

BCNU

PLGA

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Preparation of BCNU-loaded PLGA Wafers and *In Vitro* Release Behavior

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:
1,3 - bis(2 -
chloroethyl) - 1 - nitrosourea (BCNU, Carmustine)가 poly(D,L - lactide - co - glycolide)
(PLGA, 75 : 25) . BCNU가
PLGA
. XRD DSC PLGA BCNU
BCNU burst effect 0 8
BCNU 가 PLGA 가 pH

ABSTRACT : 1,3 - Bis(2 - chloroethyl) - 1 - nitrosourea (BCNU, Carmustine) - loaded poly(D, L - lactide - co - glycolide) (PLGA, lactide/glycolide mole ratio 75 : 25) microparticles were prepared and fabricated into wafers in an attempt to study the possibility for the treatment of malignant glioma by direct inserting the wafers to the tumor or the cavity remained after surgical resection of the tumor. SEM observation of the microparticles prepared by spray drying method revealed that the microparticles were spherical, i. e. microspheres. Significant reduction of the crystallinity of BCNU encapsulated in PLGA was confirmed by X - ray diffraction and differential scanning calorimetry analyses of the BCNU - loaded PLGA microparticles. Release pattern of BCNU was dependent on several preparation parameters, such as the molecular weight and concentration of PLGA, and initial BCNU loading amount, etc. In vitro release of BCNU was prolonged over 8 weeks with close to zero - order release pattern after initial burst effect. Observations of morphological change of wafers and pH change of release media during release test period confirmed that hydration and degradation of PLGA would be facilitated with an increase of BCNU - loading amount.

Keywords : brain tumor, BCNU, spray-drying, PLGA microparticles, wafers.

가²⁰, 3 20%가
 가 50±
 2, 30±4 psi 7
 ±2 mL/min
 BCNU
 (35 mtorr,
 -78) 가
 가 PLGA 0
 BCNU 100 mg 10.0 mm
 Carver press (MH - 50Y Cap, 50
 tons, Japan) 20 Kg/cm²
 BCNU PLGA PLGA 5 가
 BCNU 0
 (SEM, scanning electron
 microscope, S - 2250N, Hitachi, Japan)
 pH
 PLGA (SC 500K, EMscope,
 UK) 90
 platinum
 BCNU (98% , Sigma
 Chemical Co., St. Louis, MO, USA) - 20
 PLGA
 (lactide/glycolide mole ratio, 75/25) (Boehringer
 Ingelheim, Germany) 20000
 90000 g/mole
 (MC, Tedia, Japan), (Junsei, Japan)
 BCNU BCNU
 4
 37 phosphate
 buffered saline (PBS, pH 7.4) BCNU
 BCNU HPLC
 BCNU PLGA MC
 PLGA BCNU
 (Uniglatt, Glatt Co., Binzen, Germany)
 PLGA 3 30%
 BCNU loading PLGA

BCNU
 BCNU powder
 X - ray diffractometer (XRD, D/Max - III B, Rigaku,
 Japan) 5 ° /min 2 0
 80°
 differential scanning calorimetry
 (DSC, TA Instrument DSC 3100, Dupont, USA)
 10 /min 0 80
 BCNU
 100 mg 2 mL MC
 18 mL 가
 PLGA 1 mL
 100 mL
 HPLC HPLC UV (UV -
 1000, Thermo Separation Products, Fermont, CA,
 USA), (P - 2000, Thermo Separation Products),
 (AS - 3000, Thermo Separation

BCNU PLGA

Products) HPLC

m-Bondapak™ C₁₈ (3.9 × 300 mm, Waters, Milford, MA, USA)

