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Research Paper

Pectin Red Dragon Fruit Peel Pectin-Based Microspheres for Oral Quercetin Delivery: Characterization, Stability Study, Digestion Resistance, and Cytotoxicity Against HeLa Cells

Muhammad Fariez Kurniawan[1,2], Dwi Setyawan[3,4,5], Dewi Melani Hariyadi[3,4,5,6*]

[1]*Doctoral Program of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, 60115, Indonesia*
[2]*School of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Bantul, 55183, Indonesia*
[3]*Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, 60115, Indonesia*
[4]*Pharmaceutics and Delivery Systems for Drugs, Cosmetics and Nanomedicine (Pharm-DCN) Research Group, Faculty of Pharmacy, Universitas Airlangga, Surabaya, 60115, Indonesia*
[5]*Centre of Excellent (PUIPT) Skin and Cosmetic Technology, Universitas Airlangga, Surabaya, 60115, Indonesia*
[6]*Inter-University Center of Excellence (IUCoE) of Health Autonomy-Drug Discovery, Universitas Airlangga, Surabaya, 60115, Indonesia*
*__Corresponding author__: dewi-m-h@ff.unair.ac.id

Abstract
This study aims to evaluate the potential of red dragon fruit skin pectin to be used as a polymer compared with commercial pectin in the quercetin microsphere. Microspheres were made using the ionic gelation technique. Ten formulas were created, utilizing pectin from red dragon skin extracted with oxalic acid (OA75), citric acid (CA75), acetic acid (AA75), and commercial pectin at 1% and 1.5% concentrations. A gel permeation chromatography test (GPC) was performed to evaluate pectin's molecule weight. Parameters were assessed, including yield, moisture content (MC), Carr's Index, Hausner ratio, swelling index, Fourier Transform Infrared Spectroscopy (FTIR), particle size, polydispersity index (PDI), drug loading (DL), encapsulation efficiency (EE), Scanning Electron Microscope (SEM), in vitro drug release, accelerated stability test at a temperature of 40±2°C and RH 75±5% for 3 months and thermal stability test in the form of DSC and XRD at the same temperature and humidity for 9 months, digestion resistance with incubation in artificial stomach and intestinal solution for 4 hours continued with cytotoxicity test on HeLa cells with MTT Assays. Results of FTIR indicate a strong interaction between quercetin and pectin in forming a stable microsphere structure; SEM showed the spheres morphologically. The kinetics of quercetin release from microspheres was the Korsmeyer-Peppas model. DL and EE had no significant differences for 3 months and no significant changes in the glass transition in the DSC test during testing until month 9. The FF formulation (1.5% AA75) had the highest cytotoxic activity against HeLa cells and a high Selectivity Index.

Keywords
Pectin, Quercetin, Microsphere, Stability, Cytotoxicity

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1. INTRODUCTION

Red dragon fruit (*Hylocereus polyrhizus*) is consumed fresh and processed into several products. Dragon fruit skin weighs 30-35% of the weight of the fruit and has not been utilized properly. The accumulation of dragon fruit skin waste (*Hylocereus polyrhizus*), which is commonly found in the community environment, should be observed so that environmental pollution does not occur and become a breeding ground for disease (Barnossi et al., 2021). The red dragon fruit skin (*Hylocereus polyrhizus*) has greater benefits than the fruit's flesh because the skin of the dragon fruit (*Hylocereus polyrhizus*) contains antioxidants that can ward off free radicals. The skin of the red dragon fruit (*Hylocereus polyrhizus*) also contains other beneficial contents, such as dietary fibre, one of which is pectin. The pectin content in the skin of the red dragon fruit is relatively high, namely more than 10% (Liu et al., 2023). The waste obtained from dragon fruit skin can be converted into value-added products as an alternative source to extract pectin. Commercial pectin is currently produced and derived from apple pomace and citrus skin. Most pectin is made from apple pomace and leftover citrus skin after fruit juice production. The remaining raw materials would otherwise be wasted. Hence, making pectin from these materials is a good example of the application of circular economy in the food supply chain (Durga et al., 2025).

The potential for extracting pectin from red dragon fruit skin waste is very promising because red dragon fruit skin contains fibre, natural pigments, and pectin, which can be used as industrial raw materials (Liu et al., 2023). Utilising dragon fruit skin as a source of pectin can reduce waste and support a circular economy, making it a sustainable alternative to conventional pectin sources such as orange or apple skin. The potential for extracting pectin from dragon fruit skin is interesting because research shows that it has a reasonably high pectin content, so it can be extracted and used in the food, pharmaceutical, or cosmetic industries. In addition, utilising dragon fruit skin, often discarded as agro-industrial waste, can reduce environmental pollution, dependence on orange and apple skin as the primary source of pectin, and diversification of raw materials. The process of extracting pectin from dragon fruit skin can support the principles of green chemistry because it is one of the efforts to decompose waste by converting organic waste into value-added products (Joseph et al., 2024). The red dragon fruit is a fast-growing plant, so its skin can be a source of renewable raw materials. Extraction techniques using environmentally friendly solvents can also be developed, reducing the use of hazardous chemicals in the extraction of dragon fruit skin conducted in this study using ecologically friendly organic acids and very low toxicity, namely oxalic acid, citric acid, and acetic acid (Kurniawan et al., 2024a)

The use of red dragon fruit skin in pectin extraction is in line with several SDG targets, namely SDG 9 (Industry, Innovation, and Infrastructure) in the form of innovation in pectin extraction technology from waste to support sustainable industry, and SDG 2 (Zero Hunger). For example, pectin can improve food security by enabling more durable or nutritious food products. SDG 12 (Responsible Consumption and Production) is addressed because the processing of dragon fruit skin waste encourages responsible and sustainable use of waste. SDG 13 (Climate Action), which reduces waste and implements more environmentally friendly processes, contributes to lowering the carbon footprint. Overall, pectin extraction from dragon fruit skin has excellent potential to be a source of sustainable raw materials, supports a green economy, and aligns with the principles of green chemistry and the achievement of SDG targets (Ram and & Bracci, 2024).

Pectin has the potential to be developed into a polymer used in the manufacture of microparticle preparations (Nahrowi et al., 2024). The drug's anti-inflammatory and antioxidant activities were increased by quercetin-loaded pectin/casein polymer microcapsules compared to the unencapsulated form. Hence, when administered sufficiently controlled, quercetin shows potential as an effective compound for treating inflammatory bowel disease (Azeem et al., 2023). Quercetin-loaded pectin/casein microcapsules can modify oxidative stress, but they do not have a notable anti-inflammatory effect. This discovery provides evidence for the continued use of quercetin as a long-term treatment for rheumatoid arthritis, primarily as a supplement that acts as an antioxidant (Souza et al., 2021). The oligochitosan exhibited its advantageous characteristics of low molecular weight and small steric size by creating a dense layer that covered the pectin microspheres. This coating of oligochitosan not only enhanced adherence to the colon but also facilitated release in the colon. These findings highlight the potential of oligochitosan with an extremely low molecular weight (Jing et al., 2023). However, there has been no research on using pectin derived from dragon fruit skin as a polymer to coat quercetin compounds to increase their stability and bioavailability. Previous research stated that dragon fruit skin produces pectin that has almost the same characteristics as commercial pectin that is already on the market, where dragon fruit skin pectin is subjected to acid extraction using oxalic acid, citric acid, and acetic acid solvents at a temperature of 75°C (Kurniawan et al., 2024b). This result suggests that dragon fruit skin pectin also has the potential to be developed into a microencapsulation polymer like commercial pectin. Quercetin is often used as a model for testing drug stability and bioavailability.

Quercetin crystals are orange-yellow and are soluble in lipids and alcohol but insoluble in water (Shabir et al., 2022). Quercetin is included in BCS class II, where its solubility is low, but its permeability is high, thus affecting its bioavailability (Kurniawan et al., 2024a). The bioavailability of quercetin is relatively low, namely, relatively low solubility in water, 0.17 - 7 μg/mL, gastric fluid, 5.5 μg/mL, and intestinal fluid, 28.9 μg/mL (Kandemir et al., 2022). These shortcomings can be overcome by encapsulating quercetin in a strong carrier that can provide protection against oxidation, isomerisation, and degradation and increase storage stability (Shabir et al., 2022). Various techniques have been used to improve the solubility and durability of quercetin, including formulation into microparticles, microspheres, solid lipid microparticles (SLM), nanoparticles, microemulsion preparations, and microencapsulation (Kurniawan et al., 2024b).

