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Research article

Formulation and characterisation of spray-dried *o*-carborane/ poly(vinylpyrrolidone) for boron neutron capture therapy of liver and lung cancer

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Key words: Boron neutron capture therapy, BNCT, cancer, carborane, formulation, spray drying.

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Abstract

Boron neutron capture therapy (BNCT) is a non-conventional type of radio-chemotherapy that has been used to target a number of cancers, although predominantly brain tumours (gliomas). We report the co-spray-drying of *o*-carborane, as a model BNCT agent, with poly(vinylpyrrolidone) (PVP), a water-soluble polymer, to produce microparticle powders of high boron-content for BNCT treatment of liver and lung cancers. The powders have been characterised using NMR, particle sizing, electron microscopy and cytotoxicity tests. ^{1}H NMR indicated the high temperatures (180 °C) of the spray drying process did not degrade the PVP. Mean particle diameters (x_{90}) were in the 2–10 μm range, with finer fractions being present (x_{10} ≅ 1–2 μm), and were therefore considered suitable size for delivery to the lungs. SEM imaging showed particles to be spherical, with dimples and cavities, caused by the spray drier nozzle characteristics, and similarly sized irregularly-shaped crystalline particles, thought to be *o*-carborane. Boron chemical mapping was attempted using EDS, although the low atomic weight of boron did not allow this to be possible. Cytotoxicity studies, using neoplastic (human glioblastoma U-87 MG) and non-neoplastic (human fetal lung fibroblast MRC-5) cells, revealed the PVP/*o*-carborane co-spray-dried particles to be non-toxic, as expected.

Introduction

Boron neutron capture therapy (BNCT) is a non-conventional radio-chemotherapy technique that provides a way of selectively destroying malignant cells, sparing surrounding normal cells [1-3]. Boron (^{10}B) has a large neutron capture cross-section and when the element is irradiated with low-energy (thermal) neutrons, a nuclear fission reaction occurs to yield high linear energy transfer (LET) α-particles (1.47 MeV) and recoiling ^{7}Li nuclei (0.84 MeV), with only low energy γ emission (478 keV) [4,5]. The penetration of α-particles and ^{7}Li$^+$ into surrounding tissues is only 8 and 5 μm, respectively, and so the highly-ionising energy dose is confined to the original ^{10}B-containing cell or at least to the adjacent cells. Since the collateral damage is very low, this in principle, allows for a particularly targeted therapy. For this to occur, a sufficient quantity of ^{10}B must be selectively localised into the cancer cells, and a sufficient dose of thermal neutrons aimed at the ^{10}B-containing cancer cells (*ca.* 20–30 μg ^{10}B/g tumour) [4,6].

BNCT has been mainly focused on treatment of brain tumours (gliomas), predominately for the historical reasons of low-energy thermal neutron beams having low penetration through tissues [7]. Other cancers, however, are increasingly being investigated, such as head and neck, lung and liver cancers [1,8-12]. Also, non-malignant diseases, such as rheumatoid arthritis, are useful in BNCT treatment [13]. The high number of lung cancer incidences (1.6 million diagnoses *pa*) [14], prompt a wide-spectrum use of BNCT for this cancer type [15]. Diffuse, non-resectable tumours in the lung seem particularly attractive targets for BNCT [8], as does hepatocellular carcinoma, which has poor effective treatments and prognosis unless diagnosed at an early stage [10].

Carboranes, caged polyhedral molecules based on boron, exhibit high molar boron content, neutral charge and good stability and are therefore ideal candidate molecules for use in BNCT [5,6,16,17]. These molecules are highly hydrophobic [18], although can be chemically modified [19,20], exist in different forms (*ortho- 'o-'*, *meta-* 'm-' or *para 'p-'*) [18] and are biocompatible [21].

Spray drying is a convenient, attractive, one-step method of producing particles (typically, 1–10 μm dia.) from a liquid feed [22-24]. The technique can be used to microencapsulate active drugs/particles within a carrier (excipient) [22-26] and therefore might be effective in producing carriers to transport BNCT agents to cancers, such as those of the liver or lung; treatment of gliomas

would require penetration through the blood-brain-barrier and therefore spray-dried particles would not be suitable owing to their large diameters [27]. In the case of liver cancer BNCT treatments, such formulations might be delivered orally or *via* injection since they are likely to end up in this organ. For lung cancer, delivery could be administered *via* metered-dose inhaler or dry powder inhaler (DPI) systems. Control of particle size, density and morphology can be achieved by varying spray drying operating conditions, such as air flow rate, inlet temperature, pump speed and feed concentration [22,23,28]. This is particularly useful for making DPI particulates [29,30], where the particle size broadly determines the locations within the airway the dispersed powders will be deposited [29,31]. For example, the smallest particles will end up in the alveoli, slightly larger ones will reach the bronchioles and the largest particles will only travel as far as the trachea.

