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Novel powder formulations for controlled delivery of poorly soluble anticancer drug: Application and investigation of TPGS and PEG in spray-dried particulate system

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Abstract

Biodegradable poly (lactic-co-glycolic acid) (PLGA), D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and/or polyethylene glycol (PEG) were combined as pharmaceutical excipient to fabricate microparticles containing sparingly soluble drug paclitaxel by spray-drying technique with successful achievement. The effect of formulation variety on particle morphology, surface composition, thermal property, drug entrapped capability, and drug release profile was investigated. The result indicated that the use of the appropriate mixtures of PLGA, TPGS and/or PEG produced paclitaxel-loaded microparticles characterised by acceptable pharmaceutical properties. Atomic force microcopy (AFM) and scanning electron microscopy (SEM) showed that the produced microparticles were spherical in shape with dimples or pores. The particle size ranged from 0.88 to 2.44 μm with narrow distribution. The combination of TPGS and PEG in the formulation resulted in a narrow particle size distribution in general although the influence of the formulation on the particle size was not significant. Differential scanning calorimetry (DSC) study implied that all those components in consideration were compatible well in the blend formulation systems. The paclitaxel entrapped in the particles existed in an amorphous or disordered-crystalline status in the matrices and was independent of the PLGA/TPGS/PEG ratio. X-ray photoelectron spectroscope (XPS) analysis revealed that after incorporation the particle's surface was dominated with PLGA due to its hydrophobic property. The formulation variety had an important impact on the drug release that was reduced with the presence of large fraction of TPGS resulting from a strong hydrophobic interaction between various matrix materials and the drug inside the particle. A zero order release could be yielded by optimising the ratio of PLGA/TPGS/PEG. The combination of PLGA/TPGS/PEG as safe pharmaceutical excipient to formulate particulate delivery system is beneficial in improving the pharmaceutical properties for further powder dosage application.

Keywords: Pharmaceutical carrier; Biodegradable polymer; New drug delivery route; Excipients; Microparticles; Nanoparticles; Microencapsulation; D-α-tocopheryl polyethylene glycol 1000 succinate; Paclitaxel; Taxol

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1. Introduction

Dry powders of microparticulate formulation have promising and practicable applications for further and new drug delivery route such as aerosol delivery, oral delivery, implantation and transdermal delivery of various therapeutic agents [1–4]. The formulation composition and the preparation parameter could manipulate crucially the particulate properties including particle size, morphology, bulk and surface composition, matrix density, drug encapsulation capability, drug release kinetics and thus determine the future prospects of the particulate delivery system. In the development of drug delivery system, biodegradable polymeric particles provide an attractive alternative which can improve the therapeutic efficiency as well as patient convenience and compliance. However, they may be relevant to the disadvantages including the relatively slow degradation of up to 4 weeks, which might possibly cause systemic toxic effects by impairment of the reticuloendothelial system (RES) [5], and cytotoxic effects observed in vitro after phagocytosis of polylactide (PLA) and polylactide/glycolide (PLA/GA) particles by macrophages and human granulocytes [6,7], etc. We considered to develop such particulate system with addition of excipients that are either FDA-approved or endogenous to the human body in the drug formulation with the expectation to improve the properties such as particle morphology, bulk and surface composition, drug encapsulation capability, drug release kinetics. We applied D-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) and/or polyethylene glycol (PEG) into the PLGA matrix and evaluate the effect of alternating the material matrix, i.e., compositing TPGS and/or PEG into polymeric matrix and their proportion on the physicochemical properties of drug-loaded particles prepared by spray-drying technique. This formulation strategy has been successfully employed for paclitaxel nanoencapsulation by solvent emulsification freeze-drying technique in our previous work [8]. It is interesting and important to continue the investigation of the feasibility of spray-dried drug-loaded particulate systems of the relevant formulation variables for the development of pharmaceutical carriers.

Spray-drying is extensively applied in pharmaceutical industry to produce raw drug or excipients or as microencapsulation process [9–11]. This technique transforms liquid feed into dry powder in a one step that is feasible for the scaling-up of the microencapsulation, continuous particle processing operation and can be used to a wide variety of materials [12]. The colloidal drug entrapped-particles could be prepared from a variety of both water-soluble and water-insoluble polymers of synthetic, semi-synthetic, and natural origin. The produced particulate dry powder could be processed for all practical purposes such as tablets or capsules and other convenient dosage forms. One more merit of the spray-drying is that it can be applicable to both heat resistant and heat sensitive drugs, both water-soluble and water-insoluble drugs. This is meaningful for the development of pharmaceutical carriers specifically for the delivery of hydrophobic drug which represents one of the major challenges in the field of new drug delivery [13].

