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Synthesis, structural characterization, cytotoxicity and encapsulation studies of *N*,*N*′-(1, 2-dicyano-1,2-vinylene)-*bis*(4-hydroxysalicylideneaminato) di(*p*-chlorobenzyl)tin as potential anticancer drug

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Abstract: Two new diorganotin(IV) complexes with the general formula $(RC_7H_6)_2Sn(L)$ (where RC_7H_6 = *p*-ClBn, **C1**; and *p*-FBn, **C2**) were prepared based on the reaction of 2,3-*bis*(4-hydroxysalicylidene-amino)-maleic nitrile (**L**) with substituted dibenzyltin(IV) dichloride. The structures were confirmed by elemental analysis, Fourier transform infrared (FT-IR), proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR). They were tested against several cancer cell lines by using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. **C1**, which was most effective against MCF-7 breast cancer cell line, was further investigated in formulation and encapsulation studies, including drug encapsulation efficiency, particle size, morphology and *in vitro* drug release. An encapsulation of about 90% was achieved with particles of 128 nm average diameter. Field emission scanning electron microscopy (FESEM) confirmed a spherical shape for the encapsulated **C1**. The cumulative drug release over a period of 60 days in phosphate buffered saline (PBS) at pH 7.4 was 75%. Based on these results, the formulated drug has the potential of a slow release drug for cancer chemotherapy.

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1 Introduction

Organotin(IV) complexes have captured the attention of many scientists in the past decade as potential chemotherapeutic agents (Wang et al., 2014; Yao et al., 2017). Studies have indicated milder toxicity behaviour compared to *cis*-platin (Alama et al., 2009). The chemotherapeutic potential of organotin(IV) complexes is due to their apoptosis inducing behaviour and strong interaction with deoxyribonucleic acid (DNA) (Pellerito et al., 2005).

Recently, many researchers and chemists have great interest in structuring organometallic complexes with multidentate ligands (Burt et al., 2014; Yin et al., 2012). The synthesis of such ligands typically binds to the metal ion through phenolic oxygen, imine nitrogen, oxime oxygen or oxime nitrogen. The chelate effect of multidentate ligands with metals makes the compounds more versatile with a wide range of application. The choice of the coordinated ligand is crucial for the biological effects of organotin(IV) complexes in terms of solubility and bioavailability (Fani et al., 2015). The coordinated ligands at the tin atom not only can diminish drawbacks, but also embellish the biochemical activity of organotin(IV) complexes (Kumar et al., 2009). Azomethines on organotin(IV) compounds are considered as privileged ligands due to their remarkable biological properties (Pellerito, 2002) This may be due to the fact that the C=N bond is capable to obstruct enzyme activities (Sirajuddin et al., 2012). Moreover, the azomethine can enhance the antibacterial activity by the influence of structural factors, such as solubility, dipole moment and cell permeability (Li and Shen, 2000). From literature

review, a study on the synthesis and characterization of a new series of diorganotin(IV) dichloride with Schiff based ligand derived from tris(hydroxymethyl)aminomethane has been reported (Lee et al., 2015). All the mixed-ligand complexes have been evaluated with three types of cancer lines, namely HT29 (human colon carcinoma cell line), SKOV-3 (human ovarian cancer cell line) and MCF-7 (hormone-dependent breast carcinoma cell line). Lee and her co-workers have concluded that most of diorganotin(IV) complex were found to have promising anticancer activity.

Even though organotin(IV) complexes have the potential to be a chemotherapeutic drug, they might be non-selective towards the targeted site, leading to severe side effects similar to most cytotoxic anticancer drug. A widespread strategy to reduce these unwanted side effects is the encapsulation of the drug in carriers (Arias, 2008; Hamelers and de Kroon, 2007). Herein, we report the synthesis of diorganotin(IV) complexes with tetradentate ligands containing azomethine linkages and investigations of their potential as anticancer drugs, including a formulation study on vesicular drug delivery.