In this paper, *o*-carborane (an underivatised, model BNCT agent) has been co-spray dried with poly(vinylpyrrolidone) (PVP, povidone), a water-soluble polymer that is effective as a drug delivery vehicle for dispersions of microparticles [32-35], to produce powders that could be further investigated for use as BNCT treatments for liver and lung cancers. Powders were characterised using NMR, particle sizing, electron microscopy and cytotoxicity tests.

Experimental

Materials

PVP (MW 360,000 g mol^{-1}) was purchased from Sigma-Aldrich (Dorset, UK); *o*-carborane and di-sodium tetraborate ($Na_2B_4O_7.10H_2O$) were obtained from Alfa Aesar, UK and ThermoFisher Scientific (Loughborough, UK), respectively. Distilled water (MilliQ, Merck Millipore, Billerica, MA, USA) was used to prepare PVP/*o*-carborane solutions to be spray-dried. The cell culture reagents trypsin, Dulbecco's Modified Eagle's Medium (DMEM), Fetal Bovine Serum (FBS) and Penicillin-Streptomycin (PS) were obtained from Gibco (ThermoFisher Scientific).

Methods

Spray drying

Aqueous solutions of PVP (1 and 2 %w/v) with and without *o*-carborane (0.2 %w/v) were prepared (100 mL, 50 mL for *o*-carborane containing solutions) for spray drying (Table 1). Solutions were agitated (3000 rpm, electronic mini shaker) until all solids had dissolved (*ca.* 1 h) and left overnight (16 h). Spray drying was performed using a Buchi B-290 spray drier (Buchi, Manchester, UK) using high inlet temperature (180 ^oC) and low outlet temperature (130 ^oC, recorded not controlled) conditions; other spray drying conditions were kept constant (air flow rate 52 mm, aspirator 100%, pump speed 10 %, nozzle cleaner setting 3). After spray drying, % recovery for each run was calculated and the powders stored in vials in a desiccator.

NMR

^1H NMR spectra were obtained using a JEOL Eclipse+ 400 MHz NMR instrument (Oxford Instruments, Oxford, UK), operating at a field strength of 9.389766 T. PVP and *o*-carborane samples were dissolved in either $CDCl_3$ or CH_3OD.

Particle sizing

Particle sizing was performed on the spray-dried powder PVP and PVP/*o*-carborane samples. The powders were dispersed using compressed air (2 bar) *via* the RODOS dry powder dispenser (RODOS, Sympatec GmbH Germany) prior to sizing analysis with a Sympatec HELOS laser diffractometer (HELOS Sympatec). The particle size distribution was recorded as x_{10}, x_{50} and x_{90} values using WINDOW 4.0 software (Sympatec). The values presented were the mean of triplicate runs. Statistical analysis was performed using IBM Statistics SPSS (Version 21; Armonk, NY, USA) using a one-way ANOVA and post-hoc analysis (Tukey test).

SEM and EDS

Dry powders were sprinkled onto double-sided, carbon-loaded disks attached to nickel SEM stubs. Excess powder was removed using a N_2 stream and the samples were then sputter-coated with Au/Pd in an Argon atmosphere (<0.2 Torr, 18 mA for 5–10 min; Polaron E5000 SEM coating-unit, Quorum Technologies Ltd., East Grinstead, UK). SEM imaging was performed immediately using a JEOL JSM-6060LV SEM instrument (resolution = 4.5 nm, acceleration voltage=15 kV). EDS (Inca Oental FET×3 with high-angle, ultra-thin window Si(Li) detector; Oxford Instruments) analysis was also undertaken on some of the samples investigated by SEM. A spot size of 60 and a working distance of 11 was used for EDS.

Tissue culture and cytotoxicity studies

Human glioblastoma U-87 MG (cancer cell line) and human fetal lung fibroblast MRC-5 (normal cell line) cells were grown in culture at 37 ^oC in DMEM, supplemented with FBS (10 %v/v), penicillin (100 μg/mL), streptomycin (100 μg/mL) in a humidified atmosphere containing CO_2 (5 %v/v). The medium was changed every 2–3 days and cells were sub-cultured by trypsinisation before reaching ~80 % confluency in tissue culture flasks.

The effect of PVP/*o*-carborane materials (#2, #8 and #11; Table 1) on U-87 MG and MRC-5 cell proliferation capacity and viability was assessed *in vitro*. These samples were diluted in DMEM and homogenised prior to their addition in cell cultures. Briefly, cells at an initial

density of 10^5 cells/mL were seeded in a 24-well tissue culture plate. After 2 h following cell attachment to the substrate of the plate, material suspensions were added at various concentrations (0.1, 0.5 and/or 1.0 mg/mL) before cells were allowed to further grow for 48 h. At this point, cells were detached by trypsinisation and the cell density (number of cells/mL) determined using a Neubauer plate (cell counting plate). Cell proliferation was expressed as % cell growth compared to control-untreated cell cultures. Cellular death was also assessed using the trypan-blue dye exclusion method and reported as cell viability (% trypan blue negative cells in culture) [36]. The data presented were calculated based on at least four separate measurements from two biological replicate experiments.