Paclitaxel has good effects against a wide spectrum of human cancers. However, its application is limited because of its extremely hydrophobic character and poor oral bioavailability [14]. Microencapsulation of paclitaxel in various biomaterials could provide an alternative dosage form for either i.v. infusion or other specialised delivery routes. More importantly, the main advantages of TPGS include that it has the application as bioavailability enhancer and can serve to increase drug absorption of poorly soluble and poorly absorbed drugs [15]. The involvement of TPGS in the formulation would induce potential enhancement of transport of those anticancer agents to benefit the therapeutic effect. The present work used PLGA, TPGS and PEG as raw material, either as a pharmaceutical excipient, or as modifiers to formulate dry powder particulate systems loaded with paclitaxel and investigated the influence of the matrices composition on the correlate characteristics of the particulate formulations including drug content and drug release, particle size, surface morphology and surface composition. The intention is to develop new delivery formulation of poorly soluble drug paclitaxel with improved pharmaceutical properties.

2. Materials and methods

2.1. Chemicals

Poly (D,L-lactide-co-glycolide) (PLGA, 50:50, MW 40,000–75,000) was purchased from Sigma (Sigma Chemical Co., St. Louis, USA). Paclitaxel of 99.8% purity was purchased from Yunnan Hande Biotechnology Inc. (PR China). D-α-tocopheryl polyethylene glycol 1000 succinate was from Eastman Chemical Company (USA). Polyethylene glycol 4000 was from Fluka (Switzerland). Dichloromethane (Methylene chloride, DCM, analytical grade) was from Mallinckrodt (Mallinckrodt Laboratory Chemicals, Mallinckrodt Baker, Inc. USA). Acetonitrile used as mobile phase in high performance liquid chromatography (HPLC) was from EM Science (ChromAR, HPLC grade, Mallinckrodt Baker, Inc. USA). Millipore water purified by Milli Q plus purification system (USF-ELGA lab water, Millipore Singapore Pte. Ltd.) was utilised for HPLC analysis. Deionised water was used throughout the experiment. All other chemicals used were of reagent grade.

2.2. Spray-drying

A Büchi mini spray dryer model B-191 (Büchi Laboratoriums-Tecknik AG, Flawil, Switzerland) with standard nozzle (0.7 mm diameter) was used to produce the dry powders of various formulations. The compressed air for atomization was 6 bar and the aspirator setting level was 100%. The liquid feed was pumped continuously with the rate 4.5–5.0 ml/min. Both the inlet and outlet temperatures were measured and controlled manually; inlet air temperature: 50+2 °C, outlet temperature: 39+2 °C. The spray flow was controlled as 700 NL/h. PLGA, TPGS and/or PEG, paclitaxel in varying ratios were added in an appropriate volume of DCM (the total concentration of the material matrix and drug in the organic solution 2.5% was kept constant) and then stirred at room temperature using a magnetic stirrer (EYELA Magnetic stirrer RC-2) until all the components were completely dissolved or uniformly suspended. The initial drug-loading ratio was 10% (w/w) in the formulation. The solutions or suspensions were then spray-dried until no more particle powder could be obtained. The dried product was then collected, further dried and kept in a vacuum dessicator at room temperature. Placebo particle sample without drug entrapped was prepared with the same procedure.

2.3. Particle morphology, size measurement, thermal determination, and surface analysis

Particles of dry powder were viewed using a conventional scanning electron microscope (SEM, JSM-5600 LV, JEOL USA, Inc.) and high resolution observation, atomic force microscopy (AFM, MultimodeTM Scanning Probe Microscope, Digital Instruments, USA) for the shape and surface morphology. SEM required a previous coating of the sample with platinum, which was done in an Auto Fine Coater (JFC-1300, JEOL USA). AFM was performed by the tapping mode. Before operation, a small amount of sample powder was stuck on a double-sided tape attached on a metallic sample stand. The volume mean particle size and size distribution were measured by suspending powder in an aqueous solution with laser light scattering (LLS, Brookhaven Instruments Corporation 90 Plus Particle Sizer). For LLS, the dried powder samples were suspended in millipore water and sonicated slightly. The homogenous suspension obtained was tested for effective mean diameter and polydispersity. Thermograms with glass transition temperatures (T_g) and/or melting point temperatures (T_m) of raw materials, paclitaxel and various microparticles were acquired with the use of a computer-interfaced differential scanning calorimeter (DSC822e, Mettler Toledo) under a purged nitrogen atmosphere. Desiccated samples (4 mg) were weighed using and crimped in aluminum pans with a pinhole. The determination was done by first cooling the sample from 20–0 °C, then heating to 260 °C at a heating rate of 10 °C/min. The T_g or T_m values were determined from the second heating run. X-ray photoelectron microscopy (XPS, Kratos Analytical, Shimadzu Corporation, Japan) was conducted for the surface composition of particles. The survey spectrum recorded covered a binding energy range from 0 to 1200 eV with pass energy of 80 eV in fixed transmission mode. Peak curve fitting of the C1s envelope was performed using XPS Peak 4.1 software.

