Nanoencapsulation of water soluble drug,lamivudine using a double emulsion spray drying technique for improving HIV treatment

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Abstract

Current treatments available for human immunodeficiency virus, namely antiretrovirals, do not completely eradicate the virus from the body, leading to life time commitment. Many antiretrovirals suffer drawbacks from toxicity and unpleasant side effects; causing patience non-compliance. To minimize challenges associated with the antiretrovirals, biodegradable nanoparticles used as drug delivery systems hold tremendous potential to enhance patience compliance. The main objective of this work was to load lamivudine into poly(epsilon-caprolactone) (PCL) nanoparticles. Lamivudine is a hydrophilic drug suffering from low half life of 5 to 7 hours and several unpleasant side effects. Lamivudine was nanoencapsulated into PCL polymer via the double emulsion spray drying method. Formulation parameters such as the effect of solvent, excipient and drug concentration were optimized for the synthesis of the nanoparticles. Spherical nanoparticles with an average size of 215±3 nm and polydispersity index (PDI) of 0.227±0.01 were obtained, when ethyl acetate and lactose were used in the preparation. However dichloromethane presented sizes larger than 454±11 nm with PDI of more than 0.4± 0.05, irrespective of whether lactose or trehalose was used in the preparation. Some of the nanoparticles prepared with trehalose resulted in crystal formation. UV spectroscopy showed encapsulation efficiency ranging from 68±4% to 78±4% for lamivudine depending on the starting drug concentration. FTIR and XRD confirmed the possibility of preparing amorphous PCL nanoparticles containing lamivudine. Drug release extended for 4 days in pH 1.3, pH 4.5 and pH 6.8. These results indicated that lamivudine loaded PCL nanoparticles show promise for controlled delivery.

Keywords: Spray dried, poly(epsilon-caprolactone), lamivudine, nanoparticles, double emulsion

1. Introduction

Nanomedicine drug delivery systems (DDS) have revolutionised medicine in many ways. It has allowed for the accurate and early diagnosis of diseases, efficient and effective treatment of ailments with minimum toxic side effects (Mishra et al., 2010). Biodegradable and biocompatible polymers have gained ground over the years for their extensive application in DDS. The nanoencapsulation of therapeutic agents into biodegradable and biocompatible polymeric nanoparticles (PNP) results in better protection of the actives against harsh conditions encountered throughout the gastro-intestinal (GI) tract that might hinder them from reaching the target site. (Jyothi et al., 2010; Kumari et al., 2010). The functionalization of these nanocarriers with special ligand(s) ensures targeted delivery to specific compartments in the body where the therapeutic goods are delivered at the site where they are needed the most, thus increasing the efficacy of the drug while minimizing toxic side effects (Rao et al., 2009). The notion of protecting and targeting drugs stems from the very idea of minimizing the risk-to-benefit ratio (Mishra et al., 2010), which is inherent in many therapeutic drugs such as those used to treat poverty related diseases (PRDs).

PRDs such as tuberculosis (TB), human immunodeficiency virus associated/acquired immune deficiency syndrome (HIV/AIDS) and malaria have been reported to show a noticeably higher prevalence in poor countries (Look et al., 2010). A recent report on the HIV/AIDS epidemic, which is a leading deadly infectious disease in adults especially for poor countries, indicates that approximately 33.2 million people are living with the diseases worldwide (Look et al., 2010; Gupta and Jain, 2010; Wong et al., 2010; Neves et al., 2010). The sub-Saharan Africa displays an excessive number of the global HIV/AIDS burden with an estimate of approximately 22.5 million (Wong et al., 2010). Based on the information gained about HIV/AIDS replication cycle, numerous treatment options are available (Clercq, 2009) which include oral and intravenous therapy. Orally administered treatment options are prone to undergo extensive GI degradation, resulting in decreased therapeutic index of the active ingredient. The problem is usually ameliorated by frequent administration in higher doses. However this results in poor patient's compliance, increased toxicity to name a few. It is therefore evident that there is a need to develop more efficient delivery mechanisms that will ensure low dosage.

Lamivudine (LAM) is an anti-HIV drug that falls under nucleoside reverse transcriptase inhibitors (NRTIs). It is a hydrophilic drug with half-life of 5 to 7 hours, and classified as Class 1 in the biopharmaceutical classification system, denoting that it has high solubility and permeability (Jozwiakowski et al., 1996). The daily suggested dose of 150 mg is required for life time (Kao et al., 2000). The oral administration of LAM exhibits side effects such as abdominal pain, headache, nausea, fatigue and also vomiting (Caroline and Faulds, 1997).