One easy-to-use method is microencapsulation using polymers. Microencapsulation is one of the techniques used for coating or sealing materials during core substance processing. Microencapsulation can help release active compounds such as antioxidants. This technique can prevent damage to core compounds by environmental factors and increase their bioavailability (Choudhury et al., 2021). Polymer coating in microencapsulation is used to maintain various physicochemical characteristics of core compounds, including moisture properties and shelf life. One of the polymers that can be used in the microencapsulation method is the pectin polymer. Various techniques are used to modify quercetin to improve its solubility and bioavailability. One way to overcome the weaknesses of quercetin is to use the microencapsulation technique using polymer compounds (Kurniawan et al., 2024a). The advantage of the microencapsulation technique is that it can protect. Based on this, it is necessary to conduct a study on the manufacture of quercetin microencapsulation polymers using pectin polymers extracted from red dragon fruit skin to obtain data on the potential of red dragon fruit skin pectin to be developed as a microencapsulation polymer (Saavedra-Leos et al., 2022).

Pectin-chitosan beads can serve as an excellent drug delivery vehicle, highlighting the stability of chitosan nanoparticles in the low pH environment of the gastrointestinal system (Nalini et al., 2022).

Previous studies indicate that pectin-chitosan beads are effective drug delivery vehicles, demonstrating chitosan nanoparticles' durability in the gastrointestinal tract's acidic conditions. The in vitro drug release investigation of the beads showed their ability to release quercetin in a sustained manner (Nalini et al., 2022). Another study stated that quercetin made into microspheres using pectin with the help of oligochitosan as a crosslinker could relieve colitis symptoms and maintain colon length and intestinal barrier integrity (Jing et al., 2023). A further study showed that quercetin-loaded pectin/casein microcapsules when provided orally at a modest dosage, enhance oxidative stress in arthritic rats without exhibiting significant anti-inflammatory effects. This result endorses the prolonged application of quercetin as an antioxidant agent for treating rheumatoid arthritis (Souza et al., 2021).

A few researchers focused on sustained release testing of quercetin in a microencapsulation system. Still, they limited the use of commercial pectin to improve the stability of quercetin to acid and the sustained release of quercetin. There has never been any research regarding using red dragon fruit peel pectin for microencapsulation of quercetin. The objective of this research was concerned with the utilization of new pectin sources of red dragon fruit skin, which was used as a polymer in microsphere quercetin formulation, thermal stability testing of quercetin microspheres for 9 months, simultaneous digestion stability testing in artificial acid solutions and artificial intestinal solutions, followed directly by cytotoxicity testing on HeLa cancer cells. Use this research to know the potential of pectin from red dragon skin to be developed into a polymer in a drug microencapsulation system regarding thermal stability, digestion resistance, and cytotoxicity properties. Pectin from red dragon fruit skin is expected to be a new source of pectin used as a polymer in pharmaceutical formulation.

2. EXPERIMENTAL SECTION

2.1 Chemicals

Pectin derived from dragon fruit skin utilizing oxalic acid at 75°C (OA75), pectin derived from dragon fruit skin utilizing citric acid at 75°C (CA75), and pectin derived from dragon fruit skin utilizing acetic acid at 75°C (AA75) (Kurniawan et al., 2024b). Commercial pectin from citrus peel (PCP) and commercial pectin from apple pomace (PAP) (Sigma-Aldrich). Quercetin (Tokyo Chemical Industry) served as the model pharmaceutical agent. Calcium chloride dihydrate ($CaCl_2.2H_2O$), 10035-04-8, Merck, Darmstadt, Germany) was utilized as a crosslinking agent to associate negatively charged polymer chains, such as pectin, thereby establishing a more stable and structured three-dimensional network. This process aids in forming a robust polymer matrix, which protects encapsulated quercetin from external influences and facilitates controlled release. Maltodextrin (DE10-12, Qinhuangdao Lihua Starch Co. Ltd., China) was employed as a cryoprotectant to safeguard quercetin during the freezing and drying procedure utilizing a freeze-drier. Ethanol was chosen as an effective solvent for quercetin, whereas distilled water was employed to dissolve the pectin. Oxalic acid, citric acid, and an acidic solution are employed to extract pectin from the skin of red dragon fruit, and phosphate buffer solution (pH 7.4) containing 0.8 g NaOH and 2.72 g KH_2PO_4 was used for the in vitro release test. All solvents employed were of pharmaceutical grade.

2.2 Instrumentations

Glassware (IWAKI PYREX), oven (Memmert), digital scales (OHAUS), water bath (Memmert), hot plate magnetic stirrer (IKA), Ultra Thurax (IKA), pH meter (Ohauss), Freeze Dryer (Biobase), Moisture Analyzer (Ohauss), UV-Vis Spectrophotometer UV-Vis (Shimadzu), FT-IR (Fourier Transform Infrared) Spectrum 100 Perkin Elmer, Scanning Electron Microscope instrument (Thermofisher Scientific Phenom ProX), DSC instrument (Perkin Elmer DSC 400), XRD instrument (Rigaku Miniflex 600 C), Particle Size Analyzer (Malvern), Gel Permeation Chromatography instrument (TOSOH, HLC – 8320 GPC), Particle Size Analyzer (Malvern), food dehydrator.

2.3 Procedure and Analysis

2.3.1 Gel Permeation Chromatography (GPC)

GPC analysis was carried out on pectin polymers. The tools used were TOSOH, HLC–8320 GPC. The stationary phase used was TSKgel SuperAW5000 containing hydrophilic metha crylate with a particle size of 7 μm and a pore size of 100 nm with a water grade 1 solvent (ultrapure water). The pectin sample used was made with a concentration of 1000 mg/L with an injection volume of 20 µl with a flow rate of 0.3 ml/min (Hayakawa et al., 1993). The column temperature and pump temperature used were 40°C with the detector type being RI. The 5 types of pectin used were OA75 red dragon fruit peel pectin, CA75 red dragon fruit peel pectin, AA75 red dragon fruit peel pectin, commercial orange peel pectin and commercial apple pectin. Analysis results obtained were the values of Mn, Mw, Mz, and Rt.

2.3.2 Microsphere Formulation

In this research, a quercetin-pectin microsphere formulation was made using the ionic gelation method and a peristaltic dosing pump. Three types of pectin from dragon fruit skin were also used in this study: pectin from dragon fruit skin that was extracted using oxalic acid (OA75), citric acid (CA75), and acetic acid (AA75). Ten microsphere formulas were made, namely FA and FB (OA75), FC and FD (CA75), FE and FF (AA75), FG and FH (PCP), FI and FJ (PAP). Table 1 shows the formulations of microspheres.

The pectin solution was prepared according to the formula using 100 ml of purified water. The solution was then swirled using an ultra turrax at a speed of 5000 rpm for 10 minutes, as indicated in Table 1. 0.2 grams of quercetin was dissolved in 20 ml of ethanol. The mixture was stirred until it was evenly

Table 1. Quercetin-Pectin Microspheres Formulation

Material	FA	FB	FC	FD	FE	FF	FG	FH	FI	FJ
Quercetin hydrate	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Pectin OA75[a]	1%	1.5%	-	-	-	-	-	-	-	-
Pectin CA75[b]	-	-	1%	1.5%	-	-	-	-	-	-
Pectin AA75[c]	-	-	-	-	1%	1.5%	-	-	-	-
Pectin PCP[d]	-	-	-	-	-	-	1%	1.5%	-	-
Pectin PAP[e]	-	-	-	-	-	-	-	-	1%	1.5%
$CaCl_2$	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%
Maltodextrin	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%

[a]Pectin OA75: Pectin Which is Extracted from Red Dragon Fruit Skin Using Oxalic Acid at a Temperature of 75°C ;[b]Pectin CA75: Pectin Which is Extracted from Red Dragon Fruit Skin Using Citric Acid at a Temperature of 75°C; [c]Pectin AA75: Pectin Which is Extracted from Red Dragon Fruit Skin Using Acetic Acid at a Temperature of 75°C; [d]Pectin PCP: Commercial Pectin from Citrus Peel; [e]Pectin PAP: Commercial Pectin from Apple Pomace

mixed. Then, it was gradually added to the existing pectin solution and stirred using an ultra turrax at a speed of 5000 rpm for 30 minutes until the mixture was uniformly mixed, resulting in a pectin-quercetin solution. A solution of $CaCl_2$ with a concentration of 5.5% was created by dissolving it in 100 ml of distilled water. The pectin-quercetin solution was slowly introduced into the $CaCl_2$ solution using a peristaltic pump at 2 ml per minute. The mixture was stirred using a magnetic stirrer at 1000 rpm for 60 minutes. The microspheres were isolated from the $CaCl_2$ solution using centrifugation at 3500 rpm for 6 minutes. The liquid above the microspheres was removed, and the microspheres were washed with distilled water. This was done by adding distilled water and centrifuging at 3500 rpm for 6 minutes. This process was repeated twice. The microspheres were suspended in a solution containing 5% maltodextrin, which acts as a substance that protects them during lyophilization. The suspension was gently swirled with moderate agitation using a stir bar until it became uniform and consistent. The quercetin microspheres suspension underwent freeze drying at -50°C for 96 hours.