2.4. Drug incorporation and in vitro release

The amount of paclitaxel that was entrapped in the particle powder after the microencapsulation process was measured in triplicate using high performance liquid chromatography (HPLC, Agilent LC1100). The encapsulation efficiency of paclitaxel in particles was determined as the mass ratio of the entrapped paclitaxel to the theoretical amount of paclitaxel used in the preparation. To account for the inefficiency in the extraction procedure, a correction factor was needed in calculating the encapsulation efficiency, which was determined as the ratio of the paclitaxel concentration obtained from HPLC measurement to the theoretical concentration of the prepared solution which was obtained by dissolving the physical mixture of pure paclitaxel and placebo particles with relevant ratio in the same solvent and then subjected to the same procedure. The release property of paclitaxel from spray-dried particles was measured similarly in triplicate in PBS at pH 7.4 under in vitro condition. Three milligrams of paclitaxel-loaded particle powder were suspended in 10 ml of PBS in a screw-capped tube and the tube was placed in an orbital shaker water bath (GFL-1086, Lee Hung Technical Company, Bukit Batok Industrial Park A, Singapore) which was maintained at 37 °C and shaken horizontally at 110 min^{-1}. At particular time intervals, the tubes were taken out and centrifuged at 11,000 rpm for 15 min. The supernatant solution was collected from each tube for HPLC analysis and the precipitated particles were resuspended in 10 ml of fresh PBS and then put back into the water bath for continuous release.

3. Results and discussions

Various formulations of paclitaxel-loaded particulate systems composed of PLGA, TPGS and PEG were fabricated, namely the ST, SE and STE series of formulations listed in the 2nd column of Table 1.

3.1. Effect of various formulations on morphology and particle size

The scanning electron microscope (SEM) images (Fig. 1) showed that, in general, the morphology of the produced particles was fairly satisfactory upon addition of TPGS and PEG. Most of the formulations gave relatively regular and spherically shaped microparticles, with their surfaces irregular dimpled or porous. It had been found to be difficult to form smooth spherical particles by spray-drying technique due to the formation of fibres that was caused by insufficient forces present to break up the liquid into droplets during the spray-drying of the polymeric solution [16]. The formulation composition had

Table 1
The particulate samples and their properties

Formulation ID	Composition PLGA:TPGS:PEG	Property of spray-drying liquid	Mean diameter (μm)±S.E.	Polydispersity	Drug encapsulation efficiency (%)
SP	PLGA only	Solution	1.31±0.17	0.005	63.2
ST1	1:1:0	Solution			93.8
ST2	2:1:0	Solution			96.5
ST3	5:1:0	Solution	2.00±0.08	0.005	100
ST4	10:1:0	Solution	1.85±0.05	0.005	92.3
ST5	20:1:0	Solution	2.44±0.09	0.105	96.6
ST6	50:1:0	Solution	0.88±0.06	0.205	98.1
SE2	2:0:1	Suspension			96.7
SE3	5:0:1	Suspension	2.30±0.59	0.325	95.5
SE4	10:0:1	Suspension	1.81±0.29	0.147	96.1
SE5	20:0:1	Suspension	1.10±0.28	0.031	96.6
SE6	50:0:1	Suspension	0.98±0.26	0.013	97.4
STE1	5:0.5:0.5	Suspension			90.1
STE2	10:0.5:0.5	Suspension	1.01±0.28	0.005	97.5
STE3	20:0.5:0.5	Suspension	1.25±0.21	0.074	95.9
STE4	50:0.5:0.5	Suspension	1.15±0.34	0.095	94.8