Recently Dev and co-workers (2010) nanoencapsulated LAM into polylactide/chitosan (PLA/CS) nanoparticles using the double emulsion freeze-drying method. Findings showed that it was possible to synthesize the nanoparticles, without changing the structural integrity of the two polymers and the drug, as evidenced by fourier transmission infrared spectroscopy (FTIR) analysis. However, the process utilized required an evaporation step to remove the solvent overnight followed by lyophilization of the pellets collected. The latter step is a relatively time and energy consuming process.

Our group recently reported on the nanoencapsulation of efavirenz (EFV) (anti-HIV drug, water insoluble) using the double emulsion spray drying method (Katata et al., 2012). The nanoparticles produced indicated good nanoencapsulation of water insoluble drug, EFV. Preparation of spray-dried nanoparticles is an attractive alternative to freeze-drying method, since it offers the advantage of being a single-step process (Baras et al., 2000). In addition, it can be easily scaled up, and has been used in the pharmaceutical industries for the formation of nanoparticles and microparticles (Broadhead et al., 1992).

Therefore the main objective of the present work is the nanoencapsulation of LAM into biodegradable and biocompatible poly(epsilon-caprolactone) (PCL) nanoparticles using the double emulsion spray-drying method. This is of great value since it forms as the platform to nanoencapsulate both hydrophilic and hydrophobic drug. Controlled release may be achieved as the polymer degrades; resulting in a decreased frequently administration of the drug due to increased half life. Thus simultaneously minimizing side effects associated with LAM. Formulation parameters such as the effect of solvent, excipient and drug concentration were optimized for the synthesis of LAM loaded-PCL (PCL-LAM) nanoparticles. PCL polymer is known for its superior rheological and viscoelastic properties over many biodegradable and biocompatible polyesters, which renders PCL easy to manufacture (Woodruff and Hutmacher, 2010). Consequently PCL displays more advantageous features and it is less expensive when compared to other polyesters like PLA (Dash et al., 2011).

2. Materials and methods

2.1. *Materials*

PCL with average molecular weight number of 10 000 and polyvinylalcohol (PVA), molecular weight 13000-23000 (87-89% hydrolyzed), were obtained from Sigma-Aldrich (South Africa). LAM drug was purchased from Aspen Pharmacare (South Africa). Ethyl acetate (EA) and dichloromethane (DCM) were both supplied by Sigma-Aldrich (South Africa). Lactose monohydrate and trehalose (anhydrous) used as drying-aid excipients were obtained from Sigma-Aldrich and Merck chemicals (South Africa), respectively. Ultra purified water (resistivity higher than 18.2Ω) was used throughout and all other chemicals were of analytical grade.

2.2. *Synthesis of PCL-LAM nanoparticles*

PCL-LAM nanoparticles were prepared using the modified double emulsion spray-dried method as reported by Katata et al. (2012). Briefly, 2 ml of an aqueous solution of 2% PVA containing LAM drug was emulsified for 3 minutes with a solution of 100 mg PCL dissolved in 8 ml of solvent (EA or DCM or a mixture of DCM and EA), by means of a high speed homogeniser (Silverson L4R GX-10 model, Silverson Machines Limited, United Kingdom) rotating at 5000 rpm to form a water-in-oil (w_1/o) emulsion. The resulting emulsion was transferred into a specific volume of aqueous solution containing 2% PVA, 0.5% PEG, 5% lactose or 5% trehalose, and 0.3% chitosan. The mixture was homogenised for 5 minutes at 8000 rpm to form water-in-oil-in-water (w_1/o/w_2) emulsion. As soon as prepared, the nanoemulsion was immediately fed into the spray dryer (model B-290, Buchi

labortechnik AG, Switzerland) to produce a free flowing powder of PCL-LAM nanoparticles. PCL-LAM nanoparticles were then collected and kept in the dessicator at room temperature. All experiments were performed in triplicate. Standard spray drying conditions were: inlet temperature 96^{o}C, aspirator setting, 100%, pressure 7 bars, with an achieved outlet temperature varying between 65^{o}C and 70^{o}C.

2.3. Particle size, particles size distribution and zeta potential

The mean average particle size and particle size distribution of the spray-dried nanoparticles were measured using Malvern Zetasizer Nano ZS (Malvern Instruments, United Kingdom). For this purpose, a tiny amount of the PCL-LAM nanoparticles powder was suspended in deionised water and sonicated if necessary. Zeta potential (ZP) was also determined using the same method and instrument. Each sample was measured in triplicate and the results are expressed as mean ± standard deviation (SD).

2.4. Drug content of nanoparticles

The encapsulation efficiency (EE) of the drug into nanocarriers was determined using UV-visible spectrophotometer (Perkin Elmer, Lambda 35, Singapore). Briefly, 20 mg of PCL-LAM nanoparticles were dispersed in 10 ml deionised water and sonicated to obtain a homogenous particle distribution. The sample was centrifuged and the supernatant was then analyzed by UV. Each sample was measured in triplicate and the results are expressed as mean ± SD

The EE was calculated using the following equation:

$$\text{Encapsulation effiency} = \frac{\text{Initial drug amount} - \text{drug in the supernatant}}{\text{Initial drug amount}} \text{ X } 100\%$$

and is defined by the ratio of measured and initial amount of the drug encapsulated in the nanoparticles. Drug loading of the nanoparticles was calculated from the ratio of measured amount of drug encapsulated over the total amount of nanoparticles collected.

2.5. Fourier transmission infra red spectroscopy (FTIR)

FTIR spectra of pure PCL polymer, pure LAM drug, PCL-LAM and drug free PCL nanoparticles (PCL-DF) (used as a control) were obtained using Perkin Elmer spectrum 100 FTIR (spectrophotometer, USA). The samples were placed onto FTIR plate for measurements. The spectrum was recorded with wavenumbers between 4000 cm^{-1} and 650 cm^{-1}.

2.6. Scanning electron microscopy (SEM)

The morphology of the PCL-LAM and PCL-DF nanoparticles was analyzed using SEM (Field Emission Electron Microscope, JEOL JSM-7500F, Japan). The nanoparticles were mounted onto carbon stubs using a double-sided carbon adhesive tape and sputtered with conductive gold in a high vacuum evaporator under an argon atmosphere prior to imaging.

2.7. X-ray diffraction (XRD)

XRD measurements of pure PCL polymer, pure LAM drug, PCL-DF and PCL-LAM nanoparticles were carried out using Phillips X'Pert PRO diffractometer from PANalytical (Netherlands) under reflection–transmission mode. Samples were placed in glass sample holders and scanned from $2\theta = 5^{o}$ to 60^{o}, using a beam of Cu Kα radiation of λ = 0.1542 nm, operated at 45 kV, 40 mA. The scan speed and exposure time were 0.109419 ^{o}/s and 17 min 27 s, respectively.

2.8. In vitro LAM release from PCL nanoparticles

The *in vitro* drug release tests were carried out on PCL-LAM nanoparticles. Briefly, 30 mg of PCL-LAM sample was suspended in 10 ml of phosphate buffered saline (PBS) at various pH (1.3, 4.5 and 6.8) at 37^{o}C and placed in a water bath shaker at 100 rpm. At predetermined time intervals, 1.5 ml of aliquots was withdrawn and the concentration of drug released was monitored by UV spectrophotometer (Perkin Elmer, Lambda 35, Singapore). The dissolution medium was replaced with

fresh buffer to maintain the total volume. Cumulative percentage of the drug dissolved was calculated using calibration equations. Each sample was measured in triplicate and the results are expressed as mean ± SD.

3. Results and discussion

The aim of the present study was to investigate double emulsion spray-drying process for the production of PCL-LAM nanoparticles. The effect of different processing parameters on the particle size, particle size distributions as polydispersity index (PDI) and ZP are discussed in the following sections.

3.1. Effect of solvent on particle size and particle size distribution

In the present section, organic solvents namely DCM, EA and their mixtures were used as an organic phase during nanoparticles preparation. The concentration of the polymer and the drug were kept at a constant ratio of 1:1 i.e. 100 mg of PCL and LAM. The preparation of nanoparticles by double emulsion spray-drying method involves first dissolving the encapsulating polymeric material (i.e. PCL) in an organic solvent then dispersing it in the aqueous phase by means of emulsification and a subsequent evaporation process by means of a spray dryer. This allows for the removal of the organic solvent until the saturation of the polymeric shell is reached resulting into its precipitation, thus encapsulating drug molecules dispersed within its matrix. The rate of emulsification and extent of the organic phase association with aqueous phase depends on the solubility of the solvent (Chernysheva et al., 2003; Song et al., 2006; Luong-Van et al., 2007). Table 1 shows a summary of the solubility of DCM, EA in aqueous phase, and or that of PCL in DCM and EA (Song et al., 2006; Woodruff and Hutmacher, 2010). The difference between DCM and EA is that DCM is immiscible in aqueous phase whereas EA is sparingly soluble (Song et al., 2006).

Table 1: Solubility of organic phase in aqueous phase, and PCL in organic phase solvents

Figure 1 shows the mean particle size and PDI of the prepared PCL-LAM nanoparticles. PCL-LAM nanoparticles of approximately 215±3 nm and 277±28 nm were obtained when partially water soluble solvent EA was used. PCL-LAM nanoparticles ranging from 454±11 nm to 604±9 nm in mean particle size were obtained when DCM was used, and also the mixture of DCM with EA yielded large nanoparticles.

Figure 1: Properties of PCL-LAM nanoparticless 1 = DCM used as solvent, 2 = EA used as a solvent, 3= mixture of DCM and EA, a = lactose used as excipient, and b = trehalose used as excipients (data represent mean ± SD, n = 3)

The differences in size imply that the solubility of an organic solvent phase in the aqueous phase affects its diffusion through the aqueous phase, increasing with it, during the evaporation phase. The high rate of solvent removal impacts on the kinetics of the supersaturation leading to the formation of very small particles. (Maia and Santana, 2004; Jyothi et al., 2010). Small mean particle sizes for EA were attributed to low interfacial tension between organic and aqueous phase, resulting from partially solubility nature of the solvent (Song et al., 2006). On the other hand, DCM is immiscible in water, displaying non-significant adsorption at the organic/aqueous phase boundary resulting in higher interfacial tension, causing agglomeration to occur, hence the bigger particle sizes (Chernysheva et al., 2003; Song et al., 2006). All the nanoparticles prepared with DCM and DCM/EA mixture as solvents were not uniform as depicted by PDI values ranging from 0.4± 0.05to 0.5± 0.07, however PCL-LAM nanoparticles prepared with EA showed very narrow size distribution.

ZP is an important parameter, which can predict the physical stability of the nanodispersion. It also indicates the degree of electrostatic interactions within the colloidal system. Moreover, it could govern the interaction with living cells. Whether positive or negative, higher values of the ZP show that particles generally prevent agglomeration due to electrostatic repulsive forces (Das et al., 2011). ZP of more than ±13 mV indicates stable nanoparticles. The overall nanoparticles had higher positive surface charge, ranging from +18±3 mV to +23±1 mV, implying that PCL-LAM nanoparticles show a

great deal of stability. The positive surface charge of nanoparticles produced in this work is attributed to the addition of chitosan into the formulation (see method section). Chitosan is known to open the tight junctions resulting in an enhanced paracellular transport across the epithelium (Inez et al., 2003). Studies on nasal and oral drug delivery systems have shown that significantly higher amounts of drugs can be transported after co-administration with chitosan (Inez et al., 2003)

3.2. Effect of excipients

A further objective of the present section was to investigate the effect of the different excipients on the properties of the spray-dried PCL-LAM nanoparticles. For this purpose, different formulations involving two of the most commonly used excipients in the preparation of the spray-dried nanoparticles or microparticles were used, i.e. lactose and trehalose (Arpagaus et al, 2010). These excipients are approved by the United State-Food and Drug Administration, due to their non-toxicity and readily degradable properties after administration (Arpagaus et al, 2010). The inclusion of these excipients in the formulation is of importance, since PCL exhibits low melting temperatures (T_m), low glass transition temperatures (T_g) of 54^{o}C to 64^{o}C and -60^{o}C, respectively (Woodruff and Hutmacher, 2010). Thus the process with the spray drying must be carried at low inlet temperatures to avoid the sticking problems. Recently Kho and co-workers (2010) showed that the formation of PCL nanoparticles without adding excipients resulted in the collection of the polymer films on the drying chamber and walls of the cyclone. Lactose is characterized with low stickiness properties compared to other sugars like sucrose, glucose and maltose (Arpagaus et al, 2010). In addition, its higher T_g of 101^{o}C enables a simple flowing powders during spray-drying process. Similarly, trehalose has a higher T_g of between 75 and 120^{o}C compared to glucose and sucrose (Simplerler et al., 2006; Rose & Labuza, 2005), and its T_m is 210.5^{o}C (Higashiyama, 2002), comparable to that of lactose (223^{o}C).

