Core/shell microencapsulation of indomethacin/paracetamol by co-axial electrohydrodynamic atomization

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HIGHLIGHTS

• Oral drug delivery systems were prepared by single step co-axial electrohydrodynamic atomization with high processing yield.
• Polymer carrier systems (PCS) suitable for the process and drugs were developed first.
• Model drugs of different aqueous solubility were successfully incorporated in the PCS with 50-70% encapsulation efficiency.
• This technique is a versatile platform for combined drug therapy and polypharmacy.

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ABSTRACT

Core/shell microparticles for development of drug delivery systems were prepared using co-axial electrohydrodynamic atomization technique in order to develop fixed dose combined formulations incorporating paracetamol and indomethacin as model drugs. The developed drug delivery systems offered successful co-encapsulation of paracetamol and indomethacin with high drug encapsulation efficiencies of 54% and 69% for paracetamol and indomethacin, respectively. The developed formulations were further characterised with respect to their morphology, drug release profile and possible interactions. In comparison to the release rate of the free indomethacin, the developed formulation resulted in enhanced dissolution rate of indomethacin. This study demonstrates a versatile polymeric platform where multiple drug encapsulation and co-delivery is made possible by utilizing co-axial electrohydrodynamic atomization. The proposed system offered high processing yield of 60–70%, as a single-step platform for preparation of fixed dose formulations for oral drug delivery, particularly in geriatric therapy.

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1. Introduction

Fixed dose combination drugs, also known as FDCs, are essentially two or more active pharmaceutical ingredients formulated in a single dosage form [1]. These formulations are relatively common for nearly all therapeutic areas and are available for different routes of administration including oral, parenteral and inhalation; among which the oral delivery route is the most common [2]. Fixed dose combination products are of key importance in treating numerous types of diseases such as cardiovascular, HIV/AIDS, malaria and tuberculosis where multiple therapies are required [3–6]. Different pharmacological mechanisms can be introduced into one single dosing unit offered by FDC products [7]. This often presents synergistic value in therapeutic outcomes [8].

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where the efficacy is enhanced compared to co-administration of the individual drugs. The potential for drug abuse can be minimised by use of combined drugs, where one would diminish the unintended side effects of the other [9]. Moreover, incorporation of both short acting and long acting active pharmaceutical ingredients enables coverage of an extended period for therapeutic effect. These formulations also enable combination of drugs where one improves the safety and/or tolerability of the other. In addition, FDC products reduce manufacturing costs. Nonetheless, design and process development of FDC formulations are challenging compared with single entity products [10,11]. Various factors complicate the development of these formulations. These are the size of the prepared tablet of the FDC product, disproportionate drug dose combination and different aqueous solubility [1].

Electrohydrodynamic atomization (EHDA) has been utilized to assist encapsulation of both hydrophilic and hydrophobic active pharmaceutical ingredients with reported high encapsulation efficiency and fabrication yield [12–14]. This technique also offers control over particle size and morphology and hence the release profile and bioavailability of the incorporated active ingredients in the body [15]. Solvent evaporation in the process also negates the need for post processing of the developed particles [16]. Furthermore, EHDA results in preparation of polymeric particles with narrow size distributions that are extremely attractive for pharmaceutical applications [17]. In a study by Bohr et al. [18], EHDA was used for preparation of amorphous formulations of low water soluble drug, where monodispersed polymeric drug delivery systems were developed and offered an enhanced release profile and dissolution rate of celecoxib. EHDA has also been used for preparation of targeted drug release, where the site-specific delivery of an active pharmaceutical ingredient is desirable [19]. In a recent study by Jia et al. [20] nanoffbers were developed for delivery of indomethacin and mebeverine using coaxial electrospinning for targeted treatment of bowel disease and colon cancer. Careful selection of processing materials and fine-tuning of the co-axial composition system can introduce different mechanisms of release and complex structural features onto polymeric drug delivery systems. In a recent study [21] ethyl cellulose functional nano-fibres were produced and zero-order release of ketoprofen was achieved.