Table 1. Samples for spray drying and instrument inlet temperature settings

Sample number	Product	w/v % PVP	w/v% *o*-carborane	Inlet temp. °C
#1	PVP	2	0	180
#2	PVP	2	0	180
#3	PVP	2	0	180
#4	PVP	2	0	180
#5	PVP	2	0	130
#6	PVP	2	0	130
#7	PVP	2	0	130
#8	PVP	1	0	180
#9	PVP	1	0	180
#10	PVP	1	0	180
#11	PVP + *o*-carborane	2	0.2	180
#12	PVP + *o*-carborane	2	0.2	180
#13	PVP + *o*-carborane	2	0.2	180

Results and Discussion

Spray Drying

Spray drying successfully produced white, fine powdered products of PVP/*o*-carborane (Table 2). Lower % yields (% recoveries) were obtained using 1 w/v% PVP (5.7±3.5 %) than when using 2 w/v% PVP (30.1±1.4 %) and consequently, co-spray-dried formulations using *o*-carborane were carried using the higher PVP concentration; similar %yields were obtained (32.4±9.8 %; all using an inlet temperature of 180 °C). A small decrease in % yield was found when the inlet temperature was decreased from 180 °C (30.1±1.4 %) to 130 °C (23.0±11.0 %; Table 2).

^{1}H NMR of PVP/*o*-carborane

To check that the integrity of PVP had not been compromised during the spray drying process, ^{1}H NMR experiments were performed. The literature spectrum was also obtained and used to help assign peaks [37]. The spectra before and after spray drying, both in the absence of *o*-carborane, looked very similar (Figure 1). The signal corresponding to H_3 appeared slightly differently in that the sharp, single peak within the doublet shifted slightly upfield. This may be associated with hydrogen bonded water, as spray drying is known to produce hygroscopic, very fine amorphous powders. Peaks H_1, H_2, H_4 and H_5 were very similar to those in the literature [37], suggesting the PVP was unaffected by the spray drying process, as might be expected since there have been numerous reports on the spray drying of this material [38-40].

Table 2. %Yields obtained for various spray-dried formulations

Sample number	%Yield	Mean±SD %Yield
#1	31.0	30.1±1.4
#2	28.0	
#3	30.5	
#4	31.0	
#5	20.5	23.0±11.0
#6	35.0	
#7	13.5	
#8	6.0	5.7±3.5
#9	2.0	
#10	9.0	
#11	28.2	32.4±9.8
#12	43.6	
#13	25.5	

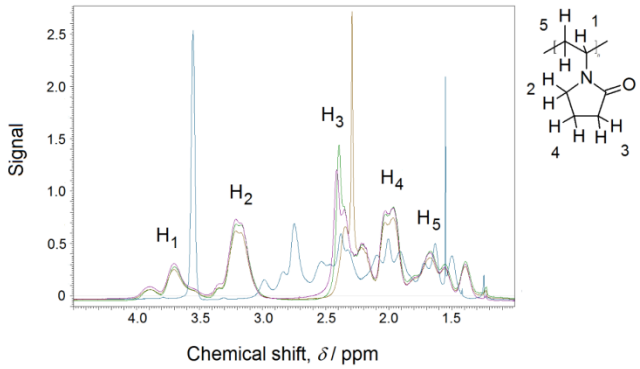

Figure 1. ^{1}H NMR spectra of 'as received' *o*-carborane (blue), 'as received' PVP (green), spray-dried PVP (2 %w/v; brown) and co-spray-dried PVP (2 %w/v) with *o*-carborane (0.2 %w/v; purple). Labels refer to hydrogen atoms in the PVP structure shown, with peak assignments having been made in [37].

^{1}H NMR spectra of co-spray-dried PVP/*o*-carborane and 'as received' *o*-carborane were also obtained to see whether *o*-carborane could be detected in the co-spray-dried powder and, if so, to ascertain whether its chemical structure had been modified (Figure 1). The multitude of peaks observed in the pure *o*-carborane were not apparent in the co-spray-dried product. This was probably due to the high molecular weight of PVP, however, with the

spectrum being swamped with the backbone CH_2 and pendant pyrrolidone signals relative to the *o*-carborane BH and CH signals. Also, *o*-carborane was only present at 10 %w/v of the PVP content. Thus, the ^{1}H NMR data were inconclusive as to whether the *o*-carborane had been incorporated into the microparticles. The technique did establish, however, that PVP was unchanged by the spray-drying process, and particularly by the high temperatures (180 °C) involved.

Particle sizing

Particle diameters for the spray-dried products were obtained from laser diffraction histogram plots (Figure 2). The mean x_{10}, x_{50} and x_{90} particle diameters (n=3) were obtained from these profiles for spray-dried PVP and PVP/*o*-carborane samples (Figure 3). The x_n value refers to the particle diameter exhibited by n % of the particles; *i.e.*, for x_{10}, 10% of the particles will have a diameter $\leq x$. The x_{50} and x_{90} are also given, which have similar definitions, and have progressively larger values since more of the particles will have these particular size thresholds. The 'bell-shaped' curve ('envelope', Figure 2), noting the log-scale axis, can have shoulders on either side of the peak maximum; shoulders on the right of the maximum almost always are an indication of agglomerated particles. Repeating the sizing measurement at higher pressures can reduce this effect.

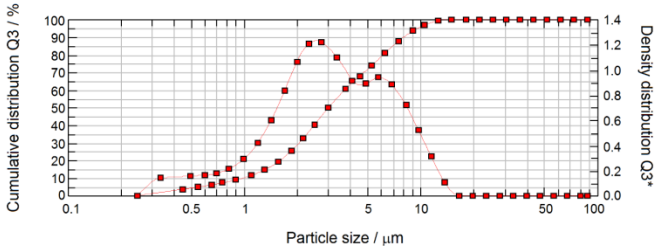

Figure 2. An example Sympatec particle size distribution output plot from sample #1 run 1 of 3; x_{10} = 1.31 µm; x_{50} = 3.47 µm; x_{90} = 8.48 µm; SMD = 2.50 µm; x_{16} = 1.65 µm; x_{84} = 7.15 µm; x_{99} = 13.43 µm; S_V = 2.40 m²/cm³; S_m = 23973.67 cm²/g. Two plots are displayed: a particle diameter frequency plot and a cumulative frequency ('S-shaped') curve of particle size from which median and interquartile range data is automatically generated. In this example, the mean particle diameter is *ca.* 3 µm, although finer particles ('fines') and larger particles, the latter of which may be agglomerates, can be observed.

The x_{90} data shows that mean particle diameters were *ca.* 2–10 µm, although #11 was 17.27±3.77 µm. No statistical differences (p>0.05) were observed between different batches of spray-dried PVP (#1 to #4), in the absence of *o*-carborane, using an inlet temperature of 180 °C. When this temperature was decreased to 130 °C, again, no significant differences (p>0.05) in x_{90} values were observed compared to the higher temperature products, although batch differences were seen between #1 and #7 (p<0.05), and #2 and #7 (p<0.05) only. Statistical differences between x_{90} values were also generally not observed (p>0.05) when the PVP concentration was lowered to 1 %w/v. When PVP was co-spray-dried with *o*-carborane, x_{90} values were unaffected (p>0.05), although for #11, x_{90} values were all much higher (p<0.01 or p<0.001) than all the other samples. The reason for this batch variation is uncertain, but may be due to variations in humidity perhaps causing agglomeration.

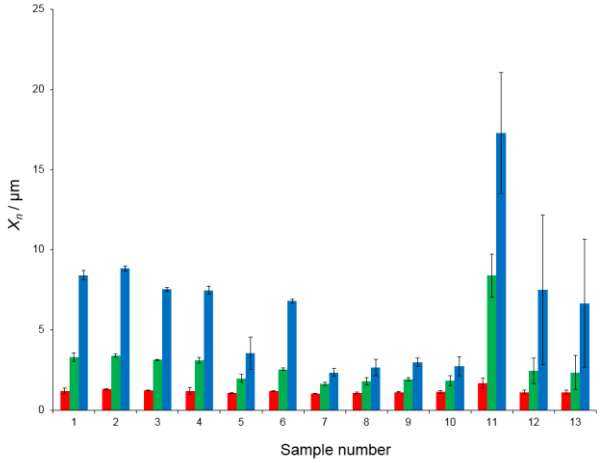

Figure 3. Mean particle diameters of spray-dried PVP and co-spray-dried PVP/*o*-carborane samples: red = x_{10}, green = x_{50}, blue = x_{90} values; particles determined using spray drying (mean ± SD, n = 3).

Particle sizes characterised by x_{50} and x_{10} values followed a very similar trend to the x_{90} values; x_{10} sizes were much less than x_{50} and, in turn, less than x_{90} sizes, due to the definition of the x_n term.

Morphology

The morphology of the spray-dried powders of PVP with and without *o*-carborane was investigated using SEM. Prior to this, imaging of the 'as received' PVP and *o*-carborane was performed (Figure 4). The former consisted of large, smooth-sided crystals with dimensions typically in the 100–500 µm range (Figure 4a,b). The particles of *o*-carborane appeared smaller, 5–100 µm (Figure 4c,d).

SEM images of spray-dried PVP, produced in the absence of *o*-carborane and using an inlet temperature of 180 °C, all showed small, rounded particles of relatively uniform size (< 5 µm; Figure 4e). Dimples and hollows in the particles were observed and have been encountered in numerous other spray-dried products [22]: they are thought to result from the nozzle characteristics as the emerging droplet is formed [41]. The particle surfaces appeared smooth, although in some cases, smaller particles were attached, possibly being due to inter-particulate forces or capillary forces causing agglomeration. No obvious differences in morphology

were seen between different batches of spray-dried PVP (samples #1 to #4, not shown). No obvious changes in morphology or particle size were observed when the inlet temperature was reduced to 130°C (not shown), in agreement with the particle size data.

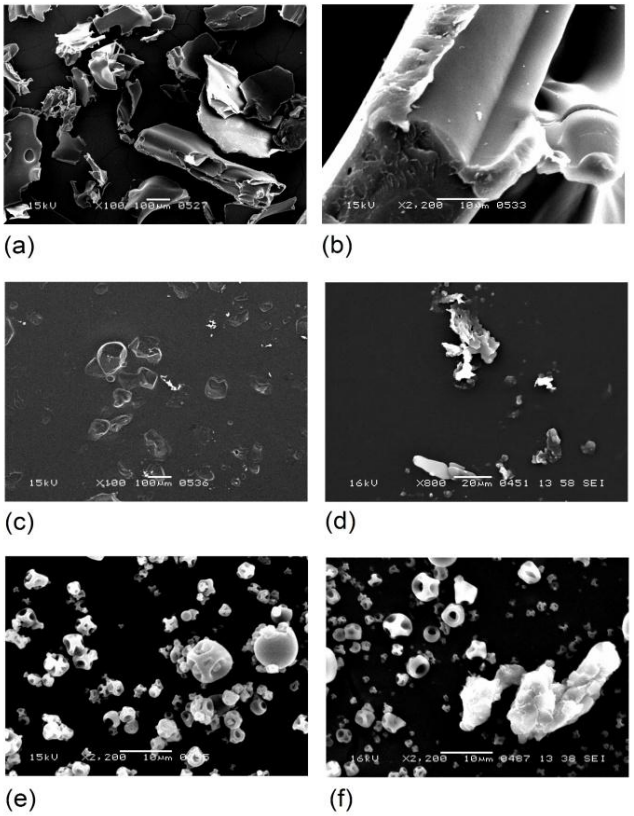

Figure 4. SEM images of (a,b) 'as received' PVP, (c,d) 'as received' *o*-carborane, (e) spray-dried PVP (sample #4, inlet temperature 180 °C), (f) co-spray-dried PVP/*o*-carborane (sample #13, inlet temperature 180 °C); magnification (a) 100×, (b) 2200×, (c) 100×, (d) 800×, (e) 2200×, (f) 2200×.

SEM imaging of PVP co-spray-dried with *o*-carborane (Figure 4f), in agreement with the particle sizing data, generally showed similarly sized particles, although some particles were larger than 10 µm. In some of the SEM images of the co-spray-dried product, small irregularly-shaped crystalline particles were seen, which were not encountered in the pure spray-dried PVP products. These crystals appeared to be similar to those seen in the 'as received' *o*-carborane material (Figure 4d). It may be that the *o*-carborane, which is not water-soluble, although assisted to form suspensions by the viscosity/swelling of the PVP, was largely unchanged by the spray drying process. A less-magnified image of the PVP/*o*-carborane spray-dried product revealed there to be a significant number of such small crystals, thought to be *o*-carborane; these were not apparent in similar images of pure spray-dried PVP (not shown). The extent of this phase separation is unknown. To address this situation, EDS mapping was attempted. The assumption was that if the PVP was intimately mixed with *o*-carborane, a boron chemical map would appear very similar to the SEM image. However, the boron signal was quite low and darker depressions marked regions where the particles resided, suggesting that the boron content was less than on the double-sided, adhesive, carbon tape. It is known that elements with atomic masses below carbon are often not shown in EDS studies and therefore this might explain the absence of boron in the EDS map of the co-spray-dried particles. This was verified by attempting to obtain boron maps from di-sodium tetraborate, where again, no contrast was observed from the low atomic mass element.

Cytotoxicity studies

To check for cytotoxicity, the spray-dried powders (PVP #2 and #8, and PVP/*o*-carborane #11) were exposed to neoplastic (human glioblastoma U-87 MG) and non-neoplastic (human fetal lung fibroblast MRC-5) cells. Cell proliferation and cell death were determined over a range of PVP/*o*-carborane concentrations (0–1.0 mg/mL; Figure 5). In all cases, cell proliferation did not fall below 87% and values were otherwise greater than 90%. Similarly, the highest cell death value was only 2.5%. No obvious change in cellular morphology, cell proliferation or cell death was noted over the duration of the experiment (48 h). Therefore, the PVP/*o*-carborane co-spray-dried product was described as being non-cytotoxic at the concentrations investigated. This is in agreement with the known low toxicity data of the constituent PVP [42,43] and *o*-carborane [44] compounds.

