Introduction

Cancer treatment strategy needs great attention because of resistant to current chemotherapy strategies and adverse side-effects on non-targeted organs <sup>1,2</sup>. Bortezomib (BTZ) as a reversible proteasome activity inhibitor <sup>3</sup> plays role in cancer treatment and would be targeted smartly through nanoparticles for tumors in several organs such as bone <sup>4</sup>, breast <sup>5</sup>, esophagus <sup>6</sup>, cervix <sup>7</sup>, colorectal <sup>8</sup>, subcutaneous <sup>9</sup>, pancreas and lung <sup>10</sup>. Nanoparticles based on some polymers such as chitosan <sup>11</sup>, dendrimer <sup>12</sup>, natural polyphenols <sup>9</sup> and other different substances were studied for delivery of BTZ (table 1). These delivery systems would also be prepared in different forms such as micelles <sup>13</sup> and hydrogels <sup>14</sup> with diverse targeted delivery methods such as pH-sensitive <sup>15</sup> and magnetic field <sup>16</sup> applications. Designing multi-functional nanoparticles as a novel delivery strategy has also the ability to be introduced as a system for overcoming multiple drug resistance through quick action <sup>17</sup>. These multiplexed nanoparticles attract researchers' attentions because of their capabilities such as co-delivery of multiple therapeutic agents <sup>18</sup>, targeting and killing diseased cells with minimal adverse effects <sup>19</sup>, controlled release of drug <sup>20</sup> and illustrating their location by imaging techniques and monitoring treatment in progress <sup>21</sup>. Owing to their features, BTZ delivery by these systems were studied by some research groups to evaluate its curative performance <sup>20,22,23</sup>.

Through loading process of BTZ in polymeric nanoparticles some reactions would be created between this drug and nanocarrier that not only promote its therapeutic effect at tumor site but also decrease its nonspecific release <sup>24</sup>. Both hydrophobic <sup>25,26</sup> and ionic interactions might be responsible in this process but

boronate linkage as an ionic interaction is the most common one <sup>27</sup>. This interaction may be composed between boronic acid moiety in BTZ and specific functional groups such as catechol <sup>27,28</sup>, carbonyl <sup>29</sup> and amine <sup>7</sup> in polymers. It is also important to say that this chemical relation have prominent influence on BTZ loading efficiency and release profile <sup>28</sup>.

This article intended to bring an attractive insight about different types of polymeric nanoparticles that had been used for targeted BTZ delivery to different tumor sites. Possible physical and chemical interactions between BTZ and polymers that might have attractive influence on its different characteristics such as loading, release, stability and potency are also mentioned. Novel BTZ delivery strategies are also other important findings that is presented in this review.

Table 1. BTZ delivery through polymeric nanosystems

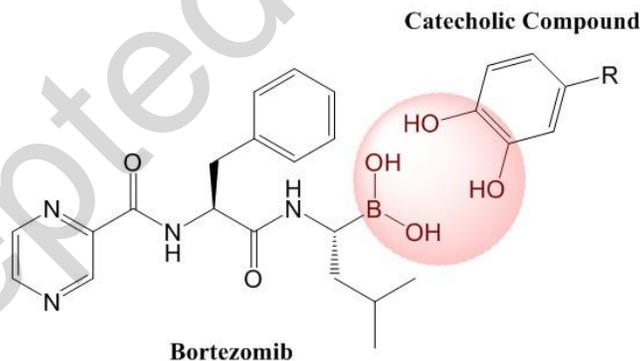
Nanocarrier	Composition	Size after loading	Cell line/ animal model	Targeted organ	Remarkable findings about BTZ	References
Polymeric Micelle	PAMPDA	62 nm	MCF7 cells	Breast	Selective accumulation in targeted tissue. Efficient cytotoxicity against tumor cells. Long circulation time. Sustained release of BTZ.	13
	PEG-P(TMC-DTC)	48-49 nm	MDA-MB-231/ Female balb/c mice	Breast		5
	HA-CCMs	76-80 nm	Balb/C mice	bone		23
	PEG-b-P(LL-g-Cat-BTZ) and ALN-PEG-b-PLLZ copolymers	Dependent to polymers ratio	MDA-MB-231 cells/ Female balb/c mice	Breast		30
	telodendrimers (PEG5k-Cys4- L8-CA8)	20 nm	KYSE30 cells	Esophagus		6
	PEG-b-PS-b-PGAMA  PEG-b-PDEA-b-PGAMA glycopolymers	60 nm  70 nm	It was not reported.	It was not reported.		31
Chitosan	Chitosan coated magnetic iron oxide	Average core size between 5–7 nm	HeLa and SiHa cells/	cervix	Improvement cytotoxicity against tumor cells. Sustained release of BTZ. Reducing the frequency and amount of administered BTZ.	7
	chitosan with chondroitin sulfate	186.5 nm	HT-29 and HCT-116 cells/ female balb/c mice	Colorectal		8
	anti-CD38 chitosan NPs	50 nm	MM.1S, H929, and RPMI8826/ female 7- week old SCID mice	bone		11