2 Results and discussion

2.1 Synthesis

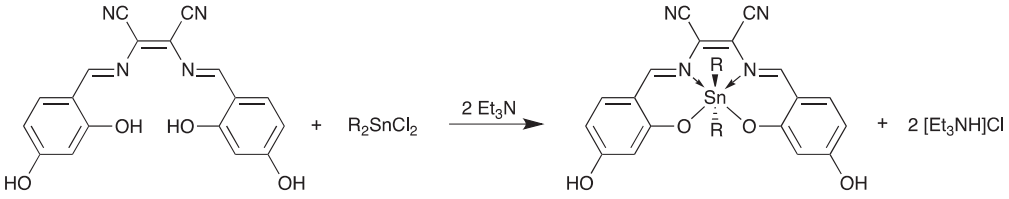
Two new complexes named as *N,N′*-(1,2-dicyano-1,2-vinylene)-*bis*(4-hydroxysalicylideneaminato)di(*p*-chlorobenzyl)tin (**C1**) and *N,N′*-(1,2-dicyano-1,2-vinylene)-*bis*(4-hydroxysalicylideneaminato)di(*p*- fluorobenzyl) tin (**C2**) were prepared by reaction of 2,3-*bis*(4-hydroxysalicylidene-amino)-maleic nitrile (**L**) (Dumur et al., 2014; Tehfe et al., 2013) with substituted dibenzyl tin(IV) dichloride and triethylamine in a molar ratio 1:1:2 in ethanol, as summarized in Scheme 1. The structure and purity of **C1** and **C2** complexes, reflecting corresponding structures to previously reported zinc (Dumur et al., 2014; Meng et al., 2013; Tehfe et al., 2013), aluminium (Hao et al., 2016) and copper(II) complexes (Hao et al., 2015), were confirmed with elemental analysis, IR and NMR spectroscopy.

2.2 Spectroscopic analysis

The strong C=N absorption of the ligand at 1626 cm^{-1} was shifted to lower energy in the complexes, indicating coordination of azomethine nitrogen to the tin metal. The characteristic absorption of the O-H bond in the complexes showed that not all phenolic hydroxyl groups participated in the coordination to the tin metal. Two new bands, at 479-496 cm^{-1} and 536-543 cm^{-1}, were assigned to the Sn-N and Sn-C stretching vibration, supporting the bonding of nitrogen and carbon to the tin atom. These findings are in line with literature reports, which stated Sn-N and Sn-C vibrations in the region 475-495 cm^{-1} and 540-575 cm^{-1}, respectively (Amini et al., 2016; Rehman et al., 2008). The ^{1}H NMR spectrum of complexes showed a new singlet peak at 1.10 and 1.18 ppm, indicative of Sn-CH_2. The ^{13}C NMR signals for the azomethine carbon in the complexes were shifted significantly upfield with respect to the free ligand to appear at 154.1 ppm. In addition, an upfield shift was observed for the carbon carrying the oxygen at the ortho-position, reflecting the tin-binding. A new peak at around 9.0 ppm was attributed to the carbon of Sn-CH_2, which suggested a bonding interaction between the organotin compounds and the ligand. The obtained data were in good agreement with previously reported values (Lee et al., 2015).

2.3 *In vitro* cytotoxic

The results for the *in vitro* cytotoxic are presented in Table 1. Ligands and complexes were screened against breast (MCF-7), lung (A549) and prostate (PC-3) cancer



R= *p*-ClBn (**C1**) and *p*-FBn (**C2**)

Scheme 1: The general scheme for the preparation of the complexes **C1** and **C2**.

Table 1: Anticancer screening result of the ligand and its complexes in comparison with known drugs.

Compound	Cytotoxicity (IC_{50} in µg/mL)		
	A549	PC-3	MCF-7
L	28.1 ± 0.4	5.4 ± 0.1	6.1 ± 0.2
C1	11.1 ± 0.7	18.9 ± 0.9	1.7 ± 0.1
C2	23.2 ± 1.1	2.5 ± 0.1	18.7 ± 0.1
Cis-platin	2.6 ± 0.1	16.9 ± 0.3	9.5 ± 0.3
Cis-platin[a]	3.9	18.3	8.4
PTX[b]	5.3	3.4	5.1

[a] adapted from (Gumulec et al., 2014; Ma et al., 2016; Mroueh et al., 2015)
[b] adapted from (Fang et al., 2011)

cell lines and compared with *cis*-platin as positive control. The experimental IC_{50} for *cis*-platin was in reasonable agreement with the previously published value (Gumulec et al., 2014; Mo et al., 2016; Mroueh et al., 2015). The data indicated **C1** as an effective drug against breast cancer cells, while **C2** was most effective against the prostate cancer cell line. Where, both tin complexes were more effective than *cis*-platin at their most responsive target cells. Interestingly, the reverse application proofed unfavourable, in these cases the sole ligand was more active than the tin complex. Neither **C1** nor **C2** exhibited promising activity against lung cancer. In fact, besides the indicated application fields above, both complexes only demonstrated about ten times lower activities compared to *cis*-platin in lung cancer cell line, thereby indicating the biological activity as highly cell-type specific. The IC_{50} obtained for **C1** for MCF-7 was three times lower than the reported activity of pacilitaxel (PTX), (Fang et al., 2011). It also exceeded the activity of a previously reported monobenzyltin Schiff base complex (2.5 ± 0.5 µg/mL) (Fani et al., 2015). These data demonstrate the potential of **C1** for breast cancer therapy. Therefore, **C1** was further investigated for drug formulation and release studies.