Indomethacin is a light-sensitive nonsteroidal anti-inflammatory drug (NSAID), which is used as a prescription medication to relieve pain and inflammatory conditions. It has poor water-solubility and is also classified as a highly permeable drug [22]. Indomethacin in an amorphous solid state is found to be the most soluble of all solid forms [23]. Indomethacin was electrosprayed onto reduced and atmospheric pressure in a study by Nyström et al. [24] and it was found that the reduced particle size gave rise to higher surface area to volume ratio. In addition to that, the resultant amorphous state of the indomethacin particles enhanced its solubility [24]. Paracetamol is an analgesic used for reducing mild to moderate body pain. It also acts as an antipyretic which helps to decrease body temperature [25]. It is completely adsorbed from the intestinal tract and metabolized by the liver. At high concentrations it can result in hepatic injury [26]. Attempts have been made to prepare oral controlled release formulations of paracetamol to enable slow release in a controlled manner into the gastrointestinal tract. With this objective, in a recent study, mucoadhesive microspheres of xanthan gum and guar were developed incorporating paracetamol [27]. Endo et al. [28] has reported development of gel formulation for the oral delivery of paracetamol with high bioavailability of 90% in rabbit. In-situ gelling formulations comprising gelatin gum and sodium alginate have also been developed for oral delivery of aqueous paracetamol solution. For this purpose, functionalised depots were developed and were able to introduce controlled release paracetamol for 6 h, with similar bioavailability to those of commercial suspensions [29].

Co-axial electrohydrodynamic atomization was used in this work in order to prepare drug delivery systems, whereby model drugs of different aqueous solubility, paracetamol (PCM) and indomethacin (INDO), were embedded in polymeric particles. For this purpose, poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) were used [30,31], as they are both biocompatible, non-toxic polymers that are approved by FDA and excessively used for biopharmaceutical applications [32–34].

The main objective of this work was to co-encapsulate the two drugs into polymeric matrices with the aim to increase the dissolution rate of indomethacin and achieving controlled release of paracetamol, using co-axial electrohydrodynamic atomization. On the basis of successful application of this technique to incorporate multiple active pharmaceutical ingredients, this work would present a potential platform for development of fixed dose combination formulations that are attracting increasing attention in the area of geriatric and cancer therapy.

The proposed system is based on the hypothesis that the placement of the non-water soluble drug in the outer layer would result in positioning of the drug at the outermost surface, hence, having higher surface area to volume ratio, in addition to minimising diffusion distance when compared to the hydrophilic drug in the inner layer. Inclusion of the water soluble paracetamol was based on the fact that the outer PLGA layer would protect it from undergoing burst release and so prolonging the release period. If the polymer combination was reversed, using PEG in the outer surface would consequently result in burst release of the incorporated drug. The aforementioned reasoning was the logic in using PEG in the inner layer and PLGA in the outer layer, also demonstrating that the system is adaptable for variant polymer/drug composition, proving it to be a viable platform for further enhancement of development of the customized polymeric drug delivery system as demanded by FDC developments.

2. Experimental details

2.1. Materials

PLGA copolymer (50:50) Resomer RG503H of average molecular weight 33,000 g/mol was obtained from Boehringer Ingelheim Germany. PEG of molecular weight 8000 g/mol, dimethylcarbonate and methanol, indomethacin (≥99.0% purity) and paracetamol (≥99.0% purity) were supplied by Sigma-Aldrich (Poole, UK). All of the above were used as received.

2.2. Solution preparation

4% w/w, 6% w/w and 8% w/w PLGA solution was made by dissolving appropriate amount of PLGA in dimethylcarbonate (DMC) followed by mechanical stirring to ensure complete dissolution of the polymer. To prepare the drug incorporated solution 0.4% w/w indomethacin (solubility in water 0.937 mg/l [35]) in DMC was then added to the 4% w/w PLGA solution followed by further stirring to facilitate thorough dissolution of both the polymer and the model drug under ambient conditions, 20 °C and 40–60% relative humidity. 2% w/w, 4% w/w and 6% w/w PEG solutions was prepared by dissolving PEG in methanol and was stirred until complete dissolution of PEG. To prepare the drug incorporated