Dendrimer	G5-PPI-NH <sub>2</sub>	It was not reported.	It was not reported.	It was not reported.	Providing targeted delivery of BTZ. Stability improvement at physiological condition.	26
	G4-PAMAM-NH <sub>2</sub>					Changing dendrimer behavior because of pH variation.
	maltose-modified hyperbranched poly(ethylene imine)	10 nm	hMSC	bone	Solubility improvement.	
	G5 PAMAM	80 nm	MDA-MB-231/ Female balb/c nude mice	Breast		
Polymeric hydrogel	Nap-GFFY	It was not reported.	HeLa and HepG2/	It was not reported.	Sustained release of BTZ. Have the potential for topical administration in tumor site.	14
Natural polyphenols	Tannic acid	125 nm	NIH 3T3 and MDA-MB-231/ mice	subcutaneous and bone	High and controllable drug loading. Acceptable biocompatibility to normal tissues with high cytotoxicity against tumor cells.	9

## 2. Polymeric based nanoparticles

### 2.1. Polymeric micelles

BTZ delivery through polymeric micellar nanostructures have been studied in different cancers such as multiple myeloma <sup>23</sup>, breast <sup>5</sup> and esophagus <sup>6</sup>. This drug showed affinity to these carrying system by physical and chemical interactions. Physical interactions were through incorporation into core of the polymeric micelles such as PAMPDA which was constructed from poly (N-acryloyl morpholine) block (PAM) and a hydrophobic catechol-bearing block- polydopamine (PDA) <sup>13</sup> and PEG-b-PS-b-PGAMA that was prepared from poly(ethylene glycol)-block-poly(styrene)-block-poly(gluconamido ethyl methacrylate) and PEG-b-PDEA-b-PGAMA which was prepared from poly(ethylene glycol)-block-poly(2(diethylamino)ethylmethacrylate)-block-poly(gluconamido ethyl methacrylate) <sup>31</sup>. It is worth to say that in a study about micellar nanoformulation based on PEG-P(TMC-DTC) (poly(ethylene glycol)-*b*-poly(trimethylene carbonate-*co*-dithiolane trimethylene carbonate)) block copolymers, physical entrapment of BTZ inside the core of micelle was because of esterification of BTZ with pinanediol <sup>5</sup>. Some studies declared that boronic acid moiety in BTZ structure could interact chemically with catecholic polymers (fig. 1) <sup>13</sup> such as PAMPDA <sup>13</sup>, PEG-b-PGAMA <sup>31</sup> and PEG-b-P(LL-g-Cat) (poly(ethylene glycol)-block-poly(L-lysine)-graft-Catechol) <sup>30</sup>. This interaction also has pH-dependent ability that lets drug release in acidic pH (almost 5) of endo/lysosomes after endocytosis by cancer cells <sup>13,32</sup>.