1.0 mL/min

237 nm,

20 mL

100 mg 20 mL

PBS 37

60 rpm

BCNU

MC BCNU

PLGA

SEM pH

PLGA

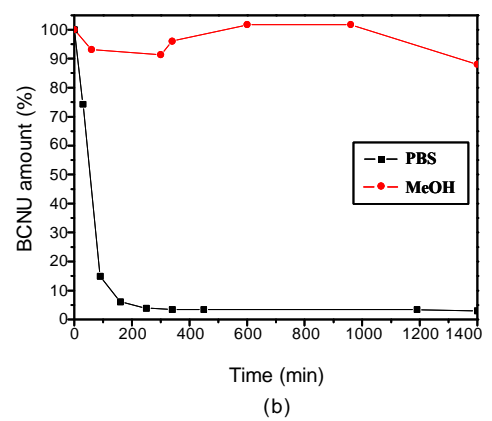
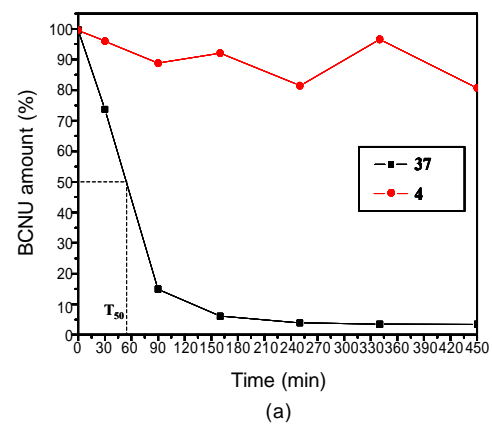
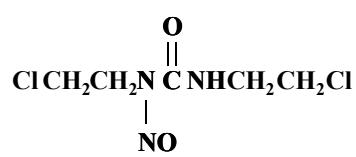
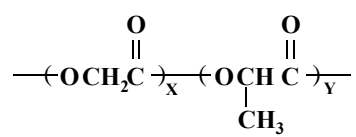


Figure 2. Degradation behavior of BCNU. (a) BCNU in PBS (pH 7.4) at 37 (■) and 4 (●), (b) BCNU in MeOH (●) and PBS (pH 7.4; ■) at 37 .



(a)



(b)

Figure 1. Chemical structure of (a) BCNU and (b) PLGA.

1, 3-bis (2-chloroethyl) - 1 - nitrosourea 가

BCNU DNA RNA

가 BCNU pH

pH 7 가

pH 4 가

20 15 가

30 32 가

HPLC

PBS

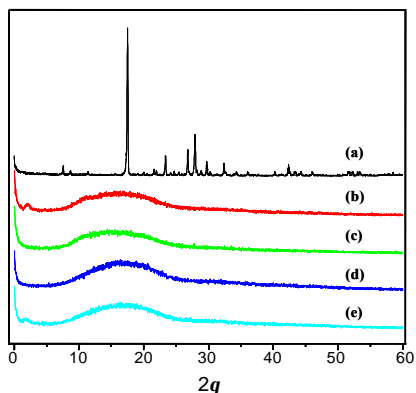


Figure 4. X-ray diffraction patterns of BCNU, PLGA, and BCNU-loaded PLGA microparticles. (a) BCNU, (b) PLGA 20 k, (c) PLGA 90 k, (d) PLGA 20 k/BCNU 10%, and (e) PLGA 90 k / BCNU 10%.

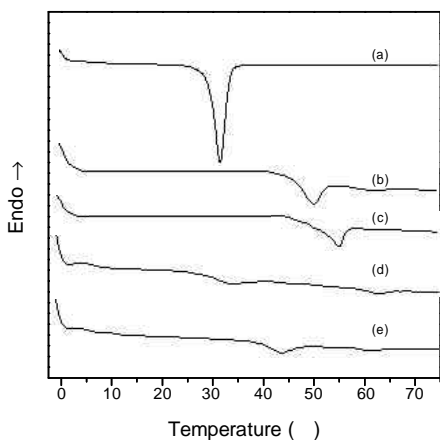


Figure 5. DSC thermograms of BCNU, PLGA, and BCNU-loaded PLGA microparticles. (a) BCNU, (b) PLGA 20 k, (c) PLGA 90 k, (d) PLGA 20 k/BCNU 10%, and (e) PLGA 90 k / BCNU 10%.

Table 2. Thermal Properties of BCNU, PLGA and BCNU-loaded PLGA Microparticles

	T_m ($^{\circ}$)	ΔH_m (J/g)	T_g ($^{\circ}$)	ΔH_g (J/g)
BCNU	30.58	114.5	-	-
PLGA 20K	-	-	50.55	8.285
PLGA 90K	-	-	55.39	6.945
BCNU/PLGA20K	33.23	21.63	62.85	1.352
BCNU/PLGA90K	43.97	21.31	61.21	2.216

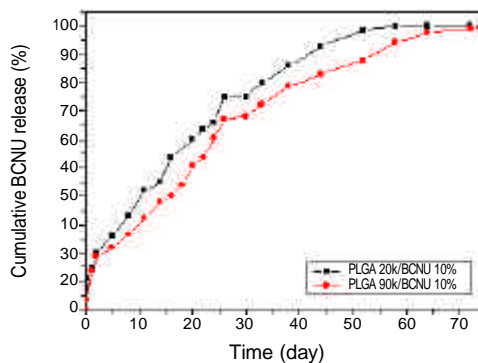


Figure 6. Effect of PLGA molecular weight on BCNU release from PLGA wafers.