2.3.3 Evaluation of Microspheres

2.2.3.1. Yield

A yield number approaching 100% indicates the production technique's high efficiency in producing ideal microspheres. The quercetin microspheres are measured in terms of weight, and the percentage is determined using the Equation (1) provided (Lee et al., 2022):

$$\text{yield} = \frac{\text{weight of microspheres}}{\text{weight of polymer + quercetin + lyoprotectant}} \times 100\% \tag{1}$$

2.2.3.2. Moisture Content (MC)

A moisture analyzer was used to quantify the moisture content of quercetin microspheres (Razak et al., 2020).

2.2.3.3. Carr's Index and Hausner-Ratio

The equation determines Carr's Index (CI) and Hausner-Ratio (HR), as shown in the Equations (2) and Equation (3) (Lourenço et al., 2020):

$$\text{CI} = \frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \times 100\% \tag{2}$$

$$\text{HR} = \frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}} \tag{3}$$

2.2.3.4. Fourier Transform Infrared (FTIR)

FTIR testing was performed using FTIR KBr with the FTIR Spectrum 100 Perkin Elmer specifications.

2.2.3.5. Microsphere Morphology

Scanning Electron Microscope (SEM) tools were used to assess dried quercetin microspheres morphologically using a Thermofisher Scientific Phenom ProX SEM testing machine (Liempepas et al., 2025).

2.2.3.6. Particle Size Analyzer (PSA) and Zeta Potential Measurement

Microspheres were dispersed in distilled water and analyzed using a Malvern Zetasizer Nano ZS PSA tool. The data obtained were Z-Average values, PDI, and particle size distribution. Samples were analyzed using the same instrument to obtain zeta potential, zeta deviation, and data quality values. Zeta values are used to assess the stability of colloidal systems (Madaniyah et al., 2025).

2.2.3.7. Swelling Index

The swelling index is a quantitative measure employed to ascertain the extent to which a substance can undergo swelling or expansion upon exposure to specific chemicals, such as water. The swelling index test was conducted by measuring the weight of 100 mg of microparticles and introducing 5 mL of PBS pH 7.4 into the vial. This experiment is conducted for a duration of 24 and 30 hours. Once the designated time has elapsed, the moist microparticles are separated by passing them through filter paper. Once all PBS droplets have disappeared, the moist microparticles are moved onto a dry filter paper until they reach a state of moderate dampness and no traces of PBS are left.

The wet microparticles were dehydrated by subjecting them to an oven set at a temperature of 37°C for 2 hours or until the weight of the microparticles reached a steady state. After drying, the microparticles were quantified by weighing them and assessing their swelling (α) degree using the Equation (4) (Purwanti et al., 2020).

$$\alpha = \frac{\text{weight before swelling} - \text{weight after swelling}}{\text{weight before swelling}} \times 100\% \quad (4)$$

2.2.3.8. Encapsulation Efficiency (EE) and Drug Loading (DL)

Encapsulation efficiency (EE) was determined by comparing the actual quantity of quercetin in the microparticles to the theoretically anticipated quantity in the microparticle formulation. Drug Loading (DL) capacity is a metric that indicates the quantity of quercetin present in microparticles relative to their weight. The quantity of quercetin encapsulated within the microparticle system was ascertained by directly comparing the total concentration within the microparticles to the concentration of quercetin incorporated into the formulation. The quercetin concentration was ascertained by dissolving 100 mg of quercetin-pectin microparticles in 100 ml of ethanol using sonication for 60 minutes until complete dissolution of the microparticles occurred. The sample was subsequently filtered and examined via UV spectrophotometry at a wavelength of 370 nm. Measurements were conducted in triplicate and calculated using Equations (5) and Equation (6) (Kalalo et al., 2022).

$$\text{EE} = \frac{\text{quercetin weight in sample}}{\text{theoretical quercetin weight}} \times 100\% \quad (5)$$

$$\text{DL} = \frac{\text{quercetin weight in sample}}{\text{microspheres sample weight}} \times 100\% \quad (6)$$

2.2.3.9. In Vitro Release

The experiment was conducted using a pH 7.4 phosphate buffer solution in a shaking water bath set at 100 rpm at a temperature of 37°C. The experiment was replicated three times. Subsequently, specimens were collected at 15, 30, 60, 120, 180, 240, 300, 360, 420, 480, 540, and 600 minutes, resulting in a cumulative volume of 5.0 mL (Yuwono et al., 2022). The original sample was substituted with an equal amount during the sampling process. Subsequently, the absorbance of each sample was measured using UV-Vis spectrophotometry at the specific wavelength of 370 nm, which corresponds to the maximum wavelength of quercetin. The data were analyzed using the kinetic release model using the zero-order, first-order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas models.

2.2.3.10. Accelerated Stability Test An accelerated stability test was conducted on FA to FF microspheres. Microsphere powder was put into a vial and then placed in a climatic chamber with a temperature of 40±2°C, RH 75±5% for 28 days with testing intervals on days 0, 7, 14, 28, and 90 days (Zhihrotulwida et al., 2025). Changes in DL and EE values were observed.

2.3.4 Thermal Analysis with Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) Months 0, 8 and 9

The temperature profiles of red dragon fruit (*Hylocereus polyrhiz us*) skin quercetin-pectin microparticles and commercial quercetin-pectin microparticles were analyzed using a Perkin Elmer DSC 4000 tool. This analysis aimed to identify the melting point and thermogram profile of the material melting process. The DSC examination procedure involves weighing a solid sample of 5 mg and sealing it in a crimper using a presser. The crimper is positioned inside a furnace with a heating rate of 10°C per minute. Measurements are conducted within the temperature range of 25-350°C (Helmy et al., 2020). DSC tests were conducted on microspheres in months 0,8 and 9 since they were stored in a climatic chamber at a temperature of 45°C and RH 75%. The characterization of microspheres was determined by X-ray diffraction (XRD) analysis in a Rigaku Miniflex 600 C diffractometer operated at 45 kV, 40 mA. Scanning was carried out in the 2θ range of 5–50° (Samat et al., 2025). The intensity that occurred was measured. XRD analysis was carried out on FI-FJ microparticle samples that were subjected to stability tests at 45°C and RH 75% conditions at months 0, 8 and 9 (Rubini et al., 2020)).

2.3.5 Digestion Resistance and Cytotoxicity Test on HeLa Cancer Cells and Vero Cells Using MTT Assay

A total of 200 mg of FA-FJ microspheres and quercetin standards equivalent to 200 mg of microspheres were incubated in 10 ml of artificial stomach solution for 2 hours and continued incubation in 10 ml of artificial intestine solution for 2 hours. The incubation process was carried out using a shaking water bath at a temperature of 37°C at a speed of 100 rpm. After the incubation process was continued with a centrifuge process of 3500 rpm for 2 minutes, the sediment was taken and separated from the supernatant. A total of 10 mg of sediment was taken and dissolved using 1 ml of 1% DMSO then a series of concentrations of 5000, 2500, 1250, 625, 312.5 ppm were made. Cytotoxicity tests were carried out using MTT Assay on Hela Cancer cells and Vero cells, then the IC_{50} value and the Selectivity Index (SI) value were calculated (Sundaram et al., 2019).

3. RESULTS AND DISCUSSION

3.1 Gel Permeation Chromatography (GPC)

GPC is a type of liquid chromatography used to separate molecules based on their size and molecular weight. This method is often used in the analysis of polymers, proteins, or other molecules that have various molecular sizes (Papp et al., 2024). In dragon fruit peel pectin OA75, CA75 and AA75 produced 5 peaks with 1 dominant peak. The total peak data of dragon fruit peel pectin and commercial pectin are shown in table 2.

The Mn value reflects the dominance of small molecules in the molecular weight distribution. Pectin OA75, CA75, and AA75 showed small Mn values. The lowest Mn in AA75 indicates a higher small molecule content, which will increase solubility but can reduce gelation ability. In commercial pectin, PCP has the highest Mn compared to commercial pectin PAP and red dragon fruit peel pectin. These results indicate that commercial pectin PCP has fewer small molecules, making it more stable for gelation. In contrast, commercial apple pectin has a higher Mn than dragon fruit peel pectin, but lower than orange peel. So, based on the Mn value, dragon fruit peel pectin is suitable for formulations with high solubility requirements, while commercial pectin is superior in gel stability.