**Fig. 1.** Interaction site of BTZ with catechol containing compound.

BTZ has also some limitations such as poor selectivity and rapid clearance from the body that may be solved by targeting strategy. Hyaluronic acid in the shell of core-disulfide-crosslinked biodegradable micelles which was obtained from poly (trimethylene carbonate-*co*-dithiolane trimethylene carbonate, has the ability to improve BTZ selectivity by actively targeting to the CD44-overexpressed multiple myeloma

tumor in mice <sup>23</sup>. Cyclic-RGD (cRGD) peptide (Arg-Gly-Asp), as another targeting ligand showed high affinity to MDA-MB-231 triple negative breast cancer cells that overexpressed highly with  $\alpha_v\beta_3$  integrin. Wu et al. declared that cRGD-micelles showed efficient tumor accumulation in MDA-MB-231 tumor bearing mice (2.3-fold higher tumor uptake in comparison with non-targeted micelles) with less adverse effects to other tissues <sup>5</sup>. Alendronate as another targeting ligand <sup>30,33</sup> was studied because of its bone targeting property. It could be used in multi-component mixed micelles composed from poly(ethylene glycol) and poly(L-lysine) for BTZ delivery in treatment of breast cancer bone metastasis <sup>30</sup> or multiple myeloma <sup>33</sup>.

## 2.2. Chitosan

Chitosan as a natural, biocompatible and biodegradable polymer can be introduced as a preferable carrier in pharmaceutical fields <sup>7,34</sup>. Delivery of BTZ by chitosan nanoparticles had been studied for multiple myeloma <sup>11</sup> and colorectal <sup>8</sup> cancer therapies. FTIR analysis declared that BTZ might interact with chitosan through boronic acid moiety (B–O stretching <sup>7,8</sup> and B–O–H stretching <sup>7</sup> of boronic acid).

BTZ instability is one of its limitations at conventional chemotherapy that reduced its bioavailability <sup>35</sup>. Unsoy et al. research group proved that BTZ loaded in chitosan coated with magnetic iron oxide nanoparticles were quite stable after an initial release of about 15% drug in phosphate buffer solution (pH 7.4) at 37°C, and its stability did not affect by temperature variation between 37°C and 4°C <sup>7</sup>. Chitosan carriers with folic acid and anti CD38 were also used as targeting ligands to colorectal and multiple myeloma chemotherapy, respectively <sup>8,11</sup>.

## 2.3. Dendrimer

Dendrimers with special chemical structure, has terminal functional groups with hydrophobic internal architecture that made them ideal for loading of drugs with hydrophobic characteristic like BTZ. In a study about 5.0 G of poly (propylene) imine (PPI) and 4.0 G poly (amidoamine) (PAMAM) dendrimers, Chaudhary et al. showed that high encapsulation capacity of G5-PPI-NH<sub>2</sub> in comparison with PAMAM-NH<sub>2</sub>, was because of more electrostatic interactions between hydrophobic moieties of PPI and BTZ <sup>26</sup>. In phase solubility studies it was concluded that both of PPI and PAMAM increased solubility of BTZ more than 1000 times in comparison with plain drug (aqueous solubility 0.0532 mg/ml) and it lets dendrimers to be introduced as an ideal carrier for improving the solubility of poorly water soluble drugs <sup>26,36</sup>.

Providing a short-term retarding release of BTZ (up to 96 h) from dendritic glycopolymer PEI-Mal-B (maltose-modified hyperbranched poly (ethylene imine)) in calcium phosphate bone cements composites <sup>12</sup>, demonstrated one of the advantages of dendrimers that restricts burst-release of it in chemotherapeutic processes.

Cyclic RGD-targeted dendrimers could also be used in bone tumor model which was created by injection of MDA-MB-231 cells into the tibia of mice. Fluorescent analysis documented that through targeting process, drug loaded dendrimers could be internalized by breast cancer cells and depressed the development of metastasis in an efficient manner <sup>28</sup>.

