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Evaluation of Curcumin-Loaded Carboxymethyl Cellulose (CMC) Hydrogel Combined with Near-Infrared Radiation (NIR) for Breast Cancer Treatment

Nurin Umairah Risam[a], Wan Fatin Amira Binti Wan Mohd Zawawi[a]*
[a]Department of Biosciences, Faculty of Science, Universiti Teknologi Malaysia, 81310 UTM Skudai, Johor, Malaysia
*Corresponding author: wanfatinamira@utm.my

Abstract
Breast cancer remains a major global health concern, with the second leading cause of cancer-related death among women worldwide. Conventional therapy is often expensive, has a poorly targeted and non-specific distribution. Curcumin, a natural compound found in turmeric, is known to have anti-cancer properties. However, its clinical application was limited due to its poor water solubility and bioavailability. This study aimed to investigate the use of carboxymethyl cellulose hydrogel (CMCH) derived from oil empty fruit bunches (OPEFB) as a drug delivery vehicle for curcumin and examined the potential synergistic effect of NIR combined with the curcumin-loaded CMC hydrogel (Cur-CMCH) in enhancing the curcumin delivery to MDA-MB-231 breast cancer cells. Cur-CMCH was prepared at a concentration of 2.5 g/L, and its loading and entrapment efficiencies were determined. Drug release analysis revealed a two-phase release: an initial burst followed by sustained release. MTT assay showed Cur-CMCH significantly reduced cell viability ($p < 0.05$), while the addition of NIR did not show further significant enhancement under current parameters. Nevertheless, these findings highlight Cur-CMCH as a promising delivery system for breast cancer therapy, with potential for improvement through NIR optimization.
Keywords: Breast cancer; curcumin; carboxymethyl cellulose; hydrogel; near-infrared

Introduction

Breast cancer is the second most common cause of women's death (Alkabban & Ferguson, 2022). In 2020, an estimated 2.3 million females were diagnosed with breast cancer worldwide, and around 685,000 of them died. The number of newly diagnosed breast cancer cases is expected to climb by more than 40%, or around 3 million per year (Arnold et al., 2022). Despite the availability of standard treatments such as surgery, chemotherapy, and radiotherapy, existing therapeutic techniques are insufficient, particularly for aggressive subtypes like triple-negative breast cancer (Burguin et al., 2021). Due to the limitations of therapy for breast cancer, it is crucial to explore more effective treatment strategies.

Curcumin is an active compound in turmeric, known for its antioxidant and anti-inflammatory properties (Mahmood et al., 2015). Several studies have found that curcumin has shown antitumor activity towards several cancer cell lines, such as breast cancer, prostate cancer, and brain cancer. The curcumin effect has also been tested on the MDA-MB-231 cells, and it has been shown to limit the proliferation of the cells by decreasing the cyclic D1 in MDA-MB-231 (Tomeh et al., 2019). However, despite its anticancer properties, curcumin has poor water solubility and bioavailability that can limit its therapeutic application (Górnicka et al., 2023). Advanced delivery methods, such as hydrogels as a drug delivery vehicle, might offer a promising solution.

Carboxymethyl cellulose (CMC) is an anionic, water-soluble derivative of cellulose, a linear polysaccharide containing anhydro-glucose, consisting of repeating units that are linked through β-1,4-glycosidic linkages (Rahman et al., 2021). Recent studies have highlighted that CMC hydrogel has been gaining attention in cancer treatment research, especially in drug delivery due to its properties such as low immunogenicity, non-toxicity, good biodegradability, and good biocompatibility (Dattilo et al., 2023). This study focuses on the application of CMCH as a delivery vehicle for curcumin and examines the effect of the CMC on curcumin solubility and bioavailability for breast cancer treatments.