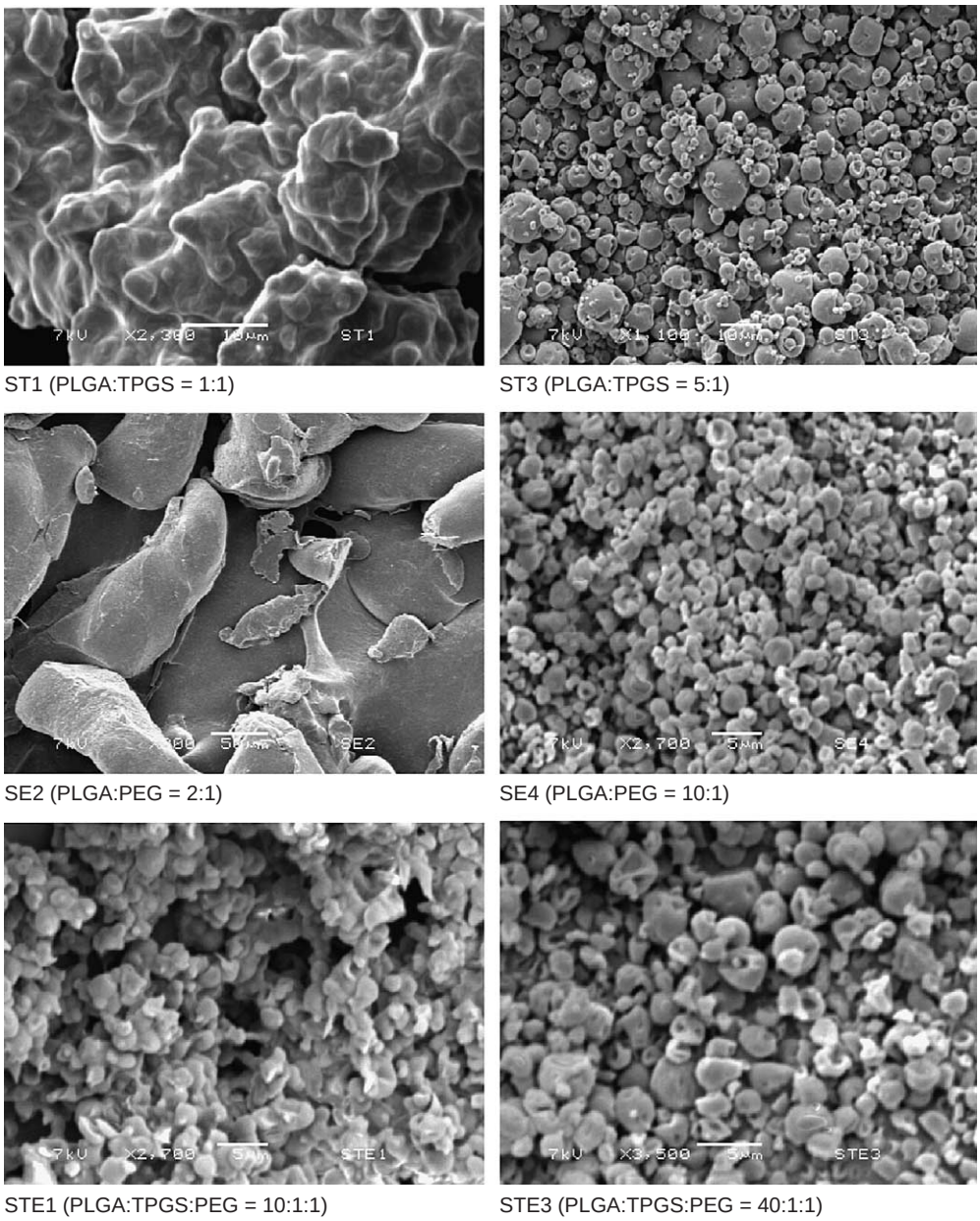

Fig. 1. SEM images of prepared particles with various ratios of PLGA/TPGS/PEG as material matrices.

obvious influence on the formation of the particles. When TPGS was too much in the composition, the particles were not well formed. They stick to each other and were not very well separated. This may be contributed by the waxy, sticky and high surfactant property of TPGS. High ratio of PEG also prevented well defined particles but tend to big irregular clump. This could be due to the insolubility of PEG in organic solvent. Besides, it seemed that TPGS tended to form porosity whilst PEG tended to form dimple. When both TPGS and PEG were added with equivalent ratio, the adherence and aggregation mitigated although they still existed when their ratio were too large. In trying to obtain a clearer and more

detailed (higher resolution) picture of the morphology of the microparticles, the atomic force microscopy (AFM) was employed even though it was very difficult to find optimal images of solid spray-dried particulate samples for the various formulations. The images of a sample from the ST5 were shown in Fig. 2 for the single particle as well as the microparticle's gather. In looking at the picture of an individual particle, the reflection of signal on the surface of the microparticle indicated that the surface was relatively smooth in the scale of observation. The microparticles were well rounded, but were not very spherical in shape. Also it can be deduced that the dimple or porosity were not too deep. This suggested that the primary drug release mechanism would be diffusion through both the material matrix and the channels and pores.