Table 2

BCNU가 PLGA	BCNU
가	PLGA
BCNU가	(ΔH_m)
BCNU	BCNU
가	9
가	가
BCNU가	(ΔH_m)
BCNU	BCNU

PLGA	PLGA	PLGA
(ΔH_g)	(ΔH_g)	(ΔH_g)
DSC	BCNU	PLGA
DSC	BCNU	PLGA
10%	BCNU	PLGA
7.4)	BCNU	PLGA
20%	burst	PLGA
0	가	PLGA
8	9	20%
burst	0	가
	10	

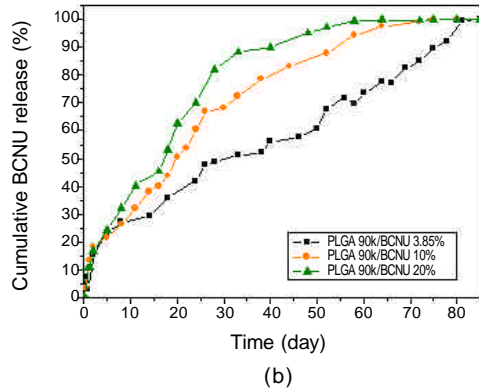
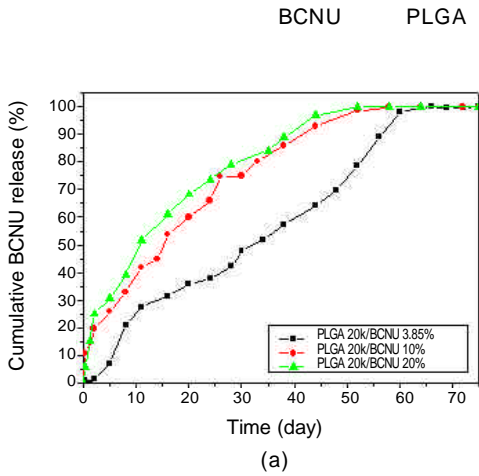
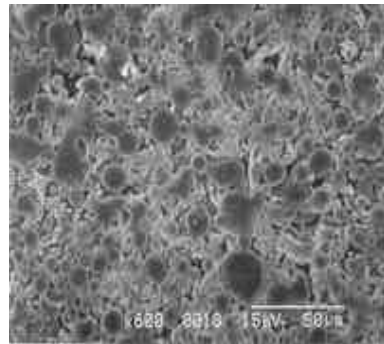
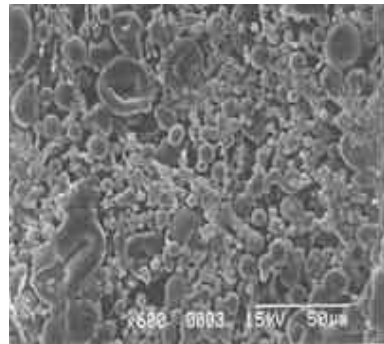


Figure 7. Effect of BCNU loading amount on BCNU release from PLGA wafers. (a) PLGA 20 k and (b) PLGA 90 k.



(a)



(b)

Figure 8. Scanning electron microscopy of surface of 3.85% BCNU - loaded PLGA 90 k wafer. (a) before release test and (b) after 10 days of release test.

가

24 PLGA BCNU

2 9

Figure 7 (a) (b)

2 PLGA BCNU BCNU

100% 9 PLGA BCNU BCNU

10 BCNU 가 가

가 100%

8 - 12 PLGA

PLGA BCNU

25-27 2

PLGA BCNU BCNU

9 PLGA BCNU BCNU

2 PLGA BCNU BCNU

9 가

PLGA 2

BCNU PLGA

1. BCNU PLGA
in vitro
 BCNU PLGA
 BCNU 2
 PLGA BCNU 9 PLGA
 BCNU
 2. BCNU PLGA XRD
 BCNU가 PLGA
 DSC
 3. PLGA 가 BCNU
 BCNU 가
 가 BCNU 가
 burst effect가 가
 0 가
 4. pH BCNU
 BCNU PLGA
 BCNU
 가 PLGA 가
 BCNU/PLGA

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