The dominant small molecules in red dragon fruit skin pectin OA75, CA75, and AA75 will produce a more porous and soluble matrix. This result will increase the initial release of quercetin due to the dissolution of the small pectin matrix in the release medium. Quercetin encapsulated in areas with small molecules tends to be released faster. In commercial quercetin-pectin microparticles, a denser and less porous matrix will be produced because there are fewer small molecules so that the release will be slower and more controlled with a more stable release profile.

The Mw value of dragon fruit peel pectin is higher than that of commercial pectin. Mw describes the average molecular weight influenced by large molecules. The higher the Mw value, the greater the contribution of large molecules in the molecular weight distribution of the sample. Mw is closely related to pectin viscosity, gelation ability, and mechanical stability. In OA75 dragon fruit peel pectin, the Mw value is 191,450,603 Daltons, the lowest compared to other red dragon fruit peel pectin. The Mw value of CA75 pectin is 266,316,437 Daltons, and the Mw value of AA75 pectin is 222,197,302 Daltons. The high Mw in OA75 pectin indicates that it has many large molecules, so it is suitable for medium to strong gelation processes and high viscosity thickener formulations. The Mw value is lower than that of CA75 dragon fruit peel pectin but still high. Capable of providing a balance between strong gelation and moderate solubility, and is suitable for standard gelation formulations or thickeners.

In AA75 dragon fruit peel pectin has a relatively high Mw value, and shows a combination of large and medium molecules, making it suitable for formulations that require high viscosity but are not as strong as CA75 pectin. The resulting Mw value is intermediate between the other two dragon fruit peel pectin types. Combining large and medium molecules will make AA75 pectin flexible for various formulations with various viscosities. CA75 pectin has the highest Mw value among all types of dragon fruit peel pectin, showing that large molecules are dominant compared to the other two types of pectin. CA75 pectin is suitable for potent gelation formulations or gel stabilization. The highest Mw value indicates that this sample has the largest molecules, making it ideal for very strong gelation and formulations with high mechanical stability requirements.

Commercial pectin PAP and commercial pectin PCP have lower Mw values than the Mw values of the three types of red dragon fruit peel pectin (OA75, CA75 and AA75). Commercial pectin PCP has a low Mw value (91,027,297), indicating a narrower molecular weight distribution. Suitable for formulations with lower viscosity requirements, while commercial apple pectin with a Mw value of 123,700,864, which is classified as moderate, provides higher stability than orange peel pectin, making it suitable for formulations that require moderate to strong viscosity.

The Mw value produced from dragon fruit peel pectin is much higher than that of commercial pectin. Large molecules in dragon fruit peel pectin provide better gelation ability and higher viscosity than commercial pectin. High Mw supports the formation of firm gels, is suitable for formulations such as controlled-release microparticle gels, and can provide better resistance to mechanical and environmental stress, such as high temperatures (Sayah et al., 2016). However, high Mw values cause longer dissolution times than commercial pectin, making it less suitable for formulations that require fast solubility. Dragon fruit peel pectin is ideal for formulations with strong gelation and high mechanical stabilization. High Mw provides a better ability for formulations with high viscosity. Dragon fruit peel pectin CA75 (highest Mw) is the best for strong gelation. Commercial orange and apple peel pectin are suitable for formulations with more uniform consistency requirements and low to medium viscosity.

The Mw value of red dragon fruit peel pectin is usually higher than that of commercial pectin because the extraction process produces large molecules with complex structures. In addition, it is also possible that there is minimal degradation during the isolation and extraction processes. High MW values such as 191–266 million Da are reasonable characteristics for pectin from sources such as dragon fruit peel, which are rich in long-chain polysaccharides. Commercial pectin often undergoes further processing, such as partial hydrolysis, to produce a lower Mw. MW ranges from 50 to 150 million Da, depending on the targeted formulation. Commercial MW values such as 91–123 million Da in commercial pectin are typical for pectin with stable and homogeneous characteristics.

High methoxyl pectin tends to have a higher Mw due to the high degree of esterification that maintains the long chain structure. Low methoxyl pectin often has a lower Mw due to de-esterification or partial hydrolysis during processing. Acid extraction usually produces pectin with a high Mw because only part of the polymer chain is degraded. Enzymatic or thermal extraction produces more small molecules due to polysaccharide degradation, resulting in a lower Mw. The Mw of natural pectin usually ranges from 50 million to 400 million Da, depending on the source and extraction method. The molecular weight of commercial pectin is generally lower, ranging from 50 million to 150 million Da, due to its more processed nature for specific consistency and formulation. The Mw value of dragon fruit peel ranges from 191–266 million Da, which is

Table 2. Total Peak Data of Red Dragon Fruit Peel Pectin and Commercial Pectin

Parameters	Pectin OA75[a]	Pectin CA75[b]	Pectin AA75[c]	Pectin PCP[d]	Pectin PAP[e]
Mn (Da)	62	66	38	501	101
Mw (Da)	191,450,603	266,316,437	222,197,302	91,027,297	123,700,864
Mz (Da)	838,794,902	854,227,311	844,544,697	838,244,346	853,549,731
Rt (minutes)	3.547-12.943	3.490-12.962	3.490-14.528	3.547-12.868	3.472-12.887

[a]Pectin OA75: Pectin Which is Extracted from Red Dragon Fruit Skin Using Oxalic Acid at a Temperature of 75°C ;[b]Pectin CA75: Pectin Which is Extracted from Red Dragon Fruit Skin Using Citric Acid at a Temperature of 75°C; [c]Pectin AA75: Pectin Which is Extracted from Red Dragon Fruit Skin Using Acetic Acid at a Temperature of 75°C; [d]Pectin PCP: Commercial Pectin from Citrus Peel; [e]Pectin PAP: Commercial Pectin from Apple Pomace

within the reasonable range for large-molecule natural pectin. According to commercial product standards, the Mw value of commercial orange and apple peel pectin ranges from 91–123 million Da. High Mw is typical for natural pectin extracted without a significant degradation process. MW of 191–266 million Da indicates the presence of large molecules, making it suitable for formulations such as strong gelation and high viscosity thickeners. Lower Mw results from a partial hydrolysis process, which is designed to improve the consistency and efficiency of use.

The Mz parameter of all samples has a very high Mz value (838–854 million g/mol), indicating the presence of the largest molecules in significant amounts. In pectin, CA75 has an Mz value of 854,227,311 Da, and apple peel has an Mz value of 853,549,731 Da. All samples have the potential for formulations requiring strong viscosity, but CA75 and pectin PAP are slightly superior in dominant large molecules.

Rt is longer in AA75 pectin, at 3.490–14.528 minutes. The longer retention time distribution indicates that AA75 has very small to giant molecules. Shorter Rt occurs in commercial pectin. Commercial pectin PCP (3.547–12.868 minutes) and pectin PAP (3.472–12.887 minutes) reflect a narrower molecular distribution. In AA75 pectin, it has the widest molecular distribution, making it flexible for various formulations. Commercial pectin is more stable because the molecular distribution is more uniform.

Pectin is a complex polysaccharide composed mainly of D-galacturonic acid units and is generally extracted from plant materials using acidic solvents. The choice of acid type in the extraction process significantly affects the pectin quality, including its molecular weight, degree of esterification (DE), and gelation capacity. The organic acids used in this study include oxalic acid, citric acid, and acetic acid. The three acids have different acid strengths and chemical properties, thus affecting the structure and function of pectin differently.

DE indicates the percentage of carboxyl groups that undergo esterification to methyl ester. The DE value is significant because it determines the type and conditions of pectin gel formation. Using strong acids risks reducing DE due to de-esterification reactions that can occur during extraction. In previous studies, the highest DE values were obtained in pectin from acetic acid (AA75), 59.68 ± 1.62%, and oxalic acid (OA75), with a value of 57.21 ± 2.09%. In contrast, the use of citric acid (CA75) produced pectin with the lowest DE (45.60 ± 3.75%) (Kurniawan et al., 2024b). This data shows that although citric acid can maintain high molecular weight, it tends to produce pectin with low DE, possibly due to pH conditions facilitating the de-esterification reaction. DE is essential because it determines the gel formation mechanism. Pectin with DE > 50%, such as OA75 and AA75, tends to form gels through hydrophobic interactions in acidic conditions and in the presence of sugar. In comparison, low DE pectin (DE < 50%), such as CA75, is more suitable for forming gels through the calcium ion binding mechanism.