Figure 1 shows the mean particle size, PDI when lactose and trehalose were used, respectively in A and B. Results indicated that small PCL-LAM nanoparticles ranging from 214±3 nm to 553±9 nm were formed when lactose was used as excipient and large PCL-LAM nanoparticles ranging from 277±28 nm to 604±9 nm were obtained with trehalose. All nanoparticles prepared with lactose had at least minimum PDI of 0.23±0.01 to 0.48±0.07, and trehalose produced PDI ranging from 0.42±0.04 to 0.47±0.07. The overall nanoparticles prepared in the presence of lactose and trehalose had higher positive surface charge ranging from +18±1 mV to +23±1 mV for lactose and +18.±1 mV to +20±1 mV for trehalose, indicating that PCL-LAM nanoparticles might be stable. These results show that lactose is a good excipient in the formulation of spray-dried PCL-LAM nanoparticles. This might be due to higher T_m of lactose when compared to that of trehalose.

3.3. The effect of drug concentration on EE of PCL-LAM nanoparticles

The previous sections showed that a partially water soluble solvent EA and lactose as excipient are good candidates for the preparation of PCL-LAM nanoparticles, thus there were further selected to produce nanoparticles. The amount of PCL, organic solvent as well as lactose were kept constant, while the amount of LAM was varied to assess its effect of mean particle size, PDI, ZP, EE, and the results are shown in Fig. 2. There were insignificant differences in mean particle size among different nanoparticles prepared with LAM drug ranging from 50 to 75 mg. The mean particle sizes obtained were 244±3 nm, 252±5 nm for 50 mg LAM and 75 mg LAM, respectively. The mean particle size decreased with increasing the amount of drug to 100 mg with the value of 215±3 nm. PCL-DF nanoparticles were also prepared as control, and showed the mean particle size of 234±3 nm. The PDI values obtained were 0.165±0.01, 0.205±0.02, 0.227±0.01 for PCL-LAM (50 mg), PCL-LAM (75 mg), PCL-LAM (100 mg) nanoparticles, respectively, and 0.155±0.02 for PCL-DF nanopartcles. These results indicate that PDI was increasing with the increase of amount of drug in the formulation. One possible reason could be the increase in viscosity of the solution with increasing drug concentration, thus posing difficulty in stirring them into smaller emulsion droplets. EE was found to decrease with increasing amount of LAM. PCL-LAM (50 mg) had higher EE of 78±4%, while PCL-LAM (75 mg) and PCL-LAM (100 mg) had EE of 71±6% and 68±4%, respectively. Moreover, irrespectively of the amount of drug nanoencapsulated in the formulation, drug loading was ranging from 20% to 35%. ZPs were greater than +20 mV in all cases, which suggest good stability of the PCL-DF and PCL-LAM nanoparticles

Figure 2: Mean particle size, PDI and EE (%) of the prepared PCL-LAM nanoparticles a) 50 mg LAM, b) 75 mg LAM and c) 100 mg LAM on the formulation (data represent mean± SD, n = 3)

3.4. Morphology of PCL-LAM nanoparticles

Figure 3 shows SEM images of the prepared PCL-LAM nanoparticles. All PCL-LAM nanoparticles prepared in the presence of lactose had spherical morphology, confirming the ability of lactose as a surface modifier and to enhance spherical morphology of the nanoparticles (Takeuchi et al, 1998). Some PCL-LAM nanoparticles prepared in the presence of trehalose showed the formation of crystals, these results also support that lactose was good drying excipient. Figure 4 shows PCL-LAM nanoparticles, when EA and lactose were used only on the formulation. All PCL-LAM nanoparticles had spherical morphology. No changes were observed when the amount of LAM drug was increased from 50 to 100 mg. PCL-DF nanoparticles also showed spherical morphology

Figure 3: SEM images: (A) PCL-LAM nanoparticles with DCM and lactose, B) PCL-LAM nanoparticles with EA and lactose, C) PCL-LAM nanoparticles with DCM/EA and lactose, D) PCL-LAM nanoparticles with DCM and trehalose, E) PCL-LAM nanoparticles with EA and trehalose, F) PCL-LAM nanoparticles with DCM/EA and trehalose

Figure 4: SEM images when EA and lactose were used to prepare the nanoparticles. A) PCL-DF nanoparticles, B) PCL-LAM (50 mg) nanoparticles C) PCL-LAM (75 mg), D) PCL-LAM (100 mg) nanoparticles