<table>
<thead>
<tr>
<th>Polymer system</th>
<th>Inner solution</th>
<th>Outer solution</th>
<th>Mean particle size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>2% w/w PEG in MeOH</td>
<td>4% w/w PLGA in DMC</td>
<td>8.06 ± 0.84</td>
</tr>
<tr>
<td>S2</td>
<td>4% w/w PEG in MeOH</td>
<td>6% w/w PLGA in DMC</td>
<td>6.74 ± 0.70</td>
</tr>
<tr>
<td>S3</td>
<td>6% w/w PEG in MeOH</td>
<td>8% w/w PLGA in DMC</td>
<td>6.40 ± 0.85</td>
</tr>
</tbody>
</table>
To ensure complete dissolution of both the polymer and the model drug, indomethacin particles, PCMINDOP: paracetamol-indomethacin particles. Processing yield of the proposed system at ambient conditions. The polymeric particles were then collected onto glass slides or needles in concentric configuration (Stainless Tube & Needle Co Ltd., Tamworth, UK) connected to a high power voltage supply (Glassman Europe Ltd., Tadley, UK) as shown in Fig. 1. Both needles were infused simultaneously with the polymeric solutions. The external and internal diameters of the outer needle were 2.03 mm and 1.52 mm, respectively; those of the inner needle were 1.07 mm and 0.69 mm, respectively. The needles were connected to plastic syringes (10 ml) (BD Plastic™, VWR, Lutterworth, UK), by means of silicone tubing (inner diameter of 1.0 mm, Sterilin Ltd., Newport, UK); the syringes were placed onto precision syringe pumps (PHD 4400, Harvard Apparatus, Edenbridge, UK). The applied voltage and flow rates were varied based on the polymeric solution properties in order to achieve a stable cone jet, resulting in formation of particles with desired characteristics. The working distance of 150 mm (distance between needle tip and the collector) was fixed for all of the experiments in order to confirm that the applied electric field strength was changed in proportion to the applied voltage values. The polymeric particles were then collected onto glass slides or a stainless steel platform connected to the ground electrode for characterization and drug release measurements, respectively. The formation of the jet and droplets was observed using a LEICA DMS300 camera. Experiments were done at ambient conditions. The yield of the process was determined by measuring the amount of collected particles for a given amount of time and comparing to that of the theoretical amount of particle collection for that specific period as a measure to examine the processing yield of the proposed system at ambient conditions.

2.3. Electrohydrodynamic atomization

In the co-axial EHDA set-up used in this work, two stainless steel needles in concentric configuration (Stainless Tube & Needle Co Ltd., Tamworth, UK) were connected to a high power voltage supply (Glassman Europe Ltd., Tadley, UK) as shown in Fig. 1. Both needles were infused simultaneously with the polymeric solutions. The external and internal diameters of the outer needle were 2.03 mm and 1.52 mm, respectively; those of the inner needle were 1.07 mm and 0.69 mm, respectively. The needles were connected to plastic syringes (10 ml) (BD Plastic™, VWR, Lutterworth, UK), by means of silicone tubing (inner diameter of 1.0 mm, Sterilin Ltd., Newport, UK); the syringes were placed onto precision syringe pumps (PHD 4400, Harvard Apparatus, Edenbridge, UK).

The applied voltage and flow rates were varied based on the polymeric solution properties in order to achieve a stable cone jet, resulting in formation of particles with desired characteristics. The working distance of 150 mm (distance between needle tip and the collector) was fixed for all of the experiments in order to confirm that the applied electric field strength was changed in proportion to the applied voltage values. The polymeric particles were then collected onto glass slides or a stainless steel platform connected to the ground electrode for characterization and drug release measurements, respectively. The formation of the jet and droplets was observed using a LEICA DMS300 camera. Experiments were done at ambient conditions. The yield of the process was determined by measuring the amount of collected particles for a given amount of time and comparing to that of the theoretical amount of particle collection for that specified period as a measure to examine the processing yield of the proposed system at ambient conditions.

solution, 0.2% w/w paracetamol (solubility in water 14 mg/ml at 25 °C [26]) was then added to the prepared 2% w/w PEG solution and stirred to ensure complete dissolution of both the polymer and the model drug at the ambient conditions, 20 °C and 40–60% relative humidity. These ambient conditions were kept in all our experiments in this work. Details of polymeric systems and the developed formulations are shown in Tables 1–4, respectively.