The size and size distribution of the particles were measured by laser light scattering (LLS) and the data was tabulated in Table 1. The size distribution was specified in the intensity of the light scattering and the polydispersity was referred to the log-normal distribution width of the particle diameter, which means the average geometric mean diameter and geometric standard deviation of log-normal distribution, respectively. It can be seen that the ST series had the mean diameter from 0.88 to 2.44 μm with polydispersity from 0.205 to 0.005. SE series gave the diameter from 0.98 to 2.3 μm with polydispersity from 0.013 to 0.325. The STE series showed the particle size from 1.01 to 1.25 μm with the polydispersity from 0.005 to 0.095. PEG is hydrophilic and not soluble in organic solution. The more it was involved in the medium, the less homogenous the resulting solution. That may be the main reason of the relatively big polydispersity for SE series of sample. The combination of TPGS and PEG in the formulation resulted in a narrow particle size distribution in general although the influence of the formulation on the particle size was not significant. Additionally, it did not mean that lower ratio of TPGS or PEG would reach fine particles although too large ratio of the additives resulted in unfit defined particles. Instead, the optimal morphology and particle size may be related to some suitable proportion of both TPGS and PEG in the formulation system, which meant that it is accepted to employ both or either of the two substances in the formulation components.

3.2. Drug encapsulation and effect of formulation variety on the in vitro release property

Encapsulation efficiency (EE) is one of the key criteria for evaluating microencapsulation process. The EE of paclitaxel in all particulate formulations were measured by HPLC and listed in Table 1. It can be seen that all formulations gave high EE, which ranged from 90.1% to 100%, and higher than that of PLGA only particulate system (63.2%). There was no observable trend when the formulation ratio PLGA/TPGS/PEG was changed. Meanwhile, various particulate formulations were determined for their cumu-

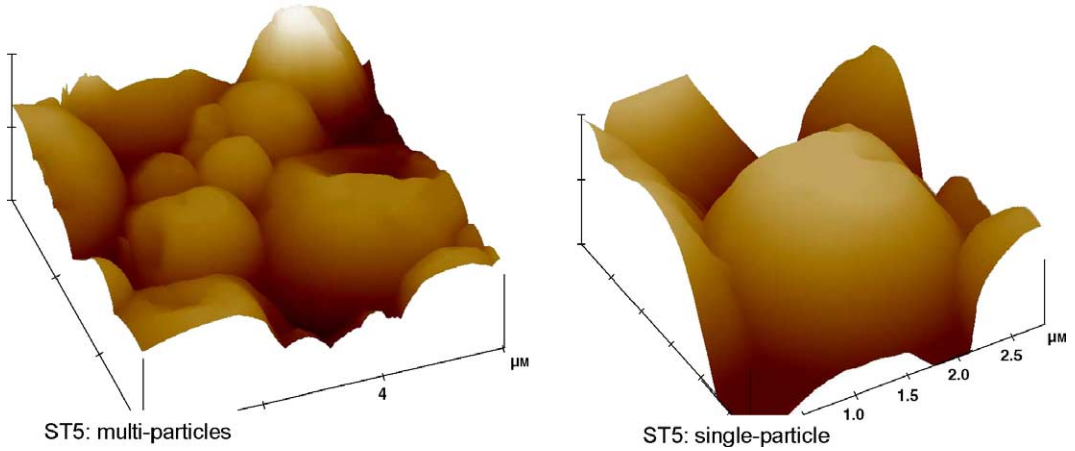

Fig. 2. AFM images of spray-dried particles with PLGA–TPGS (20:1) as material matrix.

lative release of encapsulated paclitaxel under in vitro condition. The curves were showed in Fig. 3. Normally, three basic mechanisms, namely swelling/erosion, diffusion, and degradation are present for the release of the loaded drug from polymeric particles [17,18]. Any or all of these mechanisms may occur in a given release system. The degradation of PLGA is slow, therefore the release mechanism of paclitaxel from particles may depend on either the drug diffusion or the PLGA surface and bulk erosions/swelling. Upon exposure to the aqueous medium water is taken up immediately by the PLGA microparticles. The hydrophilicity of the polymer will determine the uptake speed of water during the course of release. With the uptake of water, the particles will swell and allow the drug within to diffuse through the pores. This sort of mechanism is faster than drug diffusion through an intact polymer barrier. Particulate systems fabricated by spray-drying usually possess a porous quality that aids the water penetration into the particles, thereby promoting the release. This is one related advantage of spray-drying for controlled release of poorly soluble drugs.