3.5. Structural compositions of PCL-LAM nanoparticles

Structural compositions of the PCL-LAM nanoparticles were investigated only on the ones prepared with partially water soluble solvent (EA), lactose as an excipient and PCL-LAM (100 mg) nanoparticles because they displayed more optimal properties. Pure PCL polymer and PCL-DF nanoparticles were used as controls. An assessment on the FTIR analysis of pure PCL, PCL-DF and PCL-LAM nanoparticles showed the characteristic peak of the PCL polymer (Figure 5) at around 1721.4 cm^{-1} and 1725.9 cm^{-1} due to the C=O stretching vibration (Wu, 2005; Sahoo et al., 2010). LAM spectra presented two bands at 1634.46 cm^{-1} and 1605.24 cm^{-1}, attributed to -C=O and -C=N, respectively, similar results were obtained by Dev and co-workers (Dev et al., 2010). The new peak of the PCL-LAM nanoparticles was formed between 1750 cm^{-1} and 1600 cm^{-1}. The peak shows the interaction between the PCL polymer and the LAM drug. In addition it confirms that the drug was nanoencapsulated into the PNPs.

Figure 5: FTIR spectra of (A) PCL-LAM nanoparticles, (B) LAM drug, (C) PCL-DF nanoparticles, and (D) pure PCL.

3.6. X-ray diffraction

The XRD analysis was used to determine the crystalline and amorphous regions of the product. Figure 6 presents the XRD patterns of pure PCL polymer, LAM drug, PCL-DF and PCL-LAM (100 mg) nanoparticles. The polymer presented two sharp peaks at around 21.3^{o} and 23.9^{o} which are due to scattering from crystalline region and the "hump" can be attributed to scattering from the amorphous region (Young and Lovell, 1991). A similar spectrum was also reported by Wu (2005). The XRD patterns of LAM presented multiple sharp peaks showing the crystalline nature of the drug. However the XRD patterns of the spray dried PCL-DF and PCL-LAM nanoparticles were characterized by broad hump and the absence of any sharp peaks over the entire 2 theta, which is an indicative of their amorphous nature.

Figure 6: X-ray diffraction patterns of (A) pure PCL, (B) LAM drug, (C) PCL-DF nanoparticles, and (D) PCL-LAM nanoparticles

3.7. Drug release of the PCL-LAM nanoparticles

Figure 7 shows the drug release rate of the PCL-LAM (100 mg) nanoparticles suspended in media of various pH values i.e. 1.3, 4.5 and 6.8. After 8 hours, LAM drug concentration in buffer came around 39.0%, 38.6% and 44.0% at pH 1.3, 4.5 and 6.8, respectively. The obtained results demonstrate that drug release rates increased as the pH approaches the alkaline media. The release of the drug from polymer nanoparticles can be affected by many factors such as polymer degradation, molecular weight of the polymer, crystallinity, the binding affinity between the polymer and the drug (Shin et al., 1998), and so forth. The lower drug release rate in the pH 1.3 and pH 4.5 than pH 6.8 is attributed to the repulsion between H^+ present in the acidic media (1.3 and pH 4.5) and cations on the surface of the PCL-LAM nanoparticles by superficial chitosan layers, which slow down the hydrolysis (Proikalis et.al.,2006; Zhao et. al., 2004). The PCL-LAM nanoparticles were coated with chitosan. The slow release rates observed at low pH values is significant because those are similar to the conditions in the GI track.

Figure 7: Drug release rate of PCL-LAM nanoparticles in pH 1.3, 4.5 and pH 6.8.

4. Conclusions

Double emulsion spray-drying process resulted in the formation of small mean particle size with good PDI and spherical morphology when EA and lactose were used as solvent and excipient, respectively. However, when DCM or a mixture of DCM/EA solvent and trehalose were used as excipient, large nanoparticles were obtained with poor PDI. These highlighted that DCM is not a good solvent for the preparation of PCL-LAM nanoparticles. Different characterization methods employed in this work showed that the process did not affect the properties of the drug and the polymer, after the spray-drying method. The process parameters utilised in this study assisted to convert the crystalline drug and semi-crystalline polymer into the amorphous form, and a significant amount of drug was released from PCL nanoparticles within 24 hours and at different pHs mimicking the pH profile of the GI tract, unlike the half life of 5 to 7 hours when compared to the LAM free drug

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