Pectin extracted with three types of organic acids exhibits different characteristics relevant for specific applications. Pectin OA75 has a high DE but a relatively low molecular weight, making it more suitable for rapid gelation applications under acidic conditions, such as in jams or jellies with high sugar content. In contrast, pectin CA75 exhibits the highest molecular weight but low DE. It is ideal for gel formation that relies on ionic interactions, especially with calcium ions, such as in low-sugar products or controlled-release pharmaceutical formulations. Meanwhile, pectin AA75 has a balance between medium molecular weight and high DE, offering flexibility in various applications that require gel stability, both in the food and pharmaceutical industries.

The combination of molecular weight and DE greatly influences the gelation properties of pectin. High DE pectin will form a gel in an acidic environment and in the presence of sugar. In contrast, low DE pectin forms gel through an ion Ca^{2+} binding mechanism known as the "egg-box model". Therefore, the type of acid used during extraction will determine the gel formation mechanism and functional applications of pectin in the food and pharmaceutical fields. In further research, a gelation capacity test is needed to determine the specific value of each type of pectin used.

3.2 Yield, Moisture Content, and Swelling Index

From the yield, the value obtained ranged from 80-91%, with the highest value obtained in FF microspheres. Compared to the yield value of other microspheres formulas, the value is not significantly different (p>0.05). The manufacturing method used also influences the magnitude of the yield value obtained. A high yield value indicates that most of the starting materials have been successfully converted into microsphere products, which means the method's effectiveness. The effectiveness of the microsphere manufacturing method is often measured by looking at the yield value produced. Yield in this context refers to the percentage of the total starting material successfully converted into the desired microspheres. In this case, the ionic gelation method with a peristaltic dose pump provides high efficiency in obtaining yield values. Selecting the right solvent and its compatibility with the base material can affect process efficiency and final results. The concentration of polymers, monomers, or other active ingredients must be optimized to increase yield. If the concentration is too low or too high, the yield can decrease due to the formation of agglomerates or the breaking of microspheres during the process. A high yield value indicates that most of the starting material was successfully converted into microsphere products, indicating the method's effectiveness. Conversely, a low yield may indicate material loss or inefficiency in the process, requiring further optimization. The test results of yield and MC are shown in Figure 1.

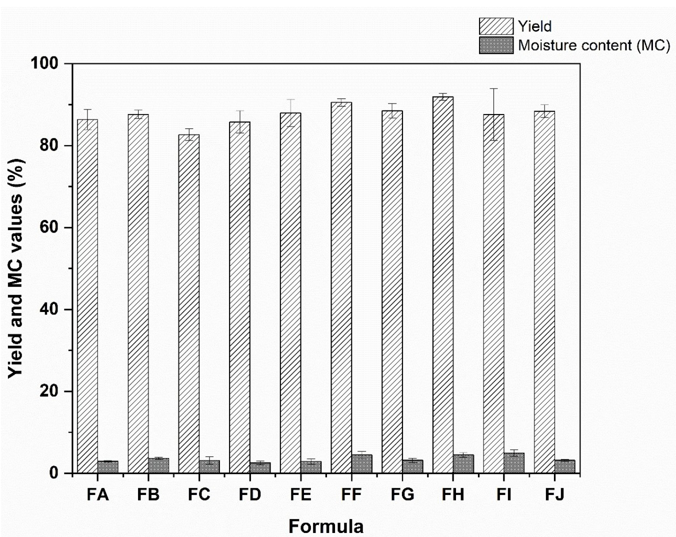


Figure 1. Yield and MC

From the results obtained, the increasing concentration of pectin polymer used to manufacture quercetin-pectin microspheres will increase the yield value. With more pectin in the system, the polymer matrix formed will be stronger and more stable. This data reduces the loss of quercetin during the microsphere manufacturing process and increases the number of microspheres successfully produced, contributing to increased yield (Chai et al., 2023). In addition, higher pectin concentrations increase the viscosity of the solution, which can help form more uniform and efficient microspheres. Well-formed microspheres will be easier to isolate and collect, increasing the total amount of the final product (Said et al., 2023). Higher amounts of pectin can help encapsulate quercetin more effectively, reducing the loss of active ingredients during the microsphere formation process. This result increases the amount of quercetin remaining in the microspheres, ultimately increasing the yield (Frent et al., 2023). At higher pectin concentrations, the possibility of agglomeration of quercetin particles may be reduced as pectin can act as a stabiliser, preventing the particles from sticking together undesirably and helping maintain higher yields. However, as in most processes, there is an optimum point beyond which further increases in pectin concentration may not provide significant yield increases or may even cause difficulties in microsphere formation or further processing.

In terms of moisture content, it is known that increasing the concentration of pectin polymer does not affect the moisture content value. The moisture content value of the ten microsphere formulas obtained ranges from 2-4% and meets the requirements, which is below 5%. Moisture content in microspheres is mainly influenced by the balance between the water content trapped in the microspheres and the rate of water evaporation during the drying process. Although the pectin concentration increases, the moisture content will not change significantly if the water remaining after drying remains constant. Pectin is a polymer with hydrophilic properties, but in microspheres, this property can change depending on how pectin interacts with quercetin and other ingredients. If increasing the concentration of pectin does not significantly change the hydrophilic properties or water absorption capacity of the microspheres, then the moisture content tends to remain the same.

Suppose the drying method, such as spray drying or freeze drying, and other drying conditions, such as temperature and time, remain constant. In that case, the moisture content of the microspheres will usually be stable, regardless of variations in pectin concentration. This result is because the drying process is designed to remove most of the water in the microspheres, so changes in polymer composition may not significantly affect the final moisture content (Nowak and & Jakubczyk, 2020). In this test, a freeze dryer is used for drying, and the results show efficiency and effectiveness (Adepu et al., 2021). In microspheres, the trapped water is often more related to the internal structure of the microspheres, such as the pore size and water distribution, rather than to the polymer concentration directly. If the increase in pectin concentration does not significantly change the internal structure of the microspheres, the moisture content will remain consistent (Adepu et al., 2021).

The swelling index value ranges from 94.53 ± 3.41 to 97.74 ± 2.43%. This value is classified as high. The high swelling index value in the microsphere test using pectin polymer indicates that the microsphere can absorb water or liquid. As a hydrophilic polymer, Pectin can absorb water and swell, reflecting the nature of the polymer network that allows water molecules to enter the structure. Pectin can form hydrogen bonds with water so the microsphere can swell more in an aqueous environment. In drug formulations, a high swelling index value can indicate that the microsphere will release the active substance more slowly and in a controlled manner because water absorption allows the polymer matrix to release the active ingredient gradually. However, if the microsphere experiences too much swelling, its physical structure can weaken, making it susceptible to breaking or breaking under certain environmental conditions. In addition, a high swelling index can indicate that the polymer network has a low level of cross-linking. With little cross-linking, the polymer network is more flexible and can absorb more liquid. So, a high swelling index indicates the potential of microspheres to function as a delivery system that relies on the slow release of active substances; there is a potential vulnerability to disintegration.

3.3 Particle Size Analyzer (PSA) and Zeta Potential

Particle size is a crucial parameter in determining drug delivery efficiency, bioavailability, and stability of microsphere preparations. Based on the results of the PSA analysis, the particle size of the FA to FJ formulas showed significant variations, ranging from submicron sizes of 451.6 nm to more than 3.6 µm. The FI formula showed an average particle size of 973.6 nm with the lowest polydispersity index (PDI) of 0.526, indicating a very homogeneous size distribution. The FH formula also showed a relatively narrow size distribution (PDI 0.613) with a dominant size of around 1023.0 nm. In contrast, FC formulas showed maximum PDI values (1,000), indicating a highly polydisperse system, requiring a reformulation strategy or additional processing techniques such as sonication or fractional filtration. Table 3 shows the best characterization test results of PSA and zeta potential.

Zeta potential is used to evaluate the electrostatic stability of colloidal systems. The zeta potential values of most formulas are in the range of -10 to -17 mV, which is still categorized as moderate stability. Formula FA displays a zeta potential value of -17.46 mV with the lowest deviation of 3.09 mV and QF = 4.43, indicating excellent system stability. Formula FB also shows good charge stability (zeta = -16.75 mV; QF = 3.53). Meanwhile, formula FJ has two zeta peaks with deviations >6 mV, indicating heterogeneous charge distribution and non-uniform potential interactions between particles.