2.4 Percentage encapsulation efficiency

The encapsulation efficiency (%EE) of **C1** based on mixed vesicle (cationic-nonionic surfactant system) and prepared by thin film hydration method was found to be about 90%. This value is relatively high. High %EE can be due to the method of preparation, concentration of the drug in the formulation and the polarity of the drugs. In thin film hydration method, larger surface areas of the film are convenient because they accelerate the hydration process of the bilayer (Kulkarni et al., 1995). As reported in the literature, the highest %EE can be attained when a large surface area of thin film was produced (Amselem et al., 1990). High %EE can also be contributed by the concentration of drug used. Previous studies have demonstrated that %EE of drug was found to increase from 80% up to 96% with increasing concentration of docetaxel (Hammadi et al., 2017). Liu et al. have found that formulation of paclitaxel with different concentration of 1,2-dilauroylphosphatidylocholine (DLPC) used in the nano-emulsification process has affect %EE from 15% (0.01% w/v) up to 56% (0.04% w/v) (Liu et al., 2010). The microencapsulation vesicle method was used to encapsulate 5-fluorouracil, ibuprofen and flurbiprofen. Results show that %EE of non-polar drugs have high compared to polar drugs, the % EE of water-soluble 5-fluorouracil showed 12-15% while lipophilic ibuprofen and flurbiprofen was around 90% (Nii and Ishii, 2005). Therefore, the thin film hydration method, using high concentration of **C1** in the formulation and **C1** as non-polar drug are all the factors contributed to the high %EE of **C1**.

2.5 Particles size distribution

The particle size distribution of the encapsulated **C1** indicated a size of 130 ± 20 nm with 100% intensity. Based on the reviewed literature, the typical particle size for formulations of hydrophobic anticancer drugs, such as paclitaxel (PTX) loaded drug carriers, is below 150 nm (Mo et al., 2016). Previous findings have proved that drug carriers, sized in the range of 100-200 nm, have a good chance to be circulated in the organism for a longer time (Dhand et al., 2014).

2.6 Morphology analysis

The morphology of formulated drug was examined by field emission scanning electron microscopy (FESEM). The FESEM image in Figure 1 indicated a spherical shape for the formulated drug of **C1**. In commercial nanoparticles, shape and surface are the two important elements for efficient drug delivery. From the reported literature, most of the nanoparticles of anticancer drug revealed a fine spherical shape and various degrees of smooth surface (Bandi et al., 2017). Spherical nanoparticles are more favourable because of several factors, which includes the ease of production and also controlling on bio circulation (Mitragotri, 2009).

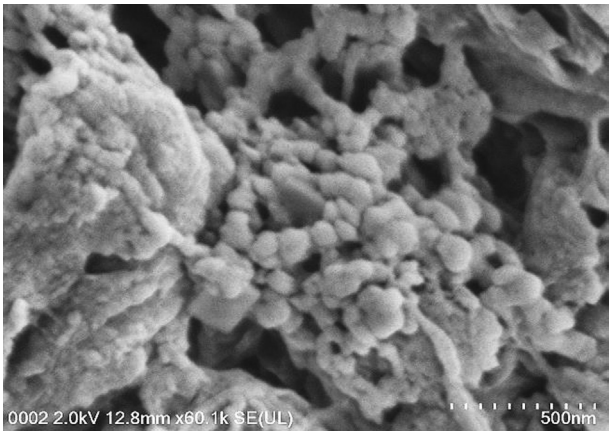


Figure 1: The FESEM image of the encapsulated **C1**.

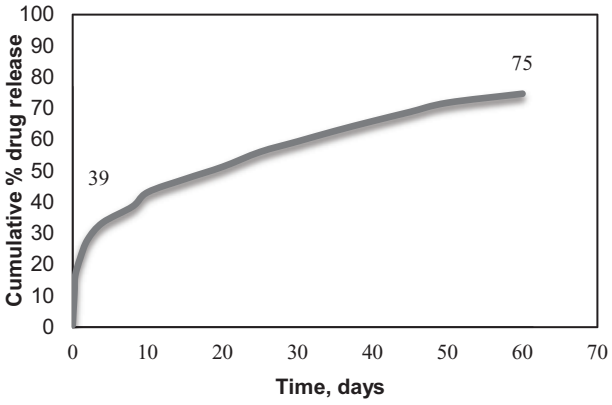


Figure 2: *In vitro* release profile of encapsulated **C1** in 60 days.