In the present typical matrix delivery system, the polymer, drug, and additive had been mixed to form a homogeneous system, in which the diffusion occurred when the drug passes from the uniform blending matrix onto the external environment. As the release continued, its rate normally decreased with this type of system, since the drug had a progressively longer distance to travel and thus required a longer diffusion time to release. Clearly, the combination of TPGS or

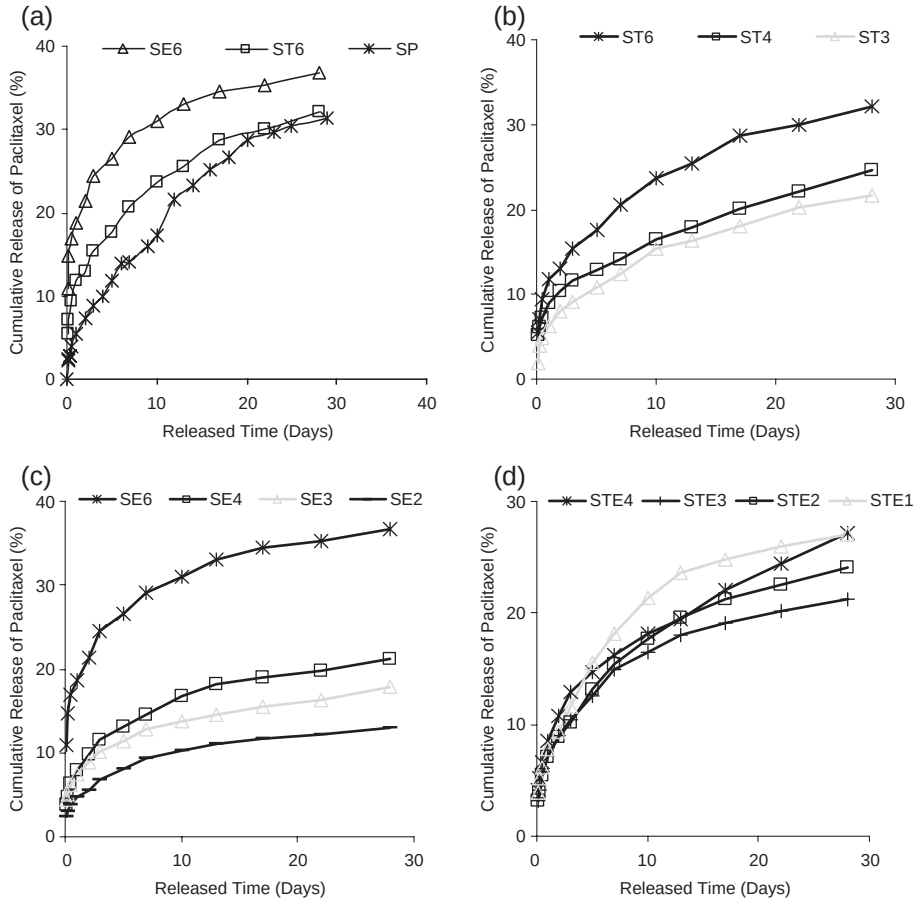

Fig. 3. Release profiles of various particulate formulations. (a) Comparison of PLGA, PLGA–TPGS and PLGA–PEG as material matrices; (b) PLGA–TPGS blend as material matrices; (c) PLGA–PEG blend as material matrices; (d) PLGA–TPGS–PEG blend as material matrices.

PEG into the formulation could influence the in vitro release kinetics. Lower proportion of TPGS or PEG in the formulation could increase the release rate whilst higher proportion of either of them would decrease the in vitro release rate (Fig. 3, a–d). After one month, the accumulative amount of paclitaxel released the fastest was about 29%, 30%, 35%, and 27% for microparticles composed from PLGA alone (SP), combination of PLGA with TPGS (ST), with PEG (SE), and both TPGS and PEG in the matrices (STE), respectively. The generally slow release would be considered for in vivo work and may be suitable for long term sustained in vivo application. Additionally, both TPGS and PEG possess hydrophilic property. The small amount of them near the particles' surface could prompt the drug release into the aqueous medium. On the other hand, when their proportion inside the formulation was high, the in vitro release was decreased obviously within the period of one month. One concern was that, the spray-dried system was an organic solution thus the formed droplet and/or particle would tend to the hydrophobic component such as PLGA present on the outside region of the particle whilst the hydrophilic TPGS or PEG concentrated at the internal part of the particle. Therefore, PLGA played a dominant effect on the release, especially in the early stage of the release. PEG is hydrophilic only and agreed with the fastest release (SE series). In contrast, TPGS is amphiphilic, both hydrophobic and hydrophilic, smaller but with bigger bulk area, being a good surfactant. Insofar TPGS would tend to a compact domain inside the particle by staying in the pores of PLGA matrix and the polymer chains, causing denser structure and resulting in lower erosion, swelling as well as slower diffusion of the encapsulated drug through the matrix (ST series). Beyond this, the homogeneous distribution of either TPGS and/or PEG may aid a stronger hydrophobic interaction than the hydrophilic interaction amongst PLGA, paclitaxel and the additives that may also decrease the drug release through the particles. Moreover, it was especially obvious when using both TPGS and PEG into the particulate formulation (STE series) in which series the deference of release rate of various formulations was not much as well. This result may imply a proper interaction amongst the components that benefit the release kinetics.