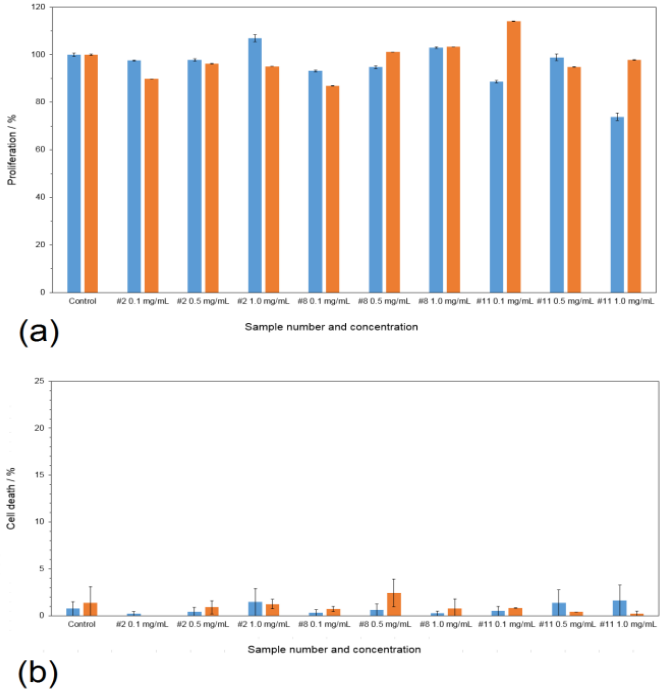

Figure 5. Effect of spray-dried PVP (samples #2 and #8) and co-spray-dried PVP/*o*-carborane (sample #11) on (a) cell proliferation and (b) cell death; blue = U-87 MG cells, orange = MRC-5 cells.

Conclusions

In this paper, PVP (2 %w/v)/*o*-carborane (0.2 %w/v) spray-dried microparticles were produced with the aim providing a boron-delivery system for use in BNCT treatment of liver and lung cancers. ^{1}H NMR studies revealed the high temperatures (180 °C) of the spray drying process did not degrade the constituent PVP. Mean particle diameters (x_{90}) were in the 2–10 μm range, with finer fractions being present ($x_{10} \cong$ 1–2 μm), and the particles were therefore considered suitable for delivery to the lungs. The particle sizes were in the micrometre range (too large to cross the blood-brain-barrier) and therefore would not be of use for the BCNT treatment of brain tumours. Further optimisation of particle sizes could be carried out to decrease x_{90}, for example, by changing air and liquid flow conditions. SEM imaging showed the particles to be spherical, with dimples and cavities caused by the spray drier nozzle characteristics, as typical with the spray drying process. Some small irregularly-shaped crystalline particles, thought to be *o*-carborane, were observed by SEM, although the proportion accounted for less than that in the formulation (10 %w/w). An attempt was made to map the boron content in spray-dried powders on a surface using EDS, although the low atomic weight of boron made detection not possible. Cytotoxicity studies, using neoplastic (human glioblastoma U-87 MG) and non-neoplastic (human fetal lung fibroblast MRC-5) cells, revealed the PVP/*o*-carborane co-spray-dried particles to be non-toxic, as expected.

References

1. Moss RL: Critical review, with an optimistic outlook, on boron neutron capture therapy (BNCT). Applied Radiation and Isotopes 2014; 88:2-11.
2. Locher GL: Biological effects and therapeutic possibilities of neutrons. The American Journal of Roentgenology and Radium Therapy 1936; 36(1):1-13.
3. Masoudi SF, Rasouli FS and Ghasemi M: BNCT of skin tumors using the high-energy D-T neutrons.Applied Radiation and Isotopes 2017; 122:158-163.
4. Barth RF, Coderre JA, Vicente MGH and Blue TE: Boron neutron capture therapy of cancer:Current status and future prospects. Clinical Cancer Research 2005; 11(11):3987-4002.
5. Hosmane NS, Yinghuai Z, Maguire JA, Kaim W and Takagaki M: Nano and dendritic structured carboranes and metallacarboranes: From materials to cancer therapy. Journal of Organometallic Chemistry 2009; 694(11):1690-1697.
6. Hawthorne MF: New horizons for therapy based on the boron neutron capture reaction. Molecular Medicine Today 1998; 4(4):174-181.
7. Andoh T, Fujimoto T, Suzuki M, Sudo T, Sakurai Y, Tanaka H, Fujita I, Fukase N, Moritake H, Sugimoto T, Sakuma T, Sasai H, Kawamoto T, Kirihata M, Fukumori Y, Akisue T, Ono K and Ichikawa H: Boron neutron capture therapy (BNCT) as a new approach for clear cell sarcoma (CCS) treatment: Trial using a lung metastasis model of CCS.Applied Radiation and Isotopes 2015; 106:195-201.
8. Trivillin VA, Garabalino MA, Colombo LL, Gonzalez SJ, Farias RO, Monti Hughes A, Pozzi ECC, Bortolussi S, Altieri S, Itoiz ME, Aromando RF, Nigg DW and Schwint AE: Biodistribution of the boron carriers boronophenylalanine (BPA) and/or decahydrodecaborate (GB-10) for boron neutron capture therapy (BNCT) in an experiment model of lung metastases.Applied Radiation and Isotopes 2014; 88:94-98.
9. Andoh T, Fujimoto T, Suzuki M, Sudo T, Sakurai Y, Tanaka H, Fujita I, Fukase N, Moritake H, Sugimoto T, Sakuma T, Sasai H, Kawamoto T, Kirihata M, Fukumori Y, Akisue T, Ono K and Ichikawa H: Boron neutron capture therapy (BNCT) as a new approach for clear cell sarcoma (CCS) treatment: Trial using a lung metastasis model of CCS. Applied Radiation and Isotopes 2015; 106:195-201.
10. Chou FI, Chung HP, Liu HM, Chi CW and Lui WY: Suitability of boron carriers for BNCT: Accumulation of boron in malignant and normal liver cells after treatment with BPA, BSH and BA. Applied Radiation and Isotopes 2009; 67:S105-S108.
11. Liao AH, Chou FI, Kuo YC, Chen HW, Kai JJ, Chang CW, Chen FD and Hwang JJ: Biodistribution of phenylboric acid derivative entrapped lipiodol and 4-borono-2-18F-fluoro-L-phenylalanine-fructose in GP7TB liver tumor bearing rats for BNCT. Applied Radiation and Isotopes 2010; 68:422-426.
12. Zonta A, Pinelli T, Prati U, Roveda L, Ferrari C, Clerici AM, Zonta C, Mazzini G, Dionigi P, Altieri S, Bortolussi S, Bruschi P and Fossati F: Extracorporeal liver BNCT for the treatment of diffuse metastases: What was learned and what is still to be learned. Applied Radiation and Isotopes 2009; 67:S67-S75.
13. Valliant JF, Schaffer P, Britten JF, Davison A, Jones AG and Yanch JC: The synthesis of corticosteroid-carborane esters for the treatment of rheumatoid arthritis via boron neutron captures synovectomy. Tetrahedron Letters 2000; 41(9):1355-1358.
14. Tsao AS, Scagliotti GV, Bunn PA Jr, Carbone DP, Warren GW, Bai C, de Koning HJ, Yousaf-Khan AU, McWilliams A, Tsao MS, Adusumilli PS, Rami-Porta R, Asamura H, Van Schil PE, Darling GE, Ramalingam SS, Gomez DR, Rosenzweig KE, Zimmermann S, Peters S, Ignatius Ou SH, Reungwetwattana T, Jänne PA, Mok TS, Wakelee HA, Pirker R, Mazières J, Brahmer JR, Zhou Y, Herbst RS, Papadimitrakopoulou VA, Redman MW, Wynes MW, Gandara DR, Kelly RJ, Hirsch FR and Pass HI: Scientific Advances in Lung Cancer. Journal of Thoracic Oncology 2015; 11(5):613-638.
15. Farias RO, Bortolussi S, Menendez PR and Gonzalez SJ: Exploring boron neutron capture therapy for non-small cell lung cancer. Physica Medica 2014; 30(8):888-897.
16. Kawasaki R, Sasaki Y and Akiyoshi K: Intracellular delivery and passive tumor targeting of a self-assembled nanogel containing carborane clusters for boron neutron capture therapy. Biochemical and Biophysical Research Communications 2017; 483(1):147-152.
17. Calabrese G, Nesnas JJ, Barbu E, Fatouros D and Tsibouklis J: The formulation of polyhedral boranes for the boron neutron capture therapy of cancer. Drug Discovery Today 2012; 17(3/4):153-159.
18. Ohta K, Goto T, Fujii S, Kawahata M, Oda A, Ohta S, Yamaguchi K, Hirono S and Endo Y: Crystal structure, docking study and structure-activity relationship of carborane-containing androgen receptor antagonist 3-(12-hydroxymethyl-1,12-dicarba-closo-dodecaboran-1yl)benzonitrile. Bioorganic and Medicinal Chemistry 2011; 19(11):3540-3548.
19. Anderson BD: Prodrugs for improved CNS delivery. Advanced Drug Delivery Reviews 1996; 19(2):171-202.
20. Hoste K, De Winne K and Schacht E: Polymeric prodrugs. International Journal of Pharmaceutics 2004; 277(1-2):119-131.
21. Di Meo C, Panza L, Campo F, Capitani D, Mannina L, Banzato A, Rondina M, Rosato A and Crescenzi V: Novel types of carborane-carrier hyaluronan derivatives via “click chemistry”. Macromolecular Bioscience 2008; 8(7):670-681.
22. Shur J, Nevell TG, Shute JK and Smith JR: The spray drying of unfractionated heparin: optimisation of the operating parameters. Drug Development and Industrial Pharmacy 2008; 34(6):559-568.
23. Shur J, Nevell TG, Ewen RJ, Price R, Smith A, Barbu E, Conway JH, Carroll MP, Shute JK and Smith JR: Co-spray-dried unfractionated heparin with L-leucine as a dry powder inhaler mucolytic for cystic fibrosis therapy. Journal of Pharmaceutical Sciences 2008; 97(11):4857-4868.
24. Okuyama K, Abdullah M, Lenggoro IW and Iskandar F: Preparation of functional nanostructured particles by spray drying. Advanced Powder Technology 2006; 17(6):587-611.
25. Desai KGH and Jin Park H: Recent developments in microencapsulation of food ingredients. Drying Technology 2005; 23(7):1361-1394.
26. Gharsallaoui A, Roudaut G, Chambin O, Voilley A and Saurel R: Applications of spray-drying in microencapsulation of food ingredients: An overview. Food Research International 2007; 40(9):1107-1121.
27. Pardridge WM: Non-invasive drug delivery to the human brain using endogenous blood-brain-barrier transport systems. Pharmaceutical Science and Technology Today 1999; 2(2):49-59.
28. Rattes ALR and Oliveira WP: Spray drying conditions and encapsulating composition effects on formation and properties of sodium diclofenac microparticles. Powder Technology 2007; 171(1):7-14.

29. Pilcer G and Amighi K: Formulation strategy and use of excipients in pulmonary drug delivery. International Journal of Pharmaceutics 2010; 392(1):1-19.
30. Anderson PJ: Delivery options and devices for aerosolized therapeutics. Chest Journal 2001; 120(3 suppl):89S-93S.
31. Steckel H and Brandes HG: A novel spray-drying technique to produce low density particles for pulmonary delivery. International Journal of Pharmaceutics 2004; 278(1):187-195.
32. Kanaze FI, Kokkalou E, Niopas I, Georgarakis M, Stergiou A and Bikiaris D: Dissolution enhancement of flavonoids by solid dispersion in PVP and PEG matrixes: A comparative study. Journal of Applied Polymer Science 2006; 102(1):460-471.
33. Papageorgiou GZ, Bikiaris D, Kanaze FI, Karavas E, Stergiou A and Georgarakis E: Tailoring the release rates of fluconazole using solid dispersions in polymer blends. Drug Development and Industrial Pharmacy 2008; 34(3):336-346.
34. Fischer F and Bauer S: Polyvinylpyrrolidon. Ein Tausendsassa in der Chemie, Chemie in unserer Zeit 2009; 43(6):376-383.
35. Gohel M, Patel M, Amin A, Agrawal R, Dave R and Bariya N: Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS PharmSciTech 2004; 5(3):10-15.
36. Vizirianakis IS and Tsiftsoglou AS: Blockade of murine erythroleukemia cell differentiation by hypomethylating agents causes accumulation of discrete small poly(A)-RNAs hybridized to 3'-end flanking sequences of β major globin gene. Biochimica et Biophysica Acta 2005; 1743(1-2):101-114.
37. Luan YX, Song AX and Xu GY: Location of probe molecule in double-chain surfactant aggregates in absence and presence of water-soluble polymer by NMR. Soft Matter 2009; 5(13):2587-2595.
38. Mahlin D, Berggren J, Gelius U, Engstrom S and Alderborn G: The influence of PVP incorporation on moisture-induced surface crystallization of amorphous spray-dried lactose particles. International Journal of Pharmaceutics 2006; 321(1-2):78-85.
39. Kim MJ, Lee JH, Yoon H, Kim SJ, Jeon DY, Jang JE, Lee D and Khang G: Preparation, characterization and in vitro dissolution of aceclofenac-loaded PVP solid dispersions prepared by spray drying or rotary evaporation method. Journal of Pharmaceutical Investigation 2013; 43(2):107-113.
40. Yuan XD, Sperger D and Munson EJ: Investigating miscibility and molecular mobility of nifedipine-PVP amorphous solid dispersions using solid-state NMR spectroscopy. Molecular Pharmaceutics 2014; 11(1):329-337.
41. Masters K: Spray Drying Handbook, 1985, New York, Longman Scientific & Technical.
42. Bourlinos AB, Georgakilas V, Zboril R, Steriotis TA, Stubos AK and Trapalis C: Aqueous-phase exfoliation of graphite in the presence of polyvinylpyrrolidone for the production of water-soluble graphenes. Solid State Communications 2009; 149(47-48):2172-2176.
43. Liu Q, Zhu X, Huo ZH, He XL, Liang Y, Xu MT: Electrochemical detection of dopamine in the presence of ascorbic acid using PVP/graphene modified electrodes. Talanta 2012; 97:557-562.
44. Theodoropoulos D, Rova A, Smith JR, Barbu E, Calabrese G, Vizirianakis IS, Tsibouklis J and Fatouros DG: Towards boron neutron capture therapy: The formulation and preliminary in vitro evaluation of liposomal vehicles for the therapeutic delivery of the dequalinium salt of bis-nido-carborane. Bioorganic and Medicinal Chemistry Letters 2013; 23(22):6161-6166.