Due to its ability to penetrate deeply into biological tissues, near-infrared (NIR) has gained significant interest in cancer treatment (Wan et al., 2020; Xu et al., 2020). NIR also serves as an external stimulus for controlled drug release, helping to overcome limitations such as poor targeting and premature release in conventional systems (Raza et al., 2019). These NIR-responsive systems offer advantages including targeted distribution, enhanced bioavailability, and the potential to overcome chemotherapy resistance (Raza et al., 2019; Zhang et al., 2017; Guo et al., 2020). Hence, this study evaluates the synergistic effect of NIR activation in enhancing curcumin delivery through CMCH, aiming to develop novel therapeutic strategies.

Materials and methods

The MDA-MB-231 cells will be cultured and seeded in 96-well plates, incubated at 37°C with 5% CO_2, until they reach 70% confluency. Curcumin loading and entrapment efficiency will be analyzed using UV-Vis spectrophotometry. Cytotoxicity will be assessed via MTT assay, and the synergistic effect of NIR will be studied using a wIRA hydrosun source. Data will be analyzed statistically using appropriate software.

Preparation of CurCMCH

Cellulose was extracted from OPEFB through a multi-step chemical process, which includes washing and drying at each stage. Carboxymethyl cellulose (CMC) powder was then synthesized and used to form a 20% CMC hydrogel, which was loaded with 2.5 g/L curcumin by soaking it for 24 hours. The hydrogel was then rinsed, dried, and weighed.

Cell culture and Treatment

MDA-MB-231 breast cancer cells were cultured in DMEM/F12 medium supplemented with 10% FBS and 1% antibiotics. Cells were seeded into 96-well plates and incubated at 37 °C with 5% CO_2.

Determination of Curcumin Loading and Entrapment Efficiency

Curcumin loading and entrapment efficiencies were determined based on the weight difference before and after loading of curcumin by using the following equation:

$$\text{Entrapment efficiency (\%)} = \frac{(Curcumin\ loaded)}{(Total\ amount\ of\ curcumin)} \times 100\% \quad (1)$$

$$\text{Loading efficiency (\%)} = \frac{(Total\ amount\ of\ curcumin) - (Free\ amount\ of\ curcumin)}{(Total\ amount\ of\ nanocomposite)} \times 100\% \quad (2)$$

Release Kinetic

CurCMCH was placed inside the phosphate-buffered saline (PBS) containing 0.1% DMSO and incubated at 37°C. For every two hours in 24 hours, 500 µL of solution was pipetted out and measured at 420nm using a UV-visible spectrometer to monitor the release of curcumin. The solution will also be replenished. The amount of curcumin released will be compared to the prepared standard curve.

Cytotoxicity Assessment

MTT assay was used to evaluate the cytotoxicity of untreated cells, free curcumin, Cur-CMCH, and CMCH after 24-hour treatment against the MDA-MB-231 cells. Each 96-well plate was seeded at a density of 1.0 ×10^4 cells per well in 100 µL of culture medium (DMEM/F12 supplemented with 10% FBS

and 1% penicillin-streptomycin) and incubated at 37 °C with 5% CO_2 in a tissue culture incubator for 24 hours to allow cell attachment. After 24 hours, the cells reach approximately 70% confluency, the culture medium is removed, and the treatment group are applied inside each well. The concentration of curcumin for all curcumin-containing treatments will be standardized to 2.5 g/L. The cells were then incubated for another 24 hours at 37 °C with 5% CO_2. After 24 hours, the medium was discarded, and 20 µL of MTT solution (5mg/mL) was added to each well and incubated at 37°C for four hours. 150 µL of DMSO was then added into each well and incubated in dark conditions at room temperature for 15 minutes. The absorbance of each well was determined by a microplate reader at 570nm. The following equation will be used to calculate the cell viability:

$$\% \text{ Cell viability} = \frac{(Absorbance\ of\ treated\ cells)}{(Absorbance\ of\ untreated\ cells)} \times 100 \quad (3)$$

NIR Activation and Curcumin Delivery Enhancement

In a 96-well plate, MDA-MB-231 cells were seeded at density 1.0 $\times 10^5$ Cells per well and incubated for 24 hours at 37 °C with 5% CO_2. The treatment group consist of the 0.2mg of CMCH, Cur-CMCH, NIR with the cells, and untreated cells with no treatment. After treatment, the cells were exposed to NIR for five minutes at an intensity of 1.5 W/cm² using a wIRA radiator. The cells were given a full day to recuperate following NIR treatment. Lastly, the MTT assay was used to measure cell viability to analyze the possible synergistic effects of NIR and curcumin. The results were used to compare the amount of curcumin released by NIR-treated and non-treated cells.

Statistical Analysis

To compare various groups, a one-way ANOVA with the Student-Newman-Keuls test was applied. A p-value of less than 0.05 ($p < 0.05$) will be considered statistically significant. The independent sample t-test was also used, and $p < 0.05$ will be deemed statistically significant. Data are presented as mean ± standard deviation (S.D.) in the tables and mean ± SEM (standard error of means) in the graphs. All experiments were conducted three times.

Results and discussion

Preparation of CMCH

Cellulose was successfully extracted from OPEFB through a three-day chemical treatment involving toluene-ethanol, NaOH, and sodium chlorite with acetic acid. 23.3 g of cellulose was successfully obtained. Carboxymethyl cellulose (CMC) was then synthesized by mixing the cellulose with NaOH and sodium monochloroacetate, followed by neutralization and washing, yielding 11.91 g of CMC powder. The CMC powder was left to crosslink with $CaCl_2$ to form a 20% CMC hydrogel for 24 hours before it was sent to freeze-dry. Subsequently, 50mg of the freeze-dried CMCH was soaked in a curcumin solution that contained 0.25g of curcumin powder dissolved in 20ml of absolute ethanol and left for 24 hours. After 24 hours, it was rinsed with distilled water three times and left to dry for 48 hours.

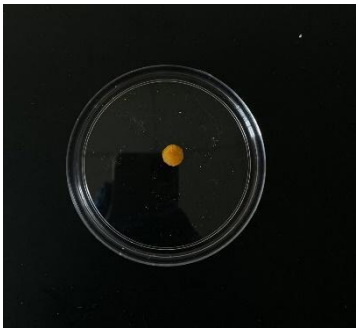

Figure 1 Curcumin-loaded CMC hydrogel (Cur-CMCH)

Determination of Curcumin Loading and Entrapment Efficiency

Table 1 shows that the weight of CMC hydrogel (CMCH) has increased by more than 50mg, confirming that the curcumin has been successfully loaded inside the CMCH. The entrapment and loading efficiencies were then calculated by using equations 1 and 2, respectively. The loading efficiency of curcumin-loaded CMC hydrogel was at 56.77% and 64.61%. These values indicate a relatively high entrapment efficiency, suggesting that the CMC hydrogel is a promising drug delivery vehicle for curcumin. According to Mohamood et al. (2021), the degree of crosslinking within the polymeric chains inside the hydrogel plays a role in the swelling properties. As the swelling properties increase, it will allow more water to be absorbed and retained, which expands the internal voids of the hydrogel. So, this facilitates the curcumin absorption and retention inside the CMCH.

Table 1: Curcumin Loading and Entrapment Efficiencies in CMC Hydrogel.

Number of hydrogels	Weight before loading (mg)	Weight after loading (mg)	Entrapment efficiencies (%)	Loading efficiencies (%)
1	50.2	78.7	36.20	56.77
2	50.3	82.8	39.25	64.61
3	50.3	82.8	39.25	64.61

Release Kinetic

Cur-CMCH samples that weighed more than 50mg were used and placed in PBS that contained 0.1% DMSO. The concentration of curcumin released every two hours over a 24-hour period was taken and plotted in the graph of curcumin concentration (µg/mL) versus Time (hours) as shown in Figure 2. The graph shows the drug release behaviour of curcumin-loaded CMC hydrogel. The two-hour interval release shows a steady increase in curcumin concentration over 24 hours, indicating a continuous release of curcumin over time. The initial phase, zero to eight hours, shows a faster release rate, suggesting a burst release of curcumin that can be due to the loosely bound curcumin on the surface of the CMC hydrogel. Meanwhile, after eight hours, the release rate began to gradually decrease, which indicates a sustained release of curcumin that was embedded inside the CMC hydrogel.