3.3. Thermal analysis of various particulate formulations

The thermal property of mixtures of a drug and excipient are of important interests in pharmaceutical technology and this can normally be processed by differential scanning calorimetry (DSC). The obtained information such as melting, recrystallisation, decomposition, out-gassing, or a change in heat capacity could help to ascertain the physicochemical status of the entrapped drug inside the excipient and assess the interaction amongst different components during the fabrication process, and may help to explain relevant properties of in vitro release. Fig. 4 depicted the DSC thermograms of pure material including paclitaxel, TPGS, PEG, and PLGA, physical mixture of paclitaxel (>10%) and placebo microparticle, as well as various drug-loaded particulate formulations [19]. All the pure material gave the peak relevant to the phase transition temperatures (T_g or T_m), for instance, the endothermic peak of melting of pure paclitaxel at

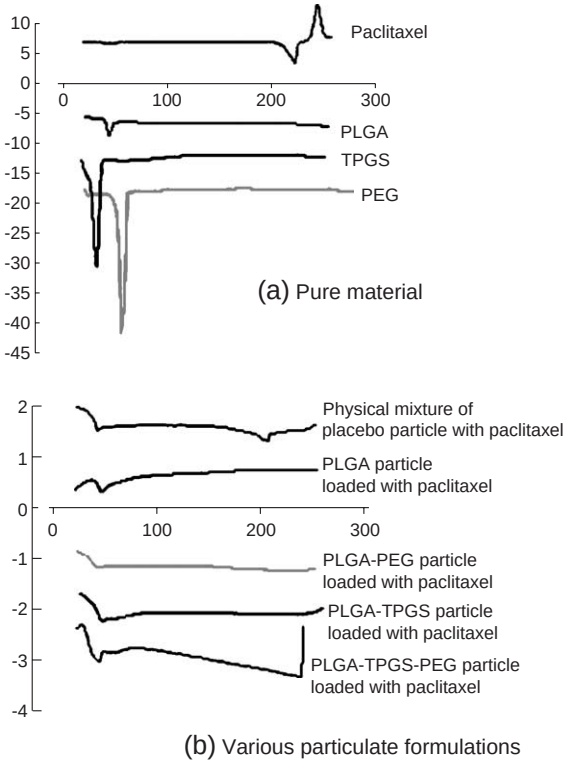

Fig. 4. DSC thermograms of raw material and various particulate formulations.

about 220.0 °C before suffering from thermal degradation at about 250.0 °C; the glass transition temperature of PLGA (50:50) at about 45 °C in the second heating cycle; the endothermic peak of melting point of pure TPGS at around 41 °C for the first heating cycle and lower value of about 37 °C for the second heating cycle; the transition at around 60 °C of PEG that was respected to its presence of extended and folded chain conformations [20]. The result of no detectable melting endotherm peak of paclitaxel in all types of spray-dried, drug-loaded microparticles indicated that the drug formulated existed in an amorphous or disordered-crystalline drug phase of a molecular dispersion or a solid solution state in matrix during rapid drying of the slurry droplets that was agreed with the general results of spray-drying [21]. The resultant increased solubility due to amorphous drug phases can benefit and improve biological activity [22]. One more point to be highlighted was that, PEG displayed an amorphous phase state after incorporation process although it was not soluble in the organic solvent for spray-drying system. This was further confirmed that the spray-drying process resulted in higher energy amorphous products showing amorphous characteristics over a wider composition range [20–24]. Over and above, it is interesting to emphasise that, PEG was difficult to spray-dry because of its low melting point. The present work successfully spray-dried PLGA/TPGS/PEG blend of various PEG content and produced amorphous PEG/amorphous drug solid dispersion systems. Such amorphous systems were likely to have higher energy and therefore showed increased solubility and increased dissolution rates and therefore should show higher bioavailability [24–26]. Meanwhile, the disappearance or decrease in T_g or T_m of all matrix material yielded with the entrapment process also implied the additive was well distributed within the polymer matrix, which was also associated with a good physical compatibility of the blended material, showing no phase separation occurred.

