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Dissolvable microarray patches of levodopa and carbidopa for Parkinson’s disease management

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ABSTRACT

Carbidopa and levodopa remain the established therapeutic standard for managing Parkinson’s disease. Nevertheless, their oral administration is hindered by rapid enzymatic degradation and gastrointestinal issues, limiting their efficacy, and necessitating alternative delivery methods. This work presents a novel strategy employing dissolving microarray patches (MAPs) loaded with carbidopa and levodopa, formulated with Tween® 80 to improve their transdermal delivery. The fabricated MAPs demonstrated an acceptable mechanical strength, resisting pressures equivalent to manual human thumb application (32 N) onto the skin. Additionally, these MAPs exhibited an insertion depth of up to 650 µm into excised neonatal porcine skin. Ex vivo dermatokinetic studies could achieve delivery efficiencies of approximately 53.35 % for levodopa and 40.14 % for carbidopa over 24 h, demonstrating their significant potential in drug delivery. Biocompatibility assessments conducted on human dermal fibroblast cells corroborated acceptable cytocompatibility, confirming the suitability of these MAPs for dermal application. In conclusion, dissolving MAPs incorporating carbidopa and levodopa represent a promising alternative for improving the therapeutic management of Parkinson’s disease.

1. Introduction

The prevalence of Parkinson’s disease (PD) presents a significant healthcare challenge, impacting around 10 million people globally [1–3]. First described by James Parkinson in 1817, this neurological disorder primarily affects the elderly population, yet its precise causes remain unclear [3]. As of now, no cure exists, but several treatment options aim to manage PD symptoms. Present therapies focus on compensating for the diminished dopaminergic activity in the brain, achieved through administering levodopa (a dopamine precursor), dopamine agonists, or dopamine enzymatic degradation inhibitors [4]. These treatments aim to maintain consistent therapeutic levels in the bloodstream to prevent “off” periods between doses [5].

The gold standard PD treatment involves levodopa and its decarboxylase inhibitor, carbidopa. Levodopa crosses the blood–brain barrier with the aid of a transporter, subsequently converting into dopamine. However, orally administered levodopa encounters obstacles, where gastrointestinal issues, common in PD patients, hinder consistent plasma levels with oral formulations [6]. Additionally, up to 80 % of PD patients experience some form of dysphagia, making oral drug administration challenging [7,8]. To address these challenges, an alternative intestinal gel (Duodopa®) bypasses the oral route, providing continuous levodopa and carbidopa delivery, reducing fluctuations and motor complications compared to oral tablets [9–11]. However, this approach involves an invasive procedure, raising concerns about peristomal infection and patient adherence [12]. Thus, seeking a non-invasive formulation for continuous levodopa and carbidopa delivery remains a critical issue in PD therapy.

Transdermal delivery of levodopa has emerged as a potential solution, overcoming problems linked to oral administration, such as metabolism and gastrointestinal issues. It offers a non-invasive alternative, potentially aiding elderly patients experiencing dementia and dysphagia symptoms. However, levodopa’s hydrophilic nature poses a challenge for skin penetration due to the stratum corneum’s barrier properties. Bypassing this barrier is essential for effective transdermal levodopa delivery.
Dissolving microarray patches (MAPs) represent a potential platform for co-administering levodopa and carbidopa. MAPs are micro-scale transdermal drug delivery devices that penetrate the stratum corneum, delivering drugs to the dermal microcirculation [13–15]. These MAPs dissolve in the skin, leaving drug reservoirs that facilitate drug release into the dermal microcirculation [16,17]. Various biocompatible polymers and sugars have been employed in dissolving MAPs, including combination of poly(vinyl alcohol) and poly(vinylpyrrolidone) [18,19], poly(acrylic acid) [20], carboxymethylcellulose [21], hyaluronic acid [22], and pullulan [23]. The combination of PVA and PVP has shown promise in producing dissolving MAPs with favourable mechanical properties and insertion abilities [24–26].

In this study, a dissolving MAP loaded with levodopa and carbidopa was formulated for the first time for transdermal delivery of both compounds. Tween® 80 was incorporated based on previous findings indicating improved ex vivo permeation efficiency [27]. The formulated MAPs had specific dimensions and underwent physical characterisations for compression and insertion abilities. Their cytotoxicity on human dermal fibroblast cells was assessed, along with evaluating ex vivo permeation profiles to explore the potential of dissolving MAPs as a transdermal levodopa and carbidopa delivery alternative.