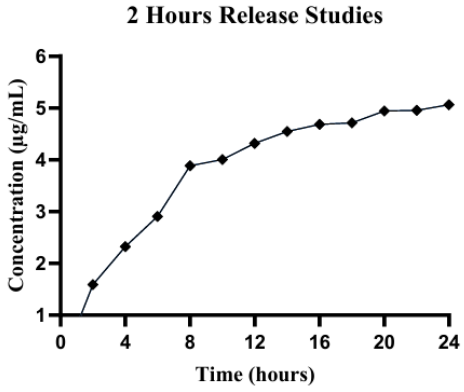

Figure 2 Cumulative release profile of curcumin from CMCH over 24 hours, with measurements taken at two-hour intervals.

Cytotoxicity Assessment

Figure 3 shows the cytotoxic effect of curcumin-loaded CMC hydrogel (Cur-CMCH) on MDA-MB-231 cells, comparing it against untreated cells (negative control), CMCH alone, and free curcumin. Cells that were treated with the CMCH only showed a minimal cytotoxicity at 70.2% of cell viability. According to Dattilo (2023), CMCH was non-toxic and had good biocompatibility. This proves that CMCH by itself is a safe and effective drug delivery vehicle. The slight reduction of the cell viability is aligned with the previous study by Pourmadadi et al. (2023), where the nanocomposite that contains the CMC has

shown to have a mild cytotoxicity, which causes a decrease in the cell viability. This implies that polymer-based drug delivery vehicles such as CMCH may cause minor metabolic changes without inducing true cell death.

Both the free curcumin and Cur-CMCH have shown a significant decrease ($p<0.05$) in cell viability compared to untreated cells, confirming the anticancer properties of curcumin. However, for the free curcumin treatment, the cell viability was reduced to 47.1% while Cur-CMCH has shown the lowest cell viability, which was at 34.8%. This indicates that the Cur-CMCH has the highest cytotoxic effect on the MDA-MB-231 cells. This suggests that CMC improved the curcumin solubility and bioavailability in targeting the cancer cells. This result was aligned with previous study that indicate that curcumin has an anticancer effect on MDA-MB-231 cells (Tomeh et al.,2019). In conclusion, the combination of Cur-CMCH has shown a promising treatment for effective therapy in treating breast cancer.

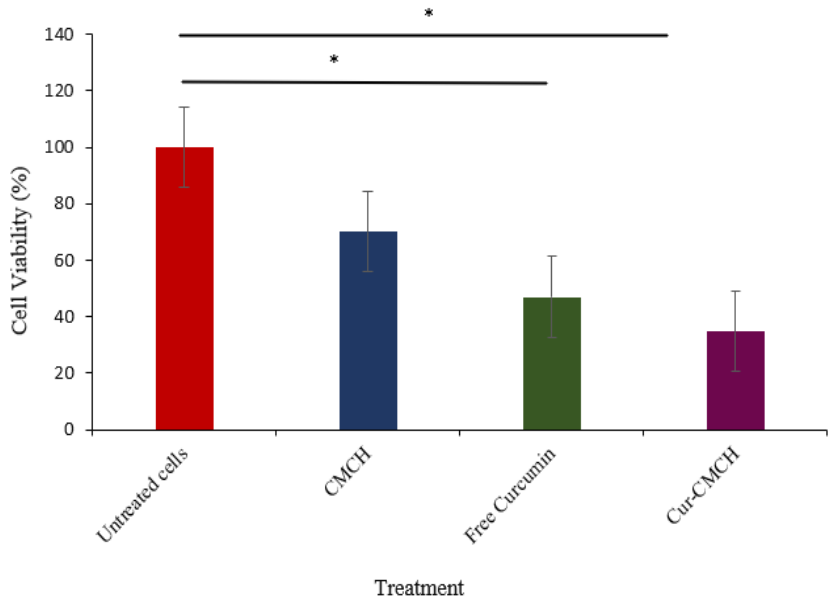

Figure 3 Cell viability (%) of MDA-MB-231 cells after treatment with CMCH, Free Curcumin, and Cur-CMCH for 24 hours. Statistical significance level is indicated as follows: *p<0.05*. Bars without indicator represent non-significant differences.