2.7 *In vitro* drug release study

The *in vitro* released profile of encapsulated **C1** is displayed in Figure 2. The release of **C1** from the carriers displayed a biphasic release pattern (Hasan et al., 2013). The initial release was about 40% at the end of the 8th day. The early rapid release of hydrophobic drug might be related to adsorbed drug on the surface of the formulation, which is subject to the spontaneous diffusion in the dissolution medium. This process is termed as a burst effect (Allison, 2008). Among drug-based nanoparticles formulations, burst release effect is typically common (Xin et al., 2010). The previous literature also indicates that vesicles formulations containing hydrophobic drugs exhibit similar release patterns (Xu et al., 2007). For another subsequent 50 days, the remaining complex which was captured in the structure was further released in a controlled manner. The amount of percentage cumulative drug release was found to be 75% for 60 days in PBS pH 7.4 as a medium. A recent studied by Martin et al., concluded that paclitaxel incorporated in poly-L-co-D,L-lactic acid (PLDLA) microspheres released 90% of the drug for 30 days period. Thus, the data obtained denote that PLDLA microspheres are promising carriers for paclitaxel (Martins et al., 2014). To sum up, these findings agree with those earlier published in the literature for mixed vesicles which can control the release of drugs (Jiang et al., 2012).

3 Conclusion

Two new complexes have been synthesized by the condensation reaction of 2,3-bis(4-hydroxysalicylideneamino)-maleic nitrile and substituted dibenzyl tin (IV) dichloride in an appropriate molar ratio. The *in vitro* cytotoxic assay revealed the potent effect of **C1** against MCF-7, justifying its selection for the further formulation studies. The complex can be encapsulated in high efficiency in nanosized carriers of spherical shape. The determined cumulative drug release of 75% within 60 days in PBS buffer at pH 7.4 is comparable with commercially known anticancer drug paclitaxel. These results suggest that a vesicular formulation of *N*,*N*′-(1,2-dicyano-1,2-vinylene)-*bis*(4-hydroxysalicylideneaminato) di(p-chlorobenzyl)tin has potential for cancer chemotherapy.

Experimental

The infrared spectra of the compounds were recorded using the ATR technique on a Perkin Elmer System 400 spectrophotometer from 4000 to 450 cm^{-1} at room temperature. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX 400MHz FT-NMR spectrometer in DMSO-*d6* and $CDCl_3$. The data are provided on the δ scale relative to $SiMe_4$. Elemental analyses were carried out on a Thermofischer Scientific FlashSMART CHNS/O analyzer.

Synthesis of ligand, L

Dieter et al. have described the preparation of **L** (Dieter et al., 1983). From the literature, a hot ethanolic solution of 1 mmol of diaminomaleonitrile was added to 2 mmol of 2,4-dihydroxybenzaldehyde. The mixture was refluxed for 2-3 h producing a reddish orange mixture at the end of the reaction. The mixture was filtered and a reddish orange precipitate was obtained upon cooling to room

temperature. The solid product obtained was then recrystallized from methanol.

Synthesis of organotin compounds

Preparation method is based on the literature without modification (Sisido et al., 1961): 3 to 5 drops of water were added to 5 mmol of tin powder and kneaded together. The tin powder was suspended in 50 mL of toluene under efficient stirring and the mixture was heated to about 110°C. Then, 5 mmol of substituted benzyl chloride was dissolved in toluene and added drop wise into the suspension mixture for 3 min while refluxing was continued for an additional 3 h. After that, fine colourless crystals started to appear on the surface of the solution. The mixture was filtered while it was hot. The greyish residue which remained at the bottom of the flask was dissolved, extracted with acetone and filtered. The second filtrate and the solution were evaporated under diminished pressure producing a yellow solid.

Synthesis of diorganotin complexes

1 mmol of **L** and 2 mmol of Et_3N were dissolved in 20 mL of hot ethanolic solution. The solution was refluxed for 1 h 30 min until clear light brown solution was formed. Then, 1 mmol of di(*p*-chlorobenzyl)tin dichloride and di(*p*-fluorobenzyl)tin dichloride to produce **C1** and **C2** respectively was dissolved in 20 mL of ethanol and added in the solution. The mixture was filtered and the filtrate was dried by rotary evaporator to get dark brown powder. The numbering scheme for the NMR assignment was shown in Figure 3.