2. Materials and methods

2.1. Materials

The (S)-(−)-Carbidopa monohydrate (carbidopa) with a purity exceeding 98 % was obtained from Abcam in Cambridgeshire, UK. Levodopa, with a purity of at least 98 %, along with poly(vinyl alcohol) (PVA) and poly(vinylpyrrolidone), were acquired from Sigma-Aldrich located in Dorset, UK. Essential materials such as Dulbecco’s Modified Eagle’s medium (DMEM), fetal bovine serum (FBS), and the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay kit, as well as dimethyl sulfoxide (DMSO), were sourced from Sigma-Aldrich in St. Louis, MO, USA. Plasdone™ K-90/32 (PVP, MW 58,000 g/mol) and Plasdone™ K-90 (PVP, MW 1,300,000 g/mol) were generously provided by Ashland Industries Europe GmbH in Schaffhausen, Switzerland. Glycerol and Tween® 80 were acquired from VWR in Wrexham, UK. Phosphate-buffered saline tablets (PBS, pH 7.3–7.5) were obtained from Sigma-Aldrich in Dorset, UK. Additionally, the enzyme-linked immunosorbent assay (ELISA) analysis kit was procured from R&D Systems in Minneapolis, MN, USA. All solvents utilized were of analytical grade and were purchased from Sigma-Aldrich in Dorset, UK.

2.2. Fabrication of dissolving MAPs

The needle tips were fabricated using a polymeric solution composed of 20 % w/w PVA (9–10 kDa) and 20 % w/w PVP (58 kDa), denoted as PP2 [27,28]. For the baseplate layer of the patches, a different polymeric solution was used, comprising 30 % w/w PVP K-90 and 1.5 % w/w glycerol. Each carbidopa and levodopa was integrated into separate MAP formulations. The procedure involved pouring approximately 50 mg of each drug-containing mixture (as specified in Table 1) into a poly(dimethylsiloxane) mould measuring 16 × 16 with pyramidal needles of 850 μm height, 300 μm width at the base, 300 μm interspacing, and covering a patch area of 0.36 cm². This mixture constituted the first layer, followed by placing the moulds in a positive pressure chamber at 4 bar for 5 min. Excess formulation was removed, and the patches were dried for 30 min at 4 bar. Elastomer rings (with an external diameter of 23 mm, internal diameter of 18 mm, and thickness of 3 mm) were then affixed onto the moulds using a solution made from an aqueous blend of 40 % w/w PVA (9–10 kDa) [17,29]. After drying for 6 h at room temperature, a second layer consisting of 850 μL of an aqueous blend of 30 % w/w PVP (90 kDa) and 1.5 % w/w glycerol was poured into the moulds. The subsequent steps included centrifugation at 3500 rpm for 10 min, followed by drying at room temperature for 24 h. Finally, the sidewalls were removed, and the moulds were further dried at 37 °C for 12 h to obtain the final MAPs.

2.3. Characterisation of mechanical resistance of MAPs

The manufactured MAPs were examined using both a digital light microscope (Leica EZ4 D, Leica Microsystems, Milton Keynes, UK) and a scanning electron microscope (SEM) (Tabletop Microscope TM3030, Hitachi). To evaluate the MAPs’ compression resistance, a TA-TX2 Texture Analyser (TA) (Stable Microsystems, Haslemere, UK) was employed in compression mode, adhering to established protocols [30,31]. The height of the needles was recorded before and after testing using a digital light microscope, and the percentage of needle height reduction was determined using Equation (1).

\[
\frac{\text{Percentage reduction}}{\text{Height reduction}} = \frac{H_h - H_s}{H_s} \times 100\%
\] (1)

where \(H_s\) is the height before compression and \(H_h\) is the height after compression.

2.4. MAP insertion properties

The penetration capability of MAPs was assessed through both in vitro and ex vivo experiments. In the in vitro study, a stack of eight layers of Parafilm® M was prepared, and the MAPs were inserted into each layer [30]. The depth of insertion was observed using a digital light microscope. For the ex vivo experiment, excised neonatal porcine skin was employed to evaluate MAPs insertion. Real-time monitoring of MAPs insertion into the skin was conducted using an EX-101 optical coherence tomography (OCT) microscope (Michelson Diagnostics Ltd., Kent, UK). The length of insertion was subsequently analyzed using ImageJ® software (National Institutes of Health, Bethesda MD, USA). The neonatal porcine skin used in the experiment was excised from stillborn piglets within 24 h after death and stored at −20 °C until use.

2.5. Calculation of drug content of MAPs

To dissolve the hydrophilic polymer in MAP, each formulation was placed in 4 mL of deionized water and sonicated for 30 min. Following this, the resulting mixture was combined with 4 mL of methanol (for levodopa) or acetone (for carbidopa) and sonicated for 30 min to dissolve the drug. After sonication, the mixture was subjected to centrifugation at 14,500 rpm for 15 min prior to analysis using high-performance liquid chromatography (HPLC) detailed in section 2.10.

2.6. Ex vivo skin dissolution studies

To examine the ex vivo dissolution of MAPs in neonatal porcine skin, an in situ skin dissolution study was conducted. Initially, full-thickness neonatal porcine skin tissue was immersed in PBS (pH 7.4) at 37 °C for 30 min. Subsequently, MAPs were manually inserted into the skin using thumb pressure for 30 sec. To prevent detachment of the patch from the skin surface, a cylindrical stainless-steel weight weighing approximately 15 g was placed on top of the patch. The samples were then incubated in an oven set at 37 °C and carefully removed from the
skin at specific time points. Finally, the MAPs were examined using a digital microscope to assess their dissolution.

2.7. Ex vivo dermatokinetic studies

The delivery efficiency of levodopa and carbidopa to different layers of full-thickness neonatal porcine skin was evaluated using a Franz cell diffusion apparatus (PermeGear, Inc., Hellertown, PA, USA) [32,33]. The full-thickness neonatal porcine skin was prepared by trimming it to fit the donor compartment of the Franz cells and attaching it with cyanoacrylate glue, ensuring the subcutaneous side faced the receiver compartment. MAPs were inserted into the skin manually (cyanoacrylate glue, ensuring the subcutaneous side faced the receiver side) using thumb pressure for 30 sec. The receiver compartment was filled with PBS (pH 7.4) as the receiver medium and maintained at 37 °C using a thermal water jacket. The medium was stirred continuously at 600 rpm. To prevent the expulsion of MAPs from the skin, a cylindrical stainless-steel weight was placed on top of them. Samples from the skin and receiver compartments were collected at various time points: 1, 3, 6, 12, and 24 h. The samples from the receiver compartment were processed by centrifugation, filtration, and analysed for drug content using HPLC. The skin samples were also collected and processed separately. The epidermis layers were homogenized with methanol and acetonitrile, respectively, while the dermal layer was homogenized in a mixture of deionized water and methanol or acetonitrile. Both epidermis and dermis samples were centrifuged, and the supernatant was used for HPLC analysis.

2.8. Biocompatibility studies

The cytotoxicity assessment of several samples (MAP loaded with levodopa, MAP loaded with carbidopa and blank MAP) was conducted in vitro using multiple assays: MTT, live/dead staining, and picogreen assays on adult human dermal fibroblasts (HDFa) cells. HDFa cells (density 5 × 10^3 cells/well) were cultured in DMEM supplemented with 10 % FBS and 1 % penicillin–streptomycin aqueous solution. The MTT assay assessed cell viability, after 48 h of culture, the formulations were treated with MTT reagent (5 mg/mL) and incubated for 5 h at 37 °C in a 5 % CO₂ atmosphere. Absorbance at 570 nm was measured using a Multiskan™ GO spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). The live/dead assay determined the impact of formulations on cell number and morphology. HDFa cells, with or without MAPs, were treated with Calcein AM and ethidium homodimer-1 and imaged using a fluorescence microscope. Image analysis was carried out using ImageJ software. The picogreen assay quantified DNA content (cell proliferation). Cells with or without MAPs were incubated with a leaching solution for 48 h, followed by freeze-thaw cycles. Tris-EDTA buffer, picogreen solution, and freeze-thawed cell samples were mixed and incubated in a dark environment. Fluorescence was measured at 480 nm excitation and 520 nm emission using a Varioskan® Flash plate reader (Thermo Fisher Scientific, Waltham, MA, USA). The calibration curve from a DNA standard facilitated the determination of unknown DNA concentrations in the samples. Media without cells served as a control. The fluorescence readings were used to calculate DNA concentrations, aiding in assessing cell proliferation in the samples.

2.9. High performance liquid chromatography (HPLC) analysis

The quantity of each drug was individually determined using HPLC with an Agilent Technologies 1220 Infinity system (Agilent UK Ltd., Stockport, UK) coupled with a UV detector. For chromatographic separation, an XSelect CSH C18 column with a 3.0 mm internal diameter, 150 mm length, 3.5 µm particle size, and a pore size of 130 Å was utilised (Waters, Dublin, Ireland). Preceding the column was a VanGuard® cartridge (3.9 mm internal diameter, 5 mm length) (Waters, Dublin, Ireland) with chemistry similar to the main column. The sample was eluted through a mobile phase consisting of 0.1 % v/v trifluoroacetic acid and acetonitrile, with ratios outlined in Table 2, at a rate of 0.6 mL/min. HPLC samples were analysed at 30 °C with an injection volume of 20 µL. Chromatograms were analyzed using Agilent ChemStation® Software B.02.01.

2.10. Statistical analysis

The statistical analysis and interpretation of the results were conducted using GraphPad Prism® version 9.4 (GraphPad Software, San Diego, California, USA). For comparisons between multiple groups, one-way analysis of variance (ANOVA) was performed, and statistical significance was defined as p < 0.05. Unless specified, the data are presented as means ± standard deviation (SD).

3. Results and discussion

3.1. Fabrication of dissolving MAPs

The dissolving MAPs loaded with levodopa or carbidopa were fabricated using a double-casting procedure. Fig. 1 illustrates the MAPs featuring sharp, uniform arrays of microprojections on the smooth, flat baseplate post-fabrication. Remarkably, the drug (levodopa or carbidopa) appeared localized at the tips of the patch. Notably, the absence of bubbles on the manufactured MAPs indicates the suitability of both the formulations and the method used, establishing them as a viable approach for fabricating dissolving MAPs loaded with levodopa or carbidopa.

3.2. Evaluation of mechanical resistance and insertion ability of dissolving MAPs

After the fabrication of dissolving MAPs, mechanical resistance evaluation was conducted to assess the mechanical properties of MAP formulations. As depicted in Fig. 2(A), the initial needle height across all formulations measured approximately 850 µm. Upon compression with an axial force mimicking the pressure exerted by a human thumb during manual insertion (32 N) [34], the reduction in needle height was less than 9 % for carbidopa and less than 14 % for levodopa. Notably, the addition of Tween® 80 as a surfactant significantly improved mechanical strength (p < 0.05). Formulations containing Tween® 80 exhibited significantly less reduction in needle height (p < 0.05) for both carbidopa and levodopa-loaded MAPs compared to formulations without the surfactant. This finding corroborates our earlier observations, indicating molecular interactions between the surfactant molecules and the polymers (PVA and PVP) used in MAP fabrication [27]. With the exception of levodopa F2, the reduction in needle height was consistently less than 10 %, aligning with previously reported dissolving MAPs [13,35,36]. This suggests that the fabricated MAPs, except for levodopa F2, possess adequate mechanical strength to withstand compression during skin insertion. Further assessment of the mechanical properties involved insertion studies using Parafilm® layers, a validated skin simulator, and excised neonatal porcine skin.

Fig. 2(B) demonstrates the successful breach of the first Parafilm® layer by all MAP formulations, resulting in 100 % hole formation upon application. However, as the MAPs penetrated subsequent Parafilm® layers, the percentage of holes created decreased, with approximately

<p>| Table 2: HPLC parameters for quantification of levodopa and carbidopa. |
|-----------------------------|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mobile phase ratio</th>
<th>Wavelength (nm)</th>
<th>Running time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>95</td>
<td>281</td>
<td>5</td>
</tr>
<tr>
<td>Carbidopa</td>
<td>85</td>
<td>220</td>
<td>7</td>
</tr>
<tr>
<td>Trifluoroacetic acid (%)</td>
<td>Acetonitrile (%)</td>
<td></td>
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</tr>
</tbody>
</table>
80% and 20% penetration observed in the second and third layers, respectively. Notably, no visible holes were apparent in the fourth- and fifth-layers following MAP insertion. Despite the inclusion of Tween® 80 in the MAP formulation, no discernible differences were observed in the insertion profiles within the Parafilm® layers for both drugs.

Visualizing the insertion depth into stacked Parafilm® layers using optical coherence tomography (OCT) in Fig. 3(A), we measured the penetration depth of MAP formulations. As shown in Fig. 3(C), the
fabricated MAPs reached a depth of approximately 400 µm, equivalent to the thickness of three layers of Parafilm®. This aligns with previous findings where the MAP formulations created roughly 20% holes in the third Parafilm® layer, indicating a penetration capability of up to approximately 390 µm, considering each layer’s thickness (~130 µm).