Synergistic Effect of NIR in Enhancing Curcumin Release and Cytotoxicity

The synergistic effect of NIR combined with the Cur-CMCH in targeting the MDA-MB-231 cells was shown at Figure 4. Figure 4 shows that they are a slightly decreased in the cell viability of the treated group compared to the untreated group. However, the statistical analysis reveals that none of the treatment has caused a significant reduction (*p>0.005*) in the cell viability. This indicate that the treatment that was exposed to the NIR radiation for five minutes was insufficient to produce a measurable cytotoxic effect in this experimental setup. These could be due to several experimental limitation. First it could be due to the size of the treatment that was used are too small (0.2mg), the part of the loaded Cur-CMCH that was cut contain less curcumin causing the minimal released of curcumin thus reducing its effectiveness. The short radiation time was and the distance between the 96-well plate and the wIRA hydrosun radiator was too far that could lead to the reduced photothermal activation. Maintaining the original weight of both the Cur-CMCH (>50mg) and CMCH (50mg) with the optimized NIR parameter such as the distance and exposure time might show a more promising cytotoxic effect on the cells. Therefore, further optimization should be done for better assess on the potential of the synergistic effects of NIR in enhancing the Cur-CMCH in targeting the breast cancer cell.

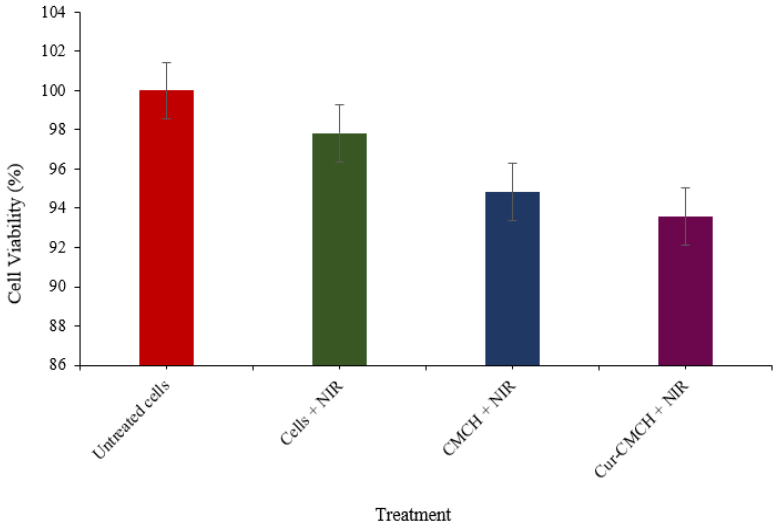

Figure 4 Cell viability (%) of MDA-MB-231 cells after treatment with Cell+NIR, CMCH + NIR, and Cur-CMCH + NIR for 24 hours. Statistical significance level indicate as follows: $p<0.05$. Bars without indicator represent non-significant differences.

Conclusion

This study investigates the use of carboxymethyl cellulose hydrogel (CMCH) as a drug delivery vehicle for curcumin and evaluates the synergistic effect of near-infrared (NIR) activation on MDA-MB-231 breast cancer cells. Curcumin was successfully encapsulated in CMCH, showing good loading efficiency and a sustained 24-hour release profile. Cur-CMCH significantly reduced cell viability, indicating improved curcumin solubility and bioavailability. CMCH alone showed low cytotoxicity, supporting its biocompatibility. Although NIR did not significantly enhance cytotoxicity under current conditions, a slight improvement was observed. With further optimization, the Cur-CMCH and NIR combination holds promise as a targeted and effective breast cancer therapy.

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