2.4. Solution characterization

The density, electrical conductivity, surface tension and viscosity of the prepared polymeric solutions used for the development of the formulations were measured. A standard density bottle (DIN ISO 3507-Gay-Lussac) was used for density measurement. A U-tube viscometer (size E, VWR, Lutterworth, UK) was used for viscosity assessments. Surface tension measurements were made with Kruss tensiometer (Model DSA100, Kruss GmbH, Hamburg, Germany) adopting the Wilhelmy’s plate method. A conductivity probe (Jenway 3540 pH/conductivity meter) was used to measure the electrical conductivity of the prepared solutions. These characteristics are presented in Table 3. All the experiments were run in triplicate at ambient conditions with calibrated equipment, at ambient conditions.

2.5. Particle characterization

2.5.1. Optical and scanning electron microscopy

Particles that were collected on glass slides were analysed primarily using an optical microscope (Nikon Eclipse ME 600) that was fitted with a camera (Micropublisher 3.3 RTV, 3.3 megapixel CCD Color-Bayer Mosaic, Real Time Viewing camera, Media Cybernetics, Marlow, UK). Particle morphology was further investigated utilizing the scanning electron microscope (SEM, XL30 FEG, Philips). Average particle size and size distribution were obtained using Image J software, where 300 particles were studied.

2.5.2. Transmission electron microscopy

Particles were collected on 400 mesh copper TEM grids. TEM studies were conducted at 120 kV (Philips CM 120 Bio-Twin) for the examination of different layer formation.

2.5.3. Focused ion beam (FIB) microscopy

Cross sectional images of the particles were prepared using focused ion beam milling (FIB) (Carl Zeiss XB 1540 “Cross-Beam”) equipped with a Gemini SEM column. Particles were gold sputtered for 120 s and mounted on metallic studs. Accelerating voltage of 5 to 10 kV was used during scanning.

2.5.4. Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) was performed using a Spectrum 100 FTIR spectrometer (FTIR-ATR-PerkinElmer) fitted with an ATR attachment. Spectra of paracetamol, indomethacin, PLGA, PEG and the prepared formulations were recorded using a frequency range of 750–4000 cm⁻¹ and a set resolution of 1 cm⁻¹. Powdered samples were positioned on the attenuated total reflectance (ATR) crystal and compressed using an axial screw.

2.5.5. Differential scanning calorimetry

Differential Scanning Calorimetry (Netzsch STA 449C Jupiter, Netzsch USA) was used to observe the thermal behaviour of pure PLGA, PEG, paracetamol and indomethacin as well as the prepared formulations including unloaded particles, paracetamol loaded particles, indomethacin loaded particles, and paracetamol and indomethacin loaded particles.

Table 2

Properties of the solutions used in this work.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Surface tension (mN/m)</th>
<th>Viscosity (mPa s)</th>
<th>Electrical conductivity (µS/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% w/w PEG in MeOH</td>
<td>22.8 ± 0.30</td>
<td>0.93 ± 0.05</td>
<td>22.3 ± 0.45</td>
</tr>
<tr>
<td>4% w/w PEG in MeOH</td>
<td>23.1 ± 0.61</td>
<td>0.99 ± 0.05</td>
<td>24.9 ± 0.88</td>
</tr>
<tr>
<td>6% w/w PEG in MeOH</td>
<td>22.87 ± 0.15</td>
<td>1.19 ± 0.04</td>
<td>29.5 ± 0.25</td>
</tr>
<tr>
<td>4% w/w PLGA in DMC</td>
<td>25.7 ± 0.16</td>
<td>1.97 ± 0.19</td>
<td>0.01 ± 0</td>
</tr>
<tr>
<td>6% w/w PLGA in DMC</td>
<td>27.9 ± 0.7</td>
<td>2.63 ± 0.09</td>
<td>0.03 ± 0</td>
</tr>
<tr>
<td>8% w/w PLGA in DMC</td>
<td>27.7 ± 0.17</td>
<td>4.59 ± 0.08</td>
<td>0.03 ± 0.005</td>
</tr>
</tbody>
</table>

Table 3

The compositions of the developed formulations. PCMP: paracetamol particles, INDOP: indomethacin particles, PCMINDOP: paracetamol-indomethacin particles.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Inner solution</th>
<th>Outer solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCMP</td>
<td>2% w/w PEG, 0.2% w/w</td>
<td>2% w/w PEG in MeOH</td>
</tr>
<tr>
<td></td>
<td>Paracetamol in MeOH</td>
<td>Paracetamol in MeOH</td>
</tr>
<tr>
<td>INDOP</td>
<td>2% w/w PEG in MeOH</td>
<td>4% w/w PLGA, 0.4% w/w</td>
</tr>
<tr>
<td></td>
<td>Paracetamol in MeOH</td>
<td>Indomethacin in MeOH</td>
</tr>
<tr>
<td>PCMINDOP</td>
<td>2% w/w PEG, 0.2% w/w</td>
<td>4% w/w PLGA, 0.4% w/w</td>
</tr>
<tr>
<td></td>
<td>Paracetamol in MeOH</td>
<td>Indomethacin in DMC</td>
</tr>
</tbody>
</table>
Samples of 5 mg were placed in aluminium pans and analysed over a temperature range of 30 °C to 200 °C at a rate of 5 °C/min.

2.5.6. Drug loading and entrapment efficiency

30 mg of drug-loaded microparticles were dissolved in dimethylacetamide (DMAc) then diluted with PBS pH 7.4 and agitated for 1 h under sealed conditions. The obtained solution was then filtered through 0.22 μm filters and the drug content was analysed using UV/VIS Spectrometer (Cary 300 UV–Vis, Agilent Technologies) at corresponding detection wavelengths (243 nm for paracetamol and 320 nm for indomethacin). Calibration curves were also obtained in the range of 1–50 μg/ml where a good correlation was found over the covered range. The drug loading and the drug entrapment efficiency were calculated using the following equations, respectively:

\[
\text{Drug Loading (\%)} = \frac{M_{\text{actual}}}{\text{weighed amount of microparticles}} \times 100
\]

\[
\text{Encapsulation Efficiency (\%)} = \frac{M_{\text{actual}}}{M_{\text{theoretical}}} \times 100
\]

M indicates the mass of the drug.

2.5.7. In vitro drug release study

20 mg of micro-particles were placed in 50 ml of PBS pH 7.4 at a set temperature of 37 °C ± 1. 3 ml of samples were taken at a predetermined time interval for 8 h and filtered using 0.22 μm filters to ensure that no particles were collected at the point of withdrawing aliquots. The samples were analysed using UV/Vis Spectrometer. Each time 3 ml of PBS was added in order to maintain constant volume of the dissolution medium.

3. Results and discussion

3.1. Jetting behaviour of polymeric solutions

In EHDA processing, physical properties of the flowing solution including viscosity, surface tension and electrical conductivity are of crucial importance as they govern the jet and consequently the particle formation [36]. In addition to these physical properties, careful selection of processing parameters such as flow rate, applied voltage and working distance further controls the establishment of the stable cone-jet mode [37]. The atomization mode could vary between cone-jet mode and dripping mode based on the variation of electric field strength, which can be increased either by increasing the applied voltage or by decreasing the working distance [38].

3.2. Polymeric drug delivery system

In this work, particles with and without the incorporation of model drugs were made. In the case of unloaded polymeric particles, the inner needle was infused with 2% w/w, 4% w/w and 6% w/w PEG in methanol and the outer needle was infused with PLGA 4% w/w, 6% w/w and 8% w/w in DMC. This was done prior to drug loading to optimize the polymeric carrier system. The selected system was chosen based on successful preparation of optimum particle size with narrow size distribution and reproducible results that was achievable due to formation of the stable cone jet. The inner and outer layer had nearly the same surface tension; which in turn results in formation of flowing mediums that are treated as one [39]. The flow rates of the inner and outer solution were set at 4 μl/min and 10 μl/min for the first polymeric solution system (S1) (Fig. 2a), the higher acquired flow rate for the outer solution was due to higher

Table 4

<table>
<thead>
<tr>
<th>Solution</th>
<th>Surface tension (mN/m)</th>
<th>Viscosity (mPa s)</th>
<th>Electrical conductivity (μS/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4% w/w PLGA in DMC</td>
<td>25.7 ± 0.16</td>
<td>1.97 ± 0.19</td>
<td>0.01 ± 0</td>
</tr>
<tr>
<td>4% w/w PLGA, 0.4% w/w Indomethacin in DMC</td>
<td>24.9 ± 0.15</td>
<td>1.9 ± 0.09</td>
<td>0.03 ± 0.02</td>
</tr>
<tr>
<td>2% w/w PEG in MeOH</td>
<td>22.8 ± 0.30</td>
<td>0.93 ± 0.05</td>
<td>22.3 ± 0.45</td>
</tr>
<tr>
<td>2% w/w PEG, 0.2% w/w Paracetamol in MeOH</td>
<td>23 ± 0.39</td>
<td>1.94 ± 0.07</td>
<td>23.8 ± 0.35</td>
</tr>
</tbody>
</table>

Fig. 1. Schematic diagram of co-axial electrohydrodynamic atomization process.
Fig. 2. SEM images and size distribution graphs of particles made with a) S1 (2% w/w PEG, 4% w/w PLGA), b) S2 (4% w/w PEG, 6% w/w PLGA), c) S3 (6% w/w PEG, 8% w/w PLGA). The first mentioned is the inner layer.

Fig. 3. SEM images and particle size distribution histograms of a) PCMP, b) INDOP and c) PCMINDOP.
electrical conductivity of the inner layer, hence allowing directing the electrical stresses toward the apex of the Taylor cone, while overcoming the surface tension and thus establishing a stable cone-jet. The slight difference in the polymer solution viscosities, as shown in Table 2, is favourable to formation of compact particles in the co-axial electrohydrodynamic atomization [40]. When compared to S2 and S3, S1 has slightly higher mean particle size (8.06 μm ± 0.85) as a result of higher flow rate in the outer needle and lower applied voltage of 16.9 kV with respect to the other systems (Fig. 2a).

As for the other two systems, the flow rate was set to 4 μl/min and 8 μl/min for the second system (S2) (Fig. 2b) and 4 μl/min and 8 μl/min for the third system (S3) (Fig. 2c); with an applied voltage of 17.9 kV and 17.6 kV respectively, in order to achieve a stable cone jet that would result in formation of nearly monodispersed particles as seen in Figs. 2b and c. The mean particle size for S2 and S3 were 6.74 μm ± 0.69 and 6.44 μm ± 0.86. It is also worth noting that the minimum required solution electrical conductivity is approximately ≈ 0.01 μS/m for EHD processing [40], which is met in this study as shown by Table 2.

Upon evaporation of solvents, microparticles are produced where the evaporation rate of the selected solvents influence the particle size distribution; the higher the evaporation rate and the lower the melting point, the smaller the particles as there is successively a greater loss of solvents as the cone-jet emits and lands on the collection platform.

The yield of the process was measured and a mean of 60–70% particle collection was achieved followed by optimization of the collection platform.

3.3. Incorporation of the model drugs

With the addition of much more soluble drug (paracetamol) in the inner layer the particles forming parameters, flow rate and applied voltage were adjusted in order to achieve the desired particle size while keeping the working distance constant. The flow rates of the inner and outer layer were 4 μl/min, 14 μl/min at 15.7 kV (Fig. 3a) for the PCMP formulation (Table 3). The mean particle size achieved was 5.3 μm ± 0.6 with a polydispersity of 10%. For preparation of INDOP formulation (Table 3), the practically water insoluble model drug (indomethacin) was then added to the system (Fig. 3b) and processed where the flow rates of the inner and outer layer were 4 μl/min, 10 μl/min at 16.4 kV. The mean particle size achieved was 7.4 μm ± 0.8 with a polydispersity of 10%.

Upon establishment of the drug delivery carriers incorporating a single drug at a time, binary drug delivery systems were developed by simultaneous incorporation of the two model drugs (Fig. 3c). Here, to prepare PCMINDOP formulation (Table 3), the processing parameters were set at 4 μl/min, 14 μl/min for the inner needle and outer needle flow rate, respectively, with an applied voltage of 15 kV, where a mean particle size of 7.7 μm ± 0.8 with 10% polydispersity was achieved. The mean particle size was lowest for PCMP, which is attributable to higher surface tension of the outer needle solution (Table 4), even though the applied voltage is lower of that of INDOP. In the INDOP formulation, the flow rate of the outer solution is set at a lower value when compared with the other two formulations, this was due to slightly higher conductivity of the outer solution that in turn resulted in adaptation of a lower flow rate [41].

From the TEM images obtained (Fig. 4) it can clearly be seen that the prepared formulations exhibit a double-layer structure as distinguished by the difference in contrast between the inner PEG and outer PLGA layer. Yellow arrows and dotted lines indicate different layers as shown in Fig. 4. It is evident that there is an overall size difference from one layer to another that is attributable to the different flow rates used for each solution. It must be noted that varying the material and processing parameters further modulates layer thickness. Moreover, the formation of a double-layered structure is preserved in all formulations.
The morphology of the microparticles S1 (unloaded particles) and the porosity of the prepared formulation were studied using FIB/SEM (Fig. 5). The particles show a smooth surface indicating high solubility of the polymers in the associated solvents used. The yellow arrows are indicative of the cross sectional cuts through the microparticles.

FTIR spectra were recorded to investigate possible interaction between PLGA and PEG with the corresponding drugs indomethacin and paracetamol during encapsulation. FTIR spectra of PLGA, PEG, indomethacin and paracetamol before and after undergoing processing are also shown in Fig. 6.

The pure indomethacin sample demonstrates characteristic peaks at 1689 cm⁻¹ (amide group) and 1721 cm⁻¹ (carboxyl stretching), the pure paracetamol exhibited O–H stretching at 3100 cm⁻¹ to 3500 cm⁻¹, N–H stretching at 3200 cm⁻¹ to 3400 cm⁻¹, and C=O stretching from 1620 cm⁻¹ to 1655 cm⁻¹, also para-distributed aromatic ring from 750 cm⁻¹ to 850 cm⁻¹. Moreover, pure PEG showed stretching C–O from 1000 cm⁻¹ to 1260 cm⁻¹, stretching C–O–C from 1050 cm⁻¹ to 1150 cm⁻¹, stretching C–H from 1300 cm⁻¹ to 1450 cm⁻¹ and 2850 cm⁻¹ to 2960 cm⁻¹. From pure PLGA the bands at 1050 cm⁻¹ to 1250 cm⁻¹ are characteristic of C=O stretching of aliphatic polyesters and also at 1760 cm⁻¹ C=O bond stretching was observed. The drug loaded particles show combination of peaks corresponding to polymers and model drugs showing there is no degrading interaction between the components.

DSC measurements (Fig. 7) indicate the physical state of paracetamol and indomethacin within the developed formulations (PCMP, INDOP and PCMINDOP). The thermographs obtained for PLGA and PEG indicates a glass transition temperature at 50 °C and 62 °C, respectively. However, these endothermic peaks were absent in the prepared formulations. Paracetamol and indomethacin melting peaks in pure form were observed at 170 °C and 160 °C, respectively. These peaks were not identified in the prepared formulations, suggesting that the incorporated drugs were well integrated in an amorphous form, which leads to development of the formulations that incorporated more water soluble form of the model drugs. This is attributed to the nature of EHDA process, whereby the polymeric system adopts a more amorphous state upon rapid evaporation of the solvent; hence the degree of crystallinity of the drug is compromised. This is favourable in case of encapsulation of drugs with low water solubility, resulting in higher degree of dissolution when introduced as a solid oral dosage unit [24].

3.4. Drug release

The encapsulation efficiency is a crucial parameter of the developed microparticles and also an indicator of the efficiency of the co-axial EHDA forming process [42]. The encapsulation efficiency of paracetamol from PCMP is 69% compared to that of PCMINDOP, which is 54%. The encapsulation efficiency of indomethacin in INDOP formulation is 78% and is higher compared to that of PCMINDOP, which is 69%.

In general, drug release from biodegradable polymers occurs by several mechanisms that couple and control the drug release rate [43]. In matrix structures, drug release occurs mainly through desorption of surface bound drug, the diffusion of the drug through a polymeric matrix and the polymer matrix erosion [43]. For particles of sub-micrometre size, due to reduced size and increased surface area to volume ratio, faster release of drug and higher degradation rate of the polymeric system is facilitated [13].
The release profiles of paracetamol were studied from PCMP and also PCMINDOP. As is suggested from Fig. 8, the release rate of paracetamol from PCMINDOP is slower than that of PCMP. However, the release pattern remained similar suggesting that drug dissolution occurred irrespective of the aqueous solubility of the drug. This is confirmed by Dubois and Ford [44] who concluded that formulations containing low drug concentration result in a polymer controlled dissolution profile that is predominantly dependent on the rate of dissolution of polymer rather than the properties of the drug. In the paracetamol release profile from PCMP 59% of the drug is released within the first 2 h. The corresponding value for PCMINDOP is 48%. The slightly higher release rate of paracetamol from the PCMP is attributed to the smaller particle size of 5 μm compared to that of 7.4 μm which further decreased the diffusion distance that the drug needs to travel in order to reach the dissolution medium.

In-vitro release profiles of indomethacin showed a small difference in release rate and profile between INDOP and PCMINDOP formulation (see Fig. 9.). This proves that there is no significant influence from incorporation of paracetamol into the polymeric drug delivery systems. The developed drug delivery systems incorporating indomethacin, which is a practically water insoluble drug, has significantly increased the dissolution of the active ingredient compared to that of the free drug. This is attributed to reduced particle size of the drug delivery carrier as previously discussed. Increased surface area to volume ratio of the particles is highly desirable for development of these formulations. Moreover, as confirmed by DSC results, the developed formulation incorporating indomethacin is in amorphous form, which further enhances the aqueous solubility of crystalline indomethacin and is accountable to the favourable nature of EHDA processing. The rate of oral absorption of the drug is often governed by the dissolution rate which is a key determinant of its oral bioavailability [45]. As it can be seen from the release profile obtained for INDOP and PCMINDOP in Fig. 9, micro-particles give an initial burst release in the first 2 h when introduced to the release medium and 72% and 68% of indomethacin is discharged, respectively. In comparison, there was only 14.8% release of free indomethacin after 2 h. After 3 h, the release rate of indomethacin from INDOP and PCMINDOP is decreased and follows a plateau. The initial release can also be attributed to the accumulation of the drug at the surface of the microparticles, which can be explained by difference in the degree solubility of polymer and the conjugating drug in the solvent used for processing. This consequently results in dislocation of the drug to a superficial level, as solvent evaporation takes place. The monomer ratio of PLGA that is used in this study contains 50% lactic acid 50% glycolic acid. Among other existing monomer ratios of this polymer, PLGA (50:50) offers the highest hydrophilicity and undergoes degradation at a faster rate [33]. Moreover, the water-soluble PEG core further enhances the hydration of the polymer matrix [46]. As the water permeates inside the drug carriers, it hydrolyses the polymer and subsequently creates a pathway for the drug to be released by diffusion and erosion until complete polymer solubilisation is achieved [33].
4. Conclusions

In this work, co-axial EHDA was used to prepare a series of core-shell polymeric systems. These comprised of using biodegradable biocompatible polymers and incorporation of drugs with different aqueous solubility. Successful formation of core/shell particles was achieved. The developed formulations offered enhanced release of the water insoluble drug (indomethacin), while controlling the release of the more highly water-soluble drug (paracetamol). The co-axial EHDA processing offered high processing yield of 70% with encapsulation efficiencies ranging between 54% and 78%. The initial burst release, during the first 2 h, ranged between 48% and 72%. The simultaneous release profiles of the model drugs satisfy the requirements of fixed dose combination products where active pharmaceutical ingredients are incorporated into the formulation for oral drug delivery systems.

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References