To further assess the MAP formulation’s insertion profile, we conducted another study using ex vivo full-thickness neonatal porcine skin, presented in Fig. 3(B). The results depicted in Fig. 3(D) revealed that the MAP formulations penetrated up to 650 µm, approximately 76% of the needle height. This penetration depth into ex vivo skin significantly surpassed that within the Parafilm® layers (p < 0.05) in all instances. This disparity aligns with previous studies, possibly attributed to the rigid nature of Parafilm® layers, lacking moisture and elasticity characteristic of skin [13,19,26,27]. Conversely, the dissolving MAP matrix, comprising hydrophilic polymers (PVA and PVP), may offer lubrication, facilitating needle insertion into the deeper skin layer enriched with interstitial fluid [27]. Remarkably, a notable difference in penetration depth was observed between F1 and F2 MAPs loaded with carbidopa (p < 0.05). This suggests that the surfactant, Tween® 80, might enhance the spread of dermal interstitial fluid, acting as a lubricant, thereby enabling deeper penetration under the same applied force [27,37].

3.3. Calculation of drug content of MAPs

The drug loading of levodopa and carbidopa in dissolving MAPs was assessed, with the findings depicted in Fig. 4. Interestingly, the inclusion of Tween® 80 demonstrated no significant impact on drug loading across all cases (p > 0.05). Specifically, it was observed that a MAP patch

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Fig. 3. Optical coherence tomography (OCT) image illustrating in situ the capability of the MAPs to be inserted into (A) Parafilm® M layers and (B) ex vivo neonatal porcine skin. Insertion depth of MAPs into (C) Parafilm® M layers and (D) ex vivo neonatal porcine skin as measured from OCT images (means ± SD, n = 20).
3.4. Ex vivo dissolution studies

To assess the dissolution duration of MAPs, dissolution studies were conducted using excised full-thickness neonatal porcine skin. As depicted in Fig. 5, after 1 h of MAP application, all formulations exhibited an undissolved needle layer. Notably, the presence of distinct ‘white dots’ in the skin indicated successful delivery and deposition of the drug-loaded layer from the MAPs into the skin, forming an intradermal depot. However, extending the MAPs’ duration on the skin to 3 h resulted in complete dissolution of the entire needle layer. Hence, based on these findings regarding wearing time and skin application, it is recommended that the fabricated MAPs, both carbidopa and levodopa loaded formulations, should be applied for approximately 3 h to achieve complete dissolution and successful delivery of their content into the skin.

3.5. Ex vivo dermatokinetic studies

Dermatokinetic studies were conducted to determine the quantity of drug permeated and deposited within different skin layers. Among the formulations assessed for both carbidopa and levodopa, only F1 (containing Tween® 80) was chosen for further evaluation based on considerations from mechanical properties, insertion profiles, and ex vivo skin dissolution studies. Fig. 6 illustrates a significant increase ($p < 0.05$) in the total amount of both carbidopa and levodopa delivered and deposited across full-thickness neonatal porcine skin over 24 h, observed across all skin layers. The receiver compartment contained the highest proportion of drugs (0.78 mg for carbidopa and 2.31 mg for levodopa), indicating predominant drug permeation post MAP application.

In the epidermis layer, levodopa deposition increased from 1 to 6 h, plateaued until 12 h, followed by a substantial increase at 24 h, resulting in approximately 0.43 mg of levodopa (equivalent to 7.85 %) deposited. Conversely, carbidopa exhibited a slow increase, reaching only 0.02 mg (equivalent to 0.88 %) deposited in the epidermis layer over 24 h. Similar to epidermal deposition, levodopa showed a significant increase in the dermis layer ($p < 0.05$) from 1 to 6 h, reaching a plateau before a
dramatic increase at 24 h, with approximately 0.51 mg (equivalent to 9.39 \%) deposited. In contrast, carbidopa displayed a delayed release until 12 h and then exhibited a burst release at 24 h, depositing 0.24 mg (equivalent to 9.03 \%). Both drugs displayed a lag-phase in transdermal delivery during the initial 2-hour period, gradually increasing over 24 h. Overall, levodopa exhibited significantly higher delivery across all skin layers than carbidopa ($p < 0.05$). This disparity may be attributed to levodopa’s higher solubility \[38\] and higher loading in the MAPs, approximately 2-folds that of carbidopa. Following the dissolution of the needle layer, the drugs and polymer matrix remained embedded in the skin and passively diffused until reaching the receiver compartment, simulating microcirculation conditions. According to Fick’s law of