#### 2.4. Other polymers

Supramolecular hydrogel as another controllable drug delivery system for hydrophobic drugs <sup>37</sup> was introduced for delivery of BTZ. Sustained release of BTZ from a supramolecular hydrogel in phosphate buffer solution within 12 h experimental period, had been studied by Pu et al. This nano-delivery system was composed of three catecholic peptides based on Nap-GFFY that only differ in the number of glutamic acids in their structures. They said that sustained release of BTZ was because of boronate ester hydrolysis in topical administration near tumor site <sup>14</sup>.

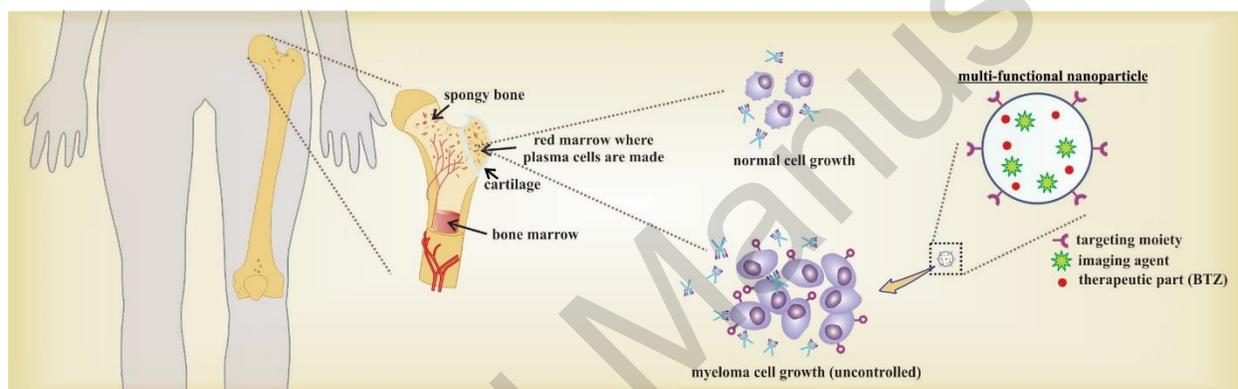
Natural polyphenols as abundant micronutrients in our dietary sources <sup>38</sup> were introduced for delivery of BTZ. They have the ability of interaction with active site of BTZ through boronate ester bonds <sup>39</sup>. Wang et al. deduced from this interaction and composed definite carrier consisting of catechol-containing natural polyphenols such as tannic acid (TA) and ferric ion. They used iron (III) for enhancing stability of supramolecular through making interchain iron (III)-catecholate coordination bonds and acting as a magnetic resonance system. They showed pH-dependent release of BTZ in that carrier because of boronate ester bond between polyphenols and BTZ and interchain iron (III)-catecholate coordination, that dissociated at acidic conditions in tumor microenvironment. This behavior dramatically induced BTZ remaining in MDA-MB-231 tumor bearing mice up to 9.27 % (%injected dose/gram tissue) after 24 h injection and improved its apoptosis in cancer cells <sup>9</sup>.

Other copolymeric nanosystems can also be introduced for the delivery of BTZ. Shen et al. used a diblock copolymer composed of poly (ethylene glycol)-block-poly (D, L-lactide) (PEG-b-PLA) with amphiphilic characteristic for delivery of BTZ. This biodegradable nanoparticle made efficient uptake of BTZ by triple negative breast cancer cells (such as MDA-MB-468 cells) in comparison with plain drug (215.9 and 91.3 ng/ $2 \times 10^5$  cells, respectively) <sup>40</sup>. Another amphiphilic polymer based on branched polyethyleneimine (PEI) and palmitic acid (PA) showed a pH-sensitive release in in-vitro buffered solution <sup>41</sup> which would make BTZ with less systemic toxicity and high release in acidic compartments of tumor cells.