3.4. Surface analysis of various particulate formulations

The surface chemistry of the microparticles was analysed by X-ray photoelectron spectroscopy (XPS). The investigation was done by inferring the relative distribution of elements C, O, and N, and the relative percentage of each carbon environment (1s, atomic orbital of 1s of carbon) from curve fitting over a binding energy range of 280–300 eV corresponding to O=C–O, C–OH(R) and C–C/C–H. The comparison between pure powder material and various particles was made. The obtained results were summarised in Table 2. It can be seen that the elemental ratios of carbon and oxygen for all samples were similar and did not seem to be affected significantly by the formulation variety. The nitrogen was detected in some formulations that contained paclitaxel. It implied the distribution of paclitaxel on the outer surface of the microparticles although the detection was irregular or on a random basis. Actually, the spray-dried system was an organic solution of matrix material mixed with the drug. It is possible for the hydrophobic drug to be present outside of the particle that was near the hydrophobic

Table 2
Surface chemistry of various particulate formulations analysed by XPS

Sample code	XPS elemental ratio (%)			XPS C1s envelope ratio (%)		
	C	O	N	C–C/C–H	C–OH (R)	O–C=O
PLGA	64.98	34.59	0	52	30	18
TPGS	69.11	30.89	0	45	53	2
Paclitaxel	68.77	28.81	1.42			
PEG	57.32	42.68	0	96	4	0
SP	52.93	47.07	0	52	24	24
STb	52.16	47.84	0	56	23	22
ST3	51.64	47.40	0.96	55	31	14
ST4	60.06	37.53	0.41	50	35	15
ST5	58.59	41.41	0	58	26	16
ST6	52.74	47.26	0	52	31	17
SEb	52.16	47.84	0	56	26	18
SE3	56.32	42.82	0.86	48	34	18
SE4	61.61	38.39	0	57	31	12
SE5	61.27	38.73	0	55	26	20
SE6	59.45	40.04	0.51	52	27	20
STEb	62.06	37.93	0	62	21	17
STE1	64.23	35.77	0	64	28	9
STE2	58.61	41.39	0	55	28	17
STE3	49.68	50.32	0	53	25	22
STE4	58.11	41.11	0.77	51	33	16

STb: microparticles with PLGA–TPGS as excipient without drug loading. SEb: microparticles with PLGA–PEG as excipient without drug loading. STEb: microparticles with PLGA–TPGS–PEG as excipient without drug loading.

solvent environment. Beyond this, drawing a comparison between the basic material PLGA, TPGS, PEG and various microparticles, it can be found that the range of percentage proportion of C–C/C–H bond from each of particulate formulations was between 48% and 64%, which was apparently closer to the values of percentage proportion of C–C/C–H bond for PLGA (52%, whilst TPGS was 45% and PEG was 96%). Similarly, the range of percentage proportion of O–C=O bond is between 9% and 24%. Again, these values are closer to the values of percentage proportion of O–C=O for PLGA (18%, whilst TPGS was 2% and PEG was 0%). For C=O bond, the range of percentage proportion was between 21% and 34% and was closer to the values for PLGA (30%, whilst TPGS was 53% and PEG was 4%). Therefore it can be concluded that PLGA was more distributed on the outer surface of the microparticles; while the TPGS and/or PEG were more distributed beneath the inner surface regardless of their blending together or not into the formulation. This is understandable, as both PEG and TPGS are hydrophilic although the latter is also hydrophobic, whilst PLGA is the only hydrophobic of the three materials in consideration. Thus PLGA tends to a close interaction with the hydrophobic solvent used in the fabrication and hence a greater concentration of PLGA could be found on the outer part of broken droplet forming the microparticles during the spray-drying process. This result was also agreed with the in vitro release behaviour.

4. Conclusions

Microparticles containing sparingly soluble drug paclitaxel with combinations of safe excipients PLGA, TPGS and PEG were formulated successfully by spray-drying technique. The effect of formulation variety on the particle morphology, surface compositions, thermal property, drug entrapped capability, as well as the drug release was investigated. The result showed that the use of the appropriate mixtures of the PLGA, TPGS and/or PEG produced paclitaxel-loaded microparticles characterised by acceptable pharmaceutical properties. It was indicated that all those components in consideration were compatible well in the blend formulation systems. The encapsulated paclitaxel existed as a molecular dispersion state in the particles, which was independent of the PLGA/TPGS/PEG ratio. The produced microparticles were spherical in shape with irregular dimples or pores. The particle size ranged from 0.88 μm to 2.44 μm with narrow distribution. The particles' surface was dominated with PLGA due to its hydrophobic property. The formulation variety had an important impact on the drug release kinetics. There was a reduced release rate when large fraction of TPGS was involved that was linked to a strong hydrophobic interaction between various matrix materials and the drug. A zero order release could be yielded by optimising the ratio of PLGA/TPGS/PEG. The result revealed that the combination of PLGA/TPGS/PEG as safe pharmaceutical excipient is beneficial to improve the characteristics of further powder dosage application.

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