![Fig. 6. Amount of levodopa and carbidopa extracted from (A) epidermis, (B) dermis of excised full-thickness neonatal porcine skin (means ± SD, n = 4). (C) Amount of levodopa and carbidopa permeated across the excised full-thickness neonatal porcine skin (means ± SD, n = 4). Total delivery and distribution of (D) levodopa and (E) carbidopa following MAP application (means ± SD, n = 4).](image)

![Fig. 7. Cytotoxicity study results. (A) MTT assay results at 48 h (means ± SD, n = 5). (B) DNA concentration presented as a percentage via picogreen assay (means ± SD, n = 5). (C) Microphotographs displaying treated cells post live dead assay (scale bar 100 \(\mu\)m).](image)
diffusion, drug molecules move from higher to lower concentration until equilibrium is reached [39,40]. Higher concentration in the donor compartment can result in increased diffusion to the receiver compartment until equilibrium is established. When viewed as a percentage, the MAPs exhibited an overall delivery efficiency of approximately 53.35 % for levodopa and 40.14 % for carbidopa.

3.6. Biocompatibility studies

To assess the formulations’ suitability for skin application, cytotoxicity studies were conducted using human dermal fibroblasts (HDFa) cells. Initially, the MTT assay was employed to evaluate the impact of formulations on cell viability. As depicted in Fig. 7A, the blank MAP, after a 48-h period, showed no adverse effects on cell viability compared to control cells or the carbidopa-loaded MAP formulation (p > 0.05). However, the levodopa-loaded MAP formulation led to a significant reduction in cell viability (approximately 82.12 %) compared to the control and blank MAP (p < 0.05). This result indicates a notable effect of the levodopa-loaded MAP formulation on skin cells, classified as a grade 1 (non-cytotoxic) effect based on predefined cytotoxicity grade levels [41]. Notably, the impact of levodopa on HDFa cells had not been previously documented concerning topical administration, unlike its known induction of skin reactions in oral administration [42]. The observed increase in toxicity aligns with a previously reported study suggesting low cytotoxicity, primarily due to the production of free radical species on HDFa cells [43]. The concentration of levodopa used resulted in a reduction in viable cells within a lower cytotoxicity grade. Thus, although the levodopa-loaded MAP showed fewer viable cells, the values obtained were still considered non-toxic.

To further assess cell numbers in the well plates, the picogreen assay measured the total DNA concentration, an indicator of cell numbers and proliferation (Fig. 7B). The results showed no significant reduction (p > 0.05) in HDFa cell proliferation after treatment with the formulations. Additionally, the live-dead assay (Fig. 7C) revealed a decrease in cell numbers following treatment with the levodopa-loaded MAP. Overall, these findings collectively demonstrate that the formulations exhibit good cytocompatibility, positioning them as promising approach for skin application.

4. Conclusion

In this study, we have designed, characterized, and assessed dissolving MAPs loaded with antiparkinson drugs, carbidopa and levodopa, as potential solutions for improving Parkinson’s disease management. The formulated MAPs displayed favourable mechanical properties, capable of withstanding pressures equivalent to 32 N, similar to the pressure exerted by a human thumb, upon MAP application to the skin. Notably, the incorporation of Tween® 80 in these MAP formulations exhibited improvements, such as enhancing the reduction in needle height for levodopa and enabling deeper insertion into ex vivo porcine skin for carbidopa. These fabricated MAPs successfully loaded approximately 2.6 mg of carbidopa and 5.5 mg of levodopa. Upon application to excised full-thickness neonatal porcine skin, all MAP formulations completely dissolved within 3 h. Ex vivo dermatoxicological studies revealed an overall delivery efficiency of about 53.35 % for levodopa and 40.14 % for carbidopa, demonstrating promising drug delivery capabilities. Furthermore, these MAPs exhibited excellent cytocompatibility and suitability for skin application. Moving forward, additional investigations such as pharmacokinetics, pharmacodynamics, stability, and safety studies are imperative before considering clinical applications in Parkinson’s disease management. These forthcoming studies will offer a more comprehensive understanding of the MAPs’ efficacy and safety profiles in therapeutic settings.

CRediT authorship contribution statement

Qonita Kurnia Anjani: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Natalia Moreno-Castellanos: Methodology, Investigation, Formal analysis, Data curation. Yao-cun Li: Writing – original draft, Formal analysis. Akmal Hidayat Bin Sabri: Formal analysis, Data curation. Ryan F. Donnelly: Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References