### 3. Novel modifications in BTZ delivery

#### 3.1. Multifunctionalization

Multifunctional nanoparticles attract researchers' attention in medical applications because of their integrated ability such as targeting, therapeutic and imaging functions in a single carrier (fig. 2). In a study by Gu et al.<sup>23</sup>, hyaluronic acid was used in the surface of single copolymeric micelles as a targeting ligand to CD44-overexpressed LP-1 multiple myeloma cells. Another multifunctional nanoparticle was developed with Wang et al. to improve treatment efficacy in MM treatment. They co-deliver BTZ and doxorubicin through telodendrimer micelles and proved that by codelivery of the mentioned drugs, their ability in tumor growth inhibition and in treatment of H929 MM and SKOV-3 ovarian cancer cells increased. DiD as a near-infrared fluorescence was also co-loaded to evaluate biodistribution of this nanoformulation<sup>20</sup>.



**Fig. 2.** Schematic representation of BTZ loaded in multifunctional nanoparticle on multiple myeloma.

#### 3.2. PH-sensitivity

PH-responsive manner of polymeric nanoparticles and BTZ as novel strategy, can be considered to be a promising method for optimizing loading and control release of this drug. Boronic acid group in BTZ is mainly responsible for the reaction with other moieties such as hydroxyl<sup>27</sup> or carbonyl<sup>29</sup> groups in delivery system. This property makes BTZ to have different loading efficiencies in different pH conditions. Demirdogen et al. reported that BTZ have the highest and lowest loading efficiency on poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) copolymer in potassium phosphate buffer at pH values ranging from 6.0 to 7.4 and in acetate buffer at pH 4.7, respectively<sup>29</sup>. Almost the same results were obtained by Unsoy et al. in chitosan nanocarrier because of the osmotic swelling property of this carrier at low pHs. Beside this ability of chitosan, ionic interactions with BTZ is high at low pH, so they choose potassium phosphate buffer at pH 6.0 as an optimum medium for obtaining best loading efficiency by providing a balance between osmotic and ionic characteristics of chitosan<sup>7</sup>. Sensitivity to pH is also an important factor in BTZ release in tumor microenvironment with acidic pH. Researchers declared that in an equilibrium

dialysis method BTZ showed 12 hours slow release (less than 5%) from dendrimer at pH 7.4 and 6 hours fast release (almost 57%) at pH 5, which were demonstrated good stability of this nanoparticle at physiological condition and targeted release at tumor microenvironment <sup>30</sup>.

Table 2. Interaction site of BTZ and polymers with pH responsive characteristics.

nanocarrier	interacted moiety of carrier	interacted moiety of BTZ	Type of interaction	references
poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)	carbonyl	boronic acid	ionic interaction	29
polydopamine	catechol	boronic acid	ionic interaction	24
chitosan	amine	boronic acid	ionic interaction	7
Catechol-conjugated dendrimers	catechol	boronic acid	ionic and hydrophobic interactions	27,28
Catechol containing poly(ethylene glycol) micelles	catechol	boric acid	ionic interaction	30

### 3.3. Magnetic nanoparticles

Magnetic nanoparticles had been introduced as another targeted drug delivery system. They have the ability to produce an efficient and precise drug delivery with minimum side effects through applying an external magnetic field <sup>42</sup>. Alvarez et al. composed a magnetic carrying system from an aqueous solution of ferric and ferrous salts at a molar ratio of 1:2 through co-precipitation method. They produced hyperthermia by magnetic field near the targeted tissue. The results proved that cytotoxicity of BTZ would be improved because of microtubule disruption and aggresome formation in cells through magnetic field hyperthermia <sup>16</sup>.

## 4. Conclusion

Bortezomib as a selective proteasome inhibitor is used in different tumors. Some polymeric nanoparticles would be introduced as an appropriate carrier due to their specific chemical structure. Hydrophobic and ionic interactions between BTZ and these systems are responsible for its efficient loading, sustained and

targeted release in tumor site. Some novel methods such as using multifunctional and pH-sensitive polymeric carriers may help to develop BTZ efficacy in cancer treatment strategies.

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## **6. Declaration of interest**

The authors have no conflicts of interest with the written content in this manuscript.

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