The FB and FI formulas showed perfect consistency between replicates in size and zeta potential. FB and FI produced very high-quality zeta data (QF >4), supporting the validity of the production method. In contrast, the FC formulas showed relatively high size variation and zeta deviation between replicates, although the zeta values generally remained stable. This result indicates the need to optimize the homogenization and aggregate size control manufacturing process.

From the overall results, it can be concluded that FB and FI formulations are the best candidates for further development because they have particle sizes in the ideal range (800–1000 nm), narrow size distribution, and good electrostatic stability. Formulations like FD and FG show potential for further development with homogenization optimization or surface stabilization. Other formulas, such as FA, FC, FH, and FJ, require a reformulation approach to improve size homogeneity and charge distribution. These results provide a strong scientific basis for selecting the best formulation in pectin microsphere-based drug delivery systems.

3.4 Carr's Index and Hausner Ratio

The data of Carr's index and Hausner ratio values from ten microsphere formulas obtained values that meet the requirements at both polymer concentrations. This data is due to the similar distribution of particle sizes. Although the polymer concentration is different, if the powder or granule particle size remains uniform, the Carr's Index and Hausner Ratio values will stay in the range that meets the requirements. Consistent particle size distribution reduces segregation and promotes good powder flow. Uniform particle shape also contributes to the flow properties of the powder (Shenoy et al., 2015). If the particle shape does not change significantly with changes in polymer concentration, then the Carr's Index and Hausner Ratio values may not be drastically affected. Rounder particles tend to flow better than angular or irregular particles. The polymer used may affect the bonding mechanism between particles in the powder or granules. If the polymer, even in different concentrations, consistently increases interparticle cohesion or does not drastically change the bonding between particles, then the powder flow values will remain stable, so that the Carr's Index and Hausner Ratio remain satisfactory (Yim et al., 2023).

Even at different concentrations, homogeneous mixtures of powders or granules containing polymers can produce similar flow properties. If the polymer is evenly distributed in the mix, then changes in concentration may not significantly affect the Carr's Index and Hausner Ratio. If the polymer coats the powder particles or forms a film around them, this can improve the powder flow in general. In other words, even if the polymer concentration is different, the powder flow properties do not change much if the coating or film-forming effect remains similar (Shah et al., 2023). The difference in polymer concentration may not be significant enough to change the cohesiveness and composition of the powder mass. If the physical consistency of the powder is maintained, the Carr's Index and Hausner Ratio values can remain within acceptable limits. These factors can cause the Carr's Index and Hausner Ratio values to stay within acceptable limits even though the polymer concentration varies. This data indicates that other properties of the powder or granule, such as particle size, shape, and distribution, have a more dominant influence on flow than variations in polymer concentration. The resulting Carr's index values ranged from 8.40 ± 2.76 to 15.63 ± 2.85, with Hausner ratio values ranging from 1.09 ± 0.03 to 1.19 ± 0.04 and showed a good to excellent flow profile.

3.5 Drug Loading (DL) and Encapsulation Efficiency (EE)

The results of the EE and DL tests are shown in Figure 2. In all microsphere formulas, 1.5% pectin polymer concentration produced higher DL and EE values than 1% pectin polymer concentration. The highest DL and EE values obtained from the red dragon fruit skin pectin were in the FB formula containing 1.5% OA75 pectin. The drug loading value and encapsulation efficiency will increase with increasing pectin polymer concentration. Increasing pectin concentration increases the amount of polymer available to hold or bind drug molecules. This

Table 3. PSA and Zeta Potential Test Results

Formulation	Particle size (nm)	PDI	Zeta potential (mV)
FA	3602.0 ± 67.5	0.979 ± 0.036	-17.46 ± 0.20
FB	1549.3 ± 30.5	0.807 ± 0.198	-16.75 ± 0.16
FC	451.6 ± 4.5	1.000 ± 0.000	-13.73 ± 0.24
FD	1916.0 ± 34.1	0.990 ± 0.008	-15.72 ± 0.16
FE	1544.0 ± 12.5	0.617 ± 0.061	-12.59 ± 0.21
FF	753.7 ± 7.2	0.801 ± 0.051	-14.77 ± 0.35
FG	639.4 ± 8.1	0.636 ± 0.060	-14.43 ± 0.27
FH	1023.0 ± 2.6	0.613 ± 0.004	-10.06 ± 0.34
FI	973.6 ± 14.6	0.526 ± 0.098	-14.78 ± 0.17
FJ	1084.0 ± 11.5	0.726 ± 0.043	-11.62 ± 0.04

result means more drug molecules can be trapped or dispersed in the polymer matrix, increasing the drug loading value.

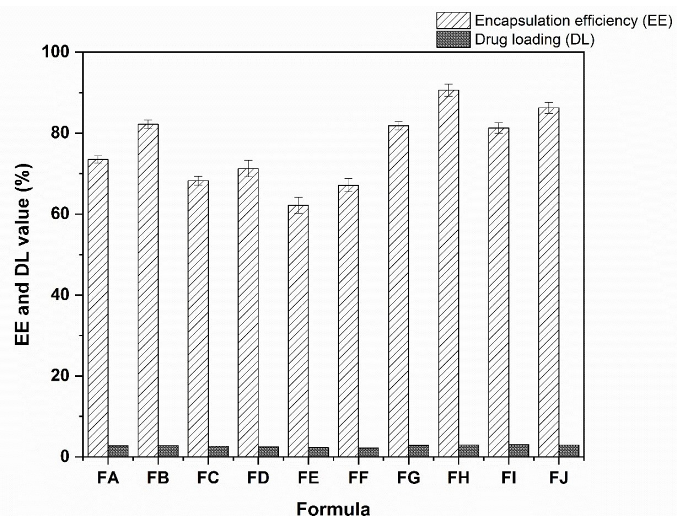


Figure 2. EE and DL Measurement

Higher polymer concentrations usually result in the formation of a denser and more compact polymer matrix. This denser matrix can reduce leakage or early release of the drug during the encapsulation process, increasing the encapsulation efficiency (Huang et al., 2023). Pectin is a natural polymer that can form non-covalent interactions with drugs, such as hydrogen bonds, electrostatic interactions, or van der Waals interactions. As the concentration of pectin increases, the number of potential interactions between the drug and the polymer increases, which can help retain more medications in the encapsulation system. More concentrated pectin can increase the viscosity of the solution, which in turn can reduce the diffusion of drugs out of the system during particle or capsule formation and will increase the amount of drug trapped in the matrix, increasing the drug loading value and encapsulation efficiency (Dranca et al., 2018). With higher pectin concentration, the diffusion of drug molecules out of the polymer matrix during the encapsulation process can be reduced. This data means more drugs remain in the matrix, increasing the encapsulation efficiency. Overall, increasing the concentration of pectin polymer allows more drugs to be bound or trapped in the polymer matrix, which improves both parameters, namely drug loading and encapsulation efficiency.

3.6 Scanning Electron Microscopy (SEM)

The SEM results and particle distribution size are shown in Figure 3 and Figure 4. Quercetin-Pectin microspheres produced a spherical shape. The spherical shape shows the method's effectiveness, and microencapsulation is carried out. The spherical shape allows for a more even distribution of particles, which is essential to ensure that the active ingredients in the capsule are dispersed homogeneously. This result contributes to a consistent and controlled release of the active ingredient. The spherical shape has a minimal surface area to volume ratio compared to other shapes, which helps to minimize degradation of the active ingredient and protect it from the external environment, such as air and light and tends to have better mechanical stability, thus protecting the active ingredient from damage during storage or transportation. The spherical shape allows for more efficient packaging, both on a micro and macro scale. On a micro-scale, less coating material is needed to coat the core material, increasing process efficiency. The spherical shape has the advantage that, due to the uniformity of shape and size, the release of active ingredients from spherical microencapsulation is more predictable and regulated, which is essential in pharmaceutical, food, and cosmetic applications. Overall, the spherical shape is considered ideal in microencapsulation because it provides several advantages that increase the effectiveness of the capsule in protecting, delivering, and releasing quercetin.

3.7 Fourier Transform Infrared (FTIR)

The FTIR results were conducted on six microsphere formulas that showed similar wave numbers and intensities between microspheres. This data indicates the existence of the same functional groups between one microsphere and another. The FTIR test results are shown in Figure 5.

Figure 5 shows that in FA to FF, there is a shift in wave numbers and the loss of several functional groups from the formula, indicating an interaction between quercetin and pectin

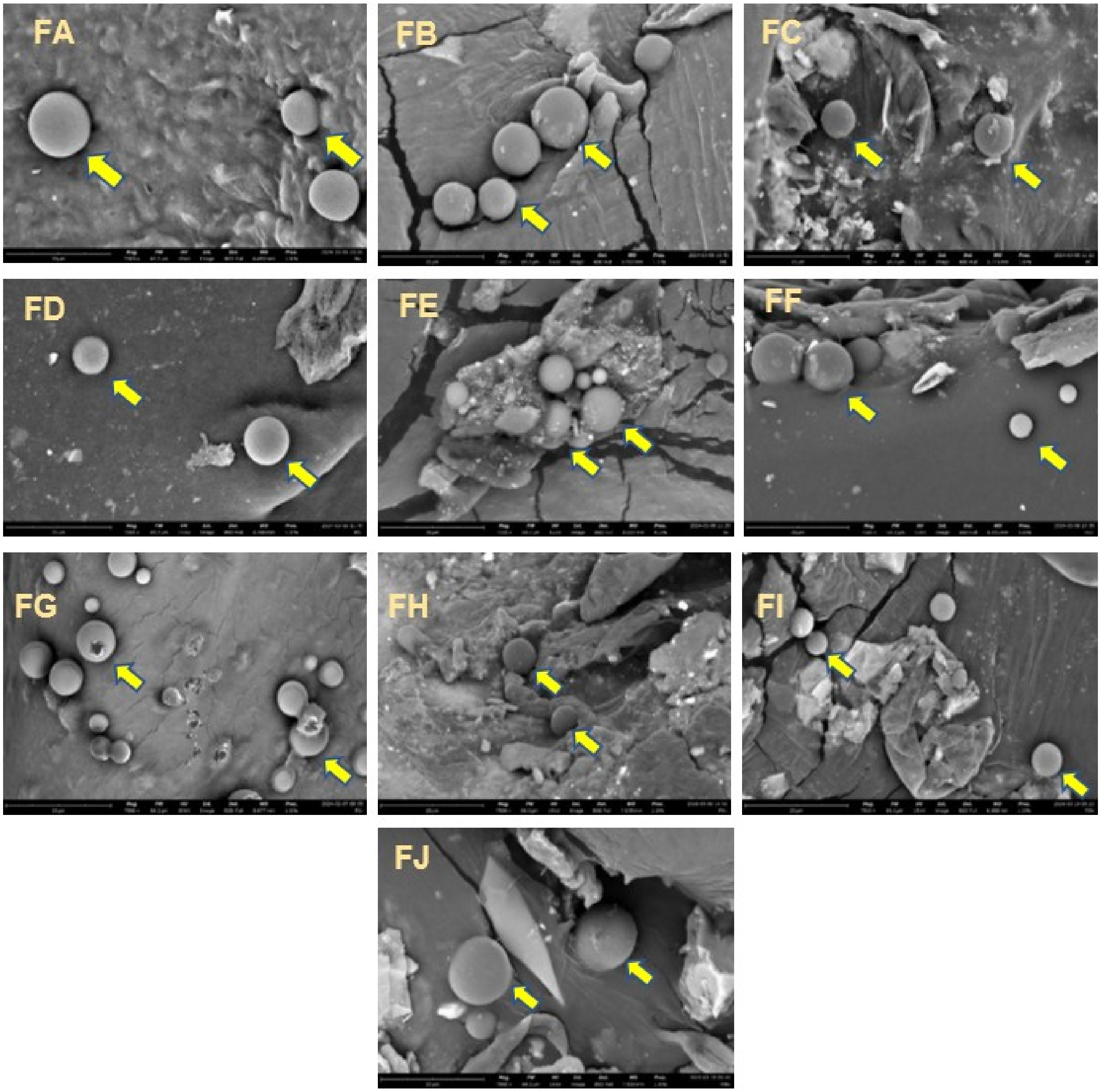


Figure 3. SEM test Results of Quercetin-Pectin Microspheres

polymers. The interaction indicates that all the constituent materials are mixed and have formed a microsphere system. In the quercetin compound, the shift in wave numbers occurs in the O−H group, C−H stretching, C=O stretching, C=C. The shift in pectin wave numbers occurs in the C−H stretching group, C=O stretching asymmetric and C=O stretching symmetric. The shift in maltodextrin wave numbers occurs in the C−O group, and the shift in $CaCl_2$ wave numbers occurs in the C−Cl group. Wavelength numbers 3411-3416 cm^{-1} show high-intensity absorption; this indicates the presence of high-intensity OH, which is the presence of the quercetin compound. At wavelength 2934-2949 cm^{-1}, absorption indicates the presence of C−H stretching (SP3), indicating pectin compound's presence in microspheres. C=O stretching group (asymmetric) appears at wavelength number 1511-1615 cm^{-1}, indicating that pectin and quercetin compounds have strong intensity in the microsphere system. Wavelength 1010-1011 cm^{-1} also shows the presence of the C=C group in the quercetin compound. C−O and C−Cl groups appear at Wavelength numbers 602-864 cm^{-1} and 412-568 cm^{-1}, indicating their presence in maltodextrin and $CaCl_2$ compounds.

There is a shift in the absorption band in the functional group, carbonyl, and hydroxyl, related to the interaction between quercetin and pectin; this indicates the interaction or

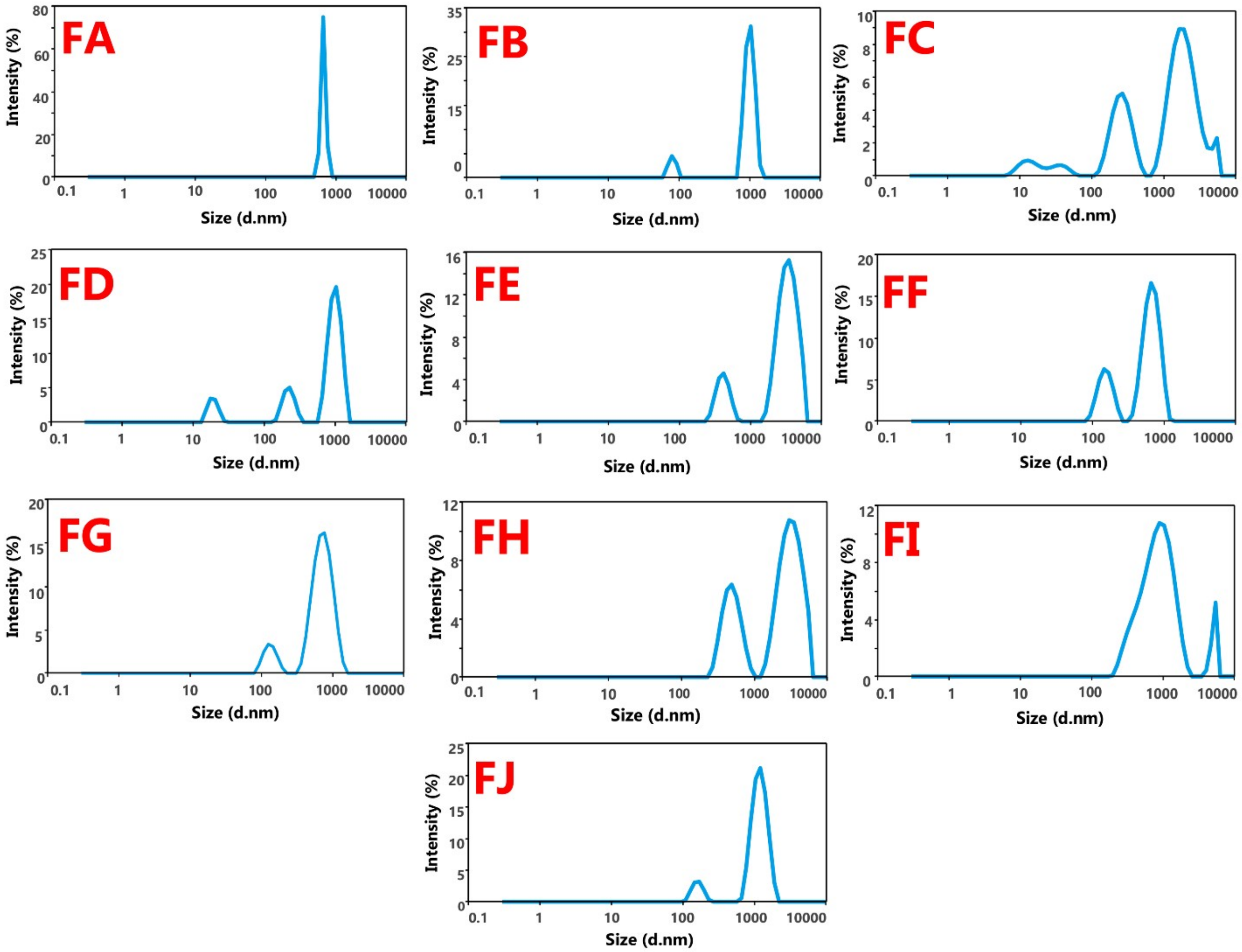


Figure 4. Particle Distribution Size of Quercetin-Pectin Microspheres

formation of bonds between molecules. Quercetin has a hydroxyl group that shows a wide peak around 3200-3600 cm^{-1}. In the FTIR results, there is a change in the intensity or position of this peak; this indicates the possibility of hydrogen interaction with pectin or maltodextrin. In addition, if there is a shift in the carbonyl band, this could indicate that quercetin has interacted with pectin in the microsphere matrix. Maltodextrin, as a polysaccharide, peaks at 1000-1200 cm^{-1}, related to the ether group. Changes in intensity or shifts in this area can also indicate the formation of microspheres involving maltodextrin. The interaction between calcium ions from $CaCl_2$ and pectin can form an "egg-box structure," which may not always be directly detected through FTIR but can affect the absorption pattern in the carboxylate band around 1400 cm^{-1} or carbonyl group. Some peaks typical for quercetin, such as the aromatic ring at 1600 cm^{-1}, show a shift or change in intensity, indicating that the quercetin molecule is in a different environment, namely in the microsphere matrix. These results indicate that quercetin is well encapsulated.

The FTIR data results were continued with deconvolution analysis using the Gaussian fit model on the FF microsphere samples to prove the presence of quercetin-pectin interactions. The results of deconvolution analysis using the Gaussian fit are shown in Figure 6.

Figure 6 shows that the analysis was carried out on 10 peaks, and the FWHM value produced shows the area. In the deconvolution results, FWHM shows how broad each Gaussian peak is. Peaks originating from pure compounds or specific functional groups usually have narrow FWHM. The larger the FWHM value, the greater the overlapping FTIR peaks. The peak of the interaction between quercetin and pectin can be wider because the groups overlap. The results show that four prominent peaks show the interaction between pectin and quercetin, namely at wave number 3070 with an FWHM value of 679.99; wave number 2363 with an FWHM value of 1952.79, and wave number 1009 with an FWHM value of 1282.18 and wave number 594 with an FWHM value of 415.41.The results of the FTIR spectrum analysis of quercetin-pectin microspheres showed the presence of several typical peaks that were further identified through the deconvolution

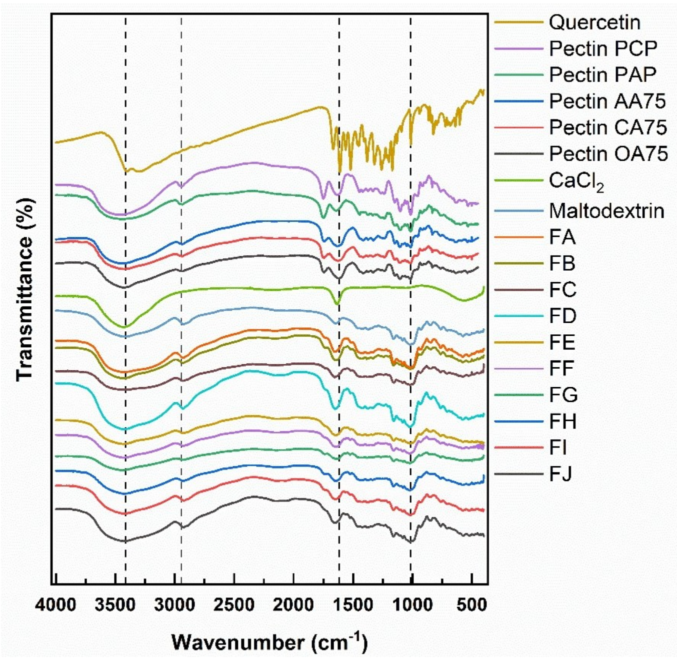
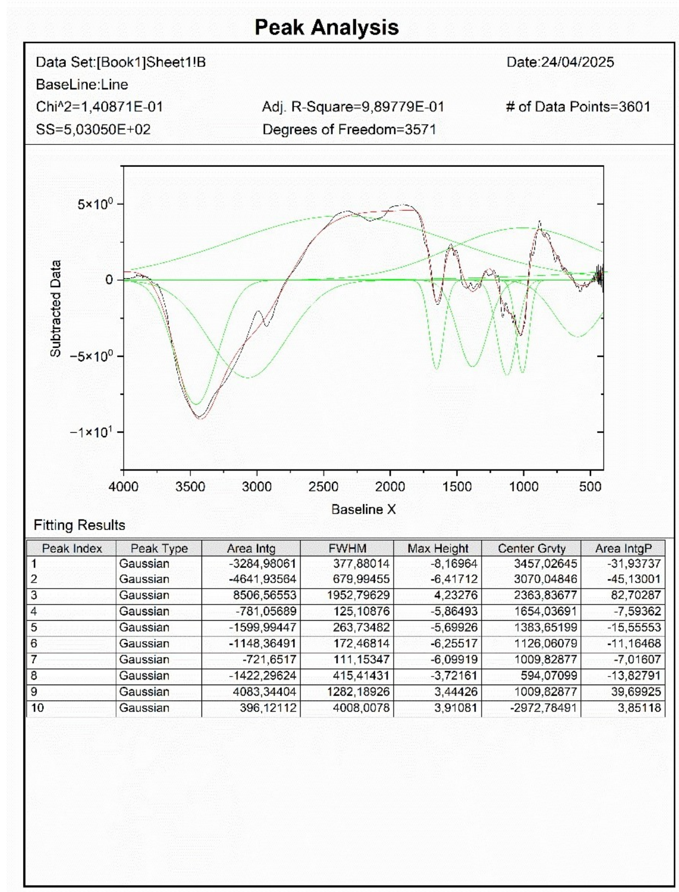


Figure 5. FTIR of All Materials and Quercetin-Pectin Microspheres



Peak Index	Peak Type	Area Intg	FWHM	Max Height	Center Grvty	Area IntgP
1	Gaussian	-3284,98061	377,88014	-8,16964	3457,02645	-31,93737
2	Gaussian	-4641,93564	679,99455	-6,41712	3070,04846	-45,13001
3	Gaussian	8506,56553	1952,79629	4,23276	2363,83677	82,70287
4	Gaussian	-781,05689	125,10876	-5,86493	1654,03691	-7,59362
5	Gaussian	-1599,99447	263,73482	-5,69926	1383,65199	-15,55553
6	Gaussian	-1148,36491	172,46814	-6,25517	1126,06079	-11,16468
7	Gaussian	-721,6517	111,15347	-6,09919	1009,82877	-7,01607
8	Gaussian	-1422,29624	415,41431	-3,72161	594,07099	-13,82791
9	Gaussian	4083,34404	1282,18926	3,44426	1009,82877	39,69925
10	Gaussian	396,12112	4008,0078	3,91081	-2972,78491	3,85118

Figure 6. FTIR Deconvolution Test Results On FF Microsphere Samples

method with the Gaussian fit approach.

The FTIR spectrum was observed in the wave number range of 4000–400 cm^{-1} and successfully separated several previously overlapped peaks. The peak that appeared at around 3457 cm^{-1} was the result of stretching vibrations of the –OH group which is commonly found in polyphenolic compounds such as quercetin, as well as in polysaccharide chains such as pectin and maltodextrin. The large FWHM of this peak indicates the possibility of strong hydrogen interactions between molecules, which broaden the –OH signal and indicate complexation in the microsphere matrix. The sharp peak at around 3070 cm^{-1} stated the presence of aromatic C–H stretching groups of quercetin. The relatively small FWHM indicated that the aromatic structure of quercetin remained stable after the encapsulation process. Meanwhile, the peak at around 1654 cm^{-1} with a very wide FWHM indicates the stretching vibration of the carbonyl group (C=O), which is likely to originate from the ester or carboxylic acid group in pectin and quercetin. The width of this peak indicates the overlapping vibrations of several interacting functional groups, including the possible involvement of Ca^{2+} ions in forming ionic cross-bridges in the pectin structure. Another peak at around 1384 cm^{-1} is interpreted as the bending vibration –CH, which originates from the alkyl group in pectin and maltodextrin. This peak also shows a relatively large width, strengthening the possibility of complex molecular interactions in the microsphere system. Overall, the FTIR deconvolution results indicate a strong interaction between quercetin and pectin and the role of maltodextrin and $CaCl_2$ in forming a stable microsphere structure. This is evