

Abstract of thesis presented to the Senate of Universiti Malaysia Terengganu in fulfilment of the requirements for the degree of Doctor of Philosophy

**DEVELOPMENT OF A MICRONEEDLE DELIVERY SYSTEM USING
P(3HB-*co*-4HB)-DOCETAXEL NANOPARTICLES FOR ENHANCED
BREAST CANCER TREATMENT**

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JULY 2025

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Breast cancer (BC) significantly contributes to the rise in mortality rate among women across the globe. However, current treatments have many limitations. Docetaxel (DTX), a commonly used chemotherapy drug, has poor solubility, requires intravenous (IV) administration, and causes severe side effects, reducing patient comfort and treatment adherence. This study developed a more precise, personalized and targeted therapy for BC treatment using dissolving microneedles (DMNs) loaded with docetaxel-incorporated poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate) [P(3HB-*co*-4HB)] nanoparticles (DTX-NP). The biopolymer P(3HB-*co*-4HB) was produced using *Cupriavidus malaysiensis* USMAA1020 in a 15L bioreactor through a single-stage fermentation process. Optimized conditions resulted in a Polyhydroxyalkanoate (PHA) content of $95.04\% \pm 9.05\%$ in crude polymer with an equimolar monomer composition of 49.83% 3HB and 50.17% 4HB, ensuring good mechanical strength and biodegradability. DTX-NPs were fabricated through solvent evaporation. Optimization showed that a 40% drug-to-polymer ratio, 4-hour solvent evaporation with D- α -Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS), and 2-minute sonication produced the most stable nanoparticles (NPs). The optimized NPs had a

size below 100 nm, a polydispersity index (PDI) of 0.238 ± 0.025 , and a Zeta potential (ZP) of -19.13 ± 0.404 mV, indicating good stability. Encapsulation efficiency (EE) was $87.07 \pm 0.043\%$, and drug loading (DL) capacity was $13.71 \pm 0.82\%$, ensuring effective delivery. The drug release study of NPs showed sustained release over 72 hours, following Korsmeyer-Peppas. Free DTX was released 100% in 24 hours, while the NPs were released 90% in 48 hours, with more controlled release. This extended-release can reduce dosing frequency and minimise side effects. The optimised NPs were further incorporated into DMNs made from polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) polymers using a stepwise centrifugation method. The microneedles (MNs) were about 976 ± 1.90 μm in height, had good mechanical strength, and effectively penetrated agarose gels mimicking breast tissues. The NP-loaded DMNs exhibited a higher fracture force of 73.67N and maintained structural integrity under forces up to 200g, ensuring effective skin penetration. Drug release from DMNs followed a similar model to NPs, with a sustained release of 97.86% of the drug over 72 hours. Compared to traditional chemotherapy, this MN system offers pain-free delivery, lower toxicity, and better patient compliance. This study could aid in revolutionising BC treatment, particularly for long-term management and self-administration.

Abstrak tesis yang dikemukakan kepada Senat Universiti Malaysia Terengganu
sebagai memenuhi keperluan untuk Doktor Falsafah

**PEMBANGUNAN SISTEM PENGHANTARAN JARUM MIKRO
MENGUNAKAN P(3HB-co-4HB)-DOCETAXEL NANOZARAH UNTUK
RAWATAN KANSER PAYUDARA TERTINGKAT**

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Salah satu faktor utama yang menyumbang kepada kadar kematian wanita di peringkat global ialah kanser payudara. Walau bagaimanapun, rawatan semasa masih mempunyai banyak keterbatasan. Docetaxel (DTX), ubat kemoterapi yang sering digunakan, mempunyai keterlarutan rendah, memerlukan pengurusan intravena (IV), dan menyebabkan kesan sampingan yang teruk, mengurangkan keselesaan pesakit serta pematuhan terhadap rawatan. Kajian ini membangunkan terapi yang lebih tepat, bersifat peribadi, dan disasarkan untuk rawatan kanser payudara menggunakan mikrojarum boleh-larut (DMNs) yang dimuatkan dengan DTX dalam poli(3-hidroksibutirat-co-4-hidroksibutirat) [P(3HB-co-4HB)]. Biopolimer P(3HB-co-4HB) dihasilkan menggunakan *Cupriavidus malaysiensis* USMAA1020 dalam bioreaktor 15L melalui proses fermentasi satu peringkat. Pengoptimuman menghasilkan kandungan Polihidroksialkanoat (PHA) sebanyak $95.04\% \pm 9.05\%$, dengan komposisi 49.83% 3HB dan 50.17% 4HB, memastikan kekuatan mekanikal dan biodegradasi yang baik. Nanozarah P(3HB-co-4HB) dimuatkan dengan DTX (DTX-NP) menggunakan kaedah penyejatan pelarut, menghasilkan saiz <100 nm, PDI 0.238 ± 0.025 , dan potensi Zeta (ZP) -19.13 ± 0.404 mV, menunjukkan kestabilan yang baik. Kecekapan pengkapsulan ialah 87.07%, dan kapasiti pemuatan ubat ialah 13.71%,

bagi memastikan penghantaran ubat berkesan. Kajian pelepasan ubat menunjukkan pelepasan berterusan selama 72 jam mengikut model Korsmeyer-Peppas. DTX bebas dilepaskan sepenuhnya dalam 24 jam, manakala 90% daripada DTX dalam nanozarah (NP) dilepaskan dalam 48 jam, memastikan pelepasan lebih terkawal. NP yang dioptimumkan dimasukkan ke dalam DMNs diperbuat daripada polimer polivinil alkohol (PVA) dan polivinil pyrrolidone (PVP) menggunakan kaedah sentrifugasi bertahap. Mikrojarum (MN) ini mempunyai ketinggian $976 \pm 1.90 \mu\text{m}$, kekuatan mekanikal tinggi, dan mampu menembusi gel agarosa yang meniru tisu normal dan tumor payudara. MN yang dimuatkan dengan NP mempunyai kekuatan patah 73.67N, mengekalkan integriti struktur sehingga 200g, memastikan penembusan kulit berkesan. Pelepasan ubat daripada DMNs menunjukkan 97.86% pelepasan dalam 72 jam. Berbanding kemoterapi konvensional, sistem ini menawarkan penghantaran tanpa rasa sakit, ketoksikan lebih rendah, dan pematuhan lebih baik. Kajian ini berpotensi merevolusikan rawatan kanser payudara, khususnya untuk pengurusan jangka panjang dan pengurusan sendiri.