2,3-bis(4-hydroxysalicylidene-amino)-maleic nitrile (L)

Reddish orange solid, Yield: 2.55 g (78%), m.p: 264°C (dec.). IR (cm^{-1}): 3306 (b, OH), 2239, 2212 (s, C≡N), 1626 (s, C=N), 1196 (s, C-O). ^{1}H NMR (DMSO-*d6*, ppm): 6.28-6.32 (m, 4H, Aryl), 7.47-7.50 (m, 2H, Aryl), 7.73-7.75 (m, 2H, Aryl), 8.39 (s, 2H, CH=N), 9.85 (s, 2H, OH). ^{13}C NMR (DMSO-*d6*, ppm): 113.7 (C1, C1'), 165.6 (C2, C2'), 102.6 (C3, C3'), 163.0 (C4, C4'), 109.1 (C5, C5'), 133.3 (C6, C6'), 163.7 (C7, C7'), 124.7 (C8, C8'), 113.7 (C9, C9').

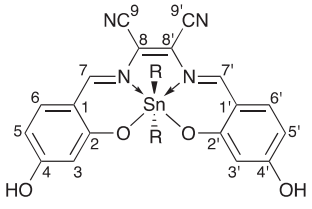


Figure 3: The numbering scheme used for NMR assignment.

N,N'-(1,2-dicyano-1,2-vinylene)*bis*(4-hydroxy-salicylideneaminato)di(*p*-chlorobenzyl)tin (C1)

Dark brown solid, Yield: 0.26 g (37%), m.p: 210-212°C (dec.). Anal. Calc. for $C_{32}H_{22}Cl_2N_4O_4Sn$: C, 53.67; H, 3.10; N, 7.82. Found: C, 53.59; H, 3.39; N, 7.66%. IR (cm^{-1}): 3306 (b, OH), 2239, 2213 (s, C≡N), 1603 (s, C=N), 1210 (s, C-O), 543 (m, Sn-C), 479 (m, Sn-N). ^{1}H NMR (DMSO-*d6*, ppm): 1.10 (s, 4H, Sn-CH_2), 6.24-6.34 (m, 4H, Aryl), 7.38-7.90 (m, 10H, Aryl), 8.10 (s, 2H, CH=N), 9.87 (s, 2H, OH). ^{13}C NMR (DMSO-*d6*, ppm): 9.0 (Sn-CH_2), 113.7 (C1, C1'), 151.5 (C2, C2'), 102.9 (C3, C3'), 160.8 (C4, C4'), 109.2 (C5, C5'), 124.8 (C6, C6'), 154.1 (C7, C7'), 127.8 (C8, C8'), 114.2 (C9, C9'), 129.0, 129.3, 131.0, 131.6, 136.6, 114.8 (R).

N,N'-(1, 2-cyano-1,2-vinylene)*bis*(4-hydroxy-salicylideneaminato)di(*p*-fluorobenzyl)tin (C2)

Reddish brown solid, Yield: 0.64 g (96%), m.p: >360°C (dec.). Anal. Calc. for $C_{32}H_{22}F_2N_4O_4Sn$: C, 56.25; H, 3.25; N, 8.20. Found: C, 56.17; H, 3.64; N, 8.38%. IR (cm^{-1}): 3307 (b, OH), 2241, 2208 (s, C≡N), 1599 (s, C=N), 1210 (s, C-O), 536 (m, Sn-C), 496 (m, Sn-N). ^{1}H NMR (DMSO-*d6*, ppm): 1.18 (s, 4H, Sn-CH_2), 6.32-6.42 (m, 4H, Aryl), 7.09-7.96 (m, 10H, Aryl), 8.27 (s, 2H, CH=N), 9.92 (s, 2H, OH). ^{13}C NMR (DMSO-*d6*, ppm): 9.0 (Sn-CH_2), 115.6 (C1, C1'), 151.5 (C2, C2'), 102.7 (C3, C3'), 163.7 (C4, C4'), 109.2 (C5, C5'), 131.9 (C6, C6'), 154.1 (C7, C7'), 128.9 (C8, C8'), 114.1 (C9, C9'), 130.7, 130.8, 129.0, 129.6, 133.7, 115.4 (R).

Cytotoxicity screening

Ligand, C1 and C2 complexes were screened against several cancer cell lines, breast (MCF-7), lung (A549) and prostate (PC-3) cancer cells. Cells were maintained in basic culture medium, containing 10% FBS and 1% penicillin/streptomycin and 0.5% amphotericin B, and were cultured at 37°C under a humidified atmosphere in a CO_2 incubator. The cells were seeded in a 96-well microtiter plate at a concentration of 7,000 cells per well. After 24 h, the cells were treated with the

samples and incubated for an additional 72 h. DMSO was used to dilute the samples, with the final dilution containing a maximum of 0.5% DMSO. At the end of the incubation period, 20 µL of MTT working solution (5 mg/mL) was added into each well and the 96-well microtiter plate was incubated for another 3 h. After the incubation period is over, the medium was removed completely and replaced with 200 µl DMSO. The plate was stirred using a shaker for 15 min to dissolve any precipitants. The absorbance values were measured at 570 nm, with a reference wavelength of 650 nm on a Multiskan GO UV/Vis microplate spectrophotometer from Thermo Scientific (Waltham, MA, USA) (Mosmann, 1983).

Encapsulation of C1

The vesicles were prepared by thin film hydration methods. The surfactant was prepared by mixing dodecyl trimethylammonium bromide and 2-hexyl-decyl lactoside in ratio 30:70 respectively. Then, **C1** was added to the mixed surfactant with concentration is fixed at 5 mM and the total concentration of the mixed surfactants are 1 mM; the details of the glycolipid surfactant can be found in the literature (Hussen, 2012; Mak et al., 2015). **C1** and the mixed surfactants were dissolved in ethanol and the solvent was subsequently removed on a rotary evaporator, yielding a thin lipid film on the wall of a round bottom flask. The thin film was thoroughly dried to remove any traces of ethanol. Then, the thin film was hydrated in 5 mL of phosphate buffer saline pH 7.4. The hydrated film was further used to investigate related characterization on the formulated drugs.

Percentage encapsulation efficiency (%EE)

The percentage of encapsulation efficiency (%EE) of vesicles was determined by ultracentrifugation. The resulting dispersion was separated by centrifugation at 15000 rpm for 30 min. The absorbance of the supernatant was measured using UV-Vis spectrophotometer at 327 nm as the maximum absorbance in PBS and the pellet was lysed in DMSO and measured at 376 nm. The concentration of **C1** in supernatant and pellet were calculated based on the calibration curves of the **C1** in PBS and DMSO separately. The percentage encapsulation efficiency was calculated with the following formula: %EE = (T - C / T) × 100% where, EE is the encapsulation efficiency of carrier, T is the total amount of drug in the suspension and C is the amount of free drug in the supernatant (Olerile et al., 2017).

Drug release studies

The release of **C1** was measured by applying dialysis tubing method. 5 mL of encapsulated **C1** was sealed in a dialysis bag and suspended in 50 mL of PBS (pH 7.4). The container that contained the dialysis bag was placed in water bath at 37°C. At predetermined time intervals (0 h up to 60 days), 1 mL of the medium was withdrawn and replaced with an equal volume of fresh PBS. The absorbance of C1 was obtained from UV-Vis spectrophotometer at 327 nm and concentration is calculated based on the calibration curve. The result is displayed in cumulative % drug release vs. time.

Visualization of the particle loaded C1

The prepared encapsulated **C1** was centrifuged to separate the non-encapsulated **C1**. Then, the pellet was collected, dried on a membrane and then coated with platinum. Then the sample was loaded into the FESEM chamber and it was subsequently viewed under FESEM. The surface was scanned and photomicrographs were taken at an accelerating voltage of 30 kV.

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References

Alama A., Tasso B., Novelli F., Sparatore F., Organometallic compounds in oncology: Implications of novel organotins as antitumor agents. Drug Discov. Today, 2009, 14, 500-508.

Allison S.D., Analysis of initial burst in PLGA microparticles. Expert Opinion Drug Deliv., 2008, 5, 615-628.

Amini M.M., Najafi E., Karami B., Khavasi H., Synthesis and characterization of a new organotin(IV) complex as a new precursor for preparation SnO_2 nanoparticles. Inorg. Nano-Metal Chem., 2016, 47, 332-339.

Amselem S., Barenholz Y., Gabizon A., Optimization and upscaling of doxorubicin-containing liposomes for clinical use. J. Pharm. Sci., 1990, 79, 1045-1052.

Arias L.L., Novel Strategies to Improve the Anticancer Action of 5-Fluorouracil by Using Drug Delivery Systems. Molecules, 2008, 13, 2340-2369.

Bandi U.M., Philip K., Reddy D.B., Swaroopa A., Prabakaran L., Parthasarathy G., Formulation and *in vitro* characterization of anticancer drug loaded solid lipid nanoparticles. Inter. J. Pharm. Sci. Res., 2017, 8, 3808-3812.

Burt J., Levason W., Reid G., Coordination chemistry of the main group elements with phosphine, arsine and stibine ligands. Coord. Chem. Rev., 2014, 260, 65-115.

Dhand C., Prabhakaran M.P., Beuerman R.W., Lakshminarayanan R., Dwivedi N., Ramakrishna S., Role of size of drug delivery carriers for pulmonary and intravenous administration with emphasis on cancer therapeutics and lung-targeted drug delivery. RSC Adv., 2014, 4, 32673-32689.

Dieter W., Heike B., Hans-Werner R., Polymeric Schiff's base chelates and their precursors, 4[a]. Syntheses of schiff's base chelates from diaminomaleonitrile and investigation of their activity for the valence isomerisation of quadricyclane to norbornadien. Macromol. Chem. Phys., 1983, 184(8), 763-778.

Dumur F., Contal E., Wantz G., Gigmes D., Photoluminescence of Zinc Complexes: Easily Tunable Optical Properties by Variation of the Bridge Between the Imido Groups of Schiff Base Ligands. Eur. J. Inorg. Chem., 2014, 2014, 4186-4198.

Fang W., Liu S., Nie Y., Anticancer activity of chamaejasmine: effect on tubulin protein. Molecules, 2011, 16, 6243-6254.

Fani S., Kamalidehghan B., Lo K.M., Hashim N.M., Chow K.M., Ahmadipour F., Synthesis, structural characterization, and anticancer activity of a monobenzyltin compound against MCF-7 breast cancer cells. Drug Des. Devel. Ther., 2015, 9, 6191-6201.

Gumulec J., Balvan J., Sztalmachova M., Raudenska M., Dvorakova V., Knopfova L., et al., Cisplatin-resistant prostate cancer model: differences in antioxidant system, apoptosis and cell cycle. Inter. J. Oncol., 2014, 44, 923-933.

Hamelers I.H., de Kroon A.L., Nanocapsules: a novel lipid formulation platform for platinum-based anti-cancer drugs. J. Liposome Res., 2007, 17(3-4), 183-189.

Hammadi N.I., Abba Y., Hezmee M.N.M., Razak I.S.A., Jaji A.Z., Isa T., et al., Formulation of a sustained release docetaxel loaded cockle shell-derived calcium carbonate nanoparticles against breast cancer. Pharm. Res., 2017, 34, 1193-1203.

Hasan A.A., Madkor H., Wageh S., Formulation and evaluation of metformin hydrochloride-loaded niosomes as controlled release drug delivery system. Drug Deliv., 2013, 20, 120-126.

Hao L., Qiu Q., Wang W., Gu L., Li H., Fluorescent Detection of Trace Water in Methanol Based on an Al(III) Chemical Sensor. Chin. J. Chem., 2016, 34, 1109-1113.

Hao L., Zhang T., Chang G., Li H., Fluorescent Recognition of Small Organic Molecules Based on Supramolecular Aggregation/Deaggregation of Planar Cu(II) Coordination Complex. Chin. J. Chem., 2015, 33, 425-430.

Hussen R.S.D., Niosomes from chain-branched glycolipids for drug delivery. Synthesis, formulation and evaluation. Lambert Academic Publishing, Latvia, 2012.

Jiang Y., Li F., Luan Y., Cao W., Ji X., Zhao L., et al., Formation of drug/surfactant catanionic vesicles and their application in sustained drug release. Inter. J. Pharm., 2012, 436, 806-814.

Kulkarni S.B., Betageri G.V., Singh M., Factors affecting microencapsulation of drugs in liposomes. J. Microencap., 1995, 12, 229-246.

Kumar S., Dhar D.N., Saxena P.N., Applications of metal complexes of Schiff bases. J. Sci. Ind. Res., 2009, 68(3), 181-187.

Lee S.M., Sim K.S., Lo K.M., Synthesis, characterization and biological studies of diorganotin(IV) complexes with tris[(hydroxymethyl) aminomethane] Schiff bases. Inorg. Chim. Acta., 2015, 429, 195-208.

Li G.J., Shen J.R., A study of pyridinium-type functional polymers. IV. Behavioral features of the antibacterial activity of insoluble pyridinium-type polymers. J. Appl. Polym. Sci., 2000, 78(3), 676-684.

Liu Y., Pan J., Feng S.S., Nanoparticles of lipid monolayer shell and biodegradable polymer core for controlled release of paclitaxel: effects of surfactants on particles size, characteristics and *in vitro* performance. Inter. J. Pharm., 2010, 395, 243-250.

Ma J., Wang Q., Yang X., Hao W., Huang Z., Zhang J., et al., Glycosylated platinum(IV) prodrugs demonstrated significant therapeutic efficacy in cancer cells and minimized side-effects. Dalton Trans., 2016, 45, 11830-11838.

Mak O.W., Seman N., Harun N.H., Hussen R.S.D., Rodzi N.M., Heidelberg T., Nanovesicles based on mixtures of a biantennary-glycolipidwith ionic co-surfactants. J. Surfactants Deterg., 2015, 18, 973-980.

Martins K.F., Messias A.D., Leite F.L., Duek E.A.R., Preparation and characterization of paclitaxel-loaded PLDLA microspheres. Mater. Res., 2014, 17, 650-656.

Meng Q.-H., Zhou P., Song F., Wang Y.-B., Liu G.-L., Li H., Controlled fluorescent properties of Zn(II) salen-type complex based on ligand design. Cryst. Eng. Comm., 2013, 15, 2786-2790.

Mitragotri S., In drug delivery, shape does matter. Pharm. Res., 2009, 26, 232-234.

Mo J., Eggers P.K., Yuan Z.X., Raston C.L., Lim L.Y., Paclitaxel-loaded phosphonated calixarene nanovesicles as a modular drug delivery platform. Sci. Rep., 2016, 6, 23489.

Mosmann T., Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J. Immunol. Methods, 1983, 65(1-2), 55-63.

Mroueh M., Daher C., Hariri E., Demirdjian S., Isber S., Choi E.S., et al., Magnetic property, DFT calculation, and biological activity of bis[(mu(2)-chloro)chloro(1,10-phenanthroline)copper(II)] complex. Chem.-Biol. Interact., 2015, 231, 53-60.

Nii T., Ishii F., Encapsulation efficiency of water-soluble and insoluble drugs in liposomes prepared by the microencapsulation vesicle method. Intern. J. Pharm., 2005, 298, 198-205.

Olerile L.D., Liu Y., Zhang B., Wang T., Mu S., Zhang J., et al., Near-infrared mediated quantum dots and paclitaxel co-loaded nanostructured lipid carriers for cancer theragnostic. Colloid. Surface. B, 2017, 150, 121-130.

Pellerito C., D'Agati P., Fiore T., Mansueto C., Mansueto V., Stocco G., et al., Synthesis, structural investigations on organotin(IV) chlorin-e6 complexes, their effect on sea urchin embryonic development and induced apoptosis. J. Inorg. Biochem., 2005, 99, 1294-1305.

Pellerito L., Organotin(IV)$^{n+}$ complexes formed with biologically active ligands: equilibrium and structural studies, and some

biological aspects. Coord. Chem. Rev., 2002, 224(1-2), 111-150.

Rehman W., Baloch M.K., Badshah A., Synthesis, spectral characterization and bio-analysis of some organotin(IV) complexes. Eur. J. Med. Chem., 2008, 43, 2380-2385.

Sirajuddin M., Ali S., Haider A., Shah N.A., Shah A., Khan M.R., Synthesis, characterization, biological screenings and interaction with calf thymus DNA as well as electrochemical studies of adducts formed by azomethine [2-((3,5-dimethylphenylimino)methyl)phenol] and organotin(IV) chlorides. Polyhedron, 2012, 40(1), 19-31.

Sisido K., Takeda Y., Kinugawa Z., Direct synthesis of organotin compounds. i. di- and tribenzyltin chlorides. J. Am. Chem. Soc., 1961, 83(3), 538-541.

Tehfe M.-A., Dumur F., Telitel S., Gigmes D., Contal E., Bertin D., et al., Zinc-based metal complexes as new photocatalysts in polymerization initiating systems. Eur. Polym. J., 2013, 49(5), 1040-1049.

Wang X., Liu X., Tian L., Synthesis, characterization and *in vitro* cytotoxic activity of bis(triorganotin) 2,6-pyridinedicarboxylates. Main Group Met. Chem., 2014, 37, 143-147.

Xin H., Chen L., Gu J., Ren X., Wei Z., Luo J., et al., Enhanced anti-glioblastoma efficacy by PTX-loaded PEGylated poly(varepsilon-caprolactone) nanoparticles: *in vitro* and *in vivo* evaluation. Int. J. Pharm., 2010, 402, 238-247.

Xu Q., Tanaka Y., Czernuszka J.T., Encapsulation and release of a hydrophobic drug from hydroxyapatite coated liposomes. Biomaterials, 2007, 28, 2687-2694.

Yao Y., Yang M., Zheng X., Tian L., Synthesis, characterization, and cytotoxic activity of triphenyltin complexes of N-(5-bromosalicylidene)-α-amino acids. Main Group Met. Chem., 2017, 40, 93-99.

Yin H., Yue C., Hong M., Cui J., Wu Q., Zhang X., Synthesis, structural characterization and *in vitro* cytotoxicity of diorganotin(IV) diimido complexes. Eur. J. Med. Chem., 2012, 58(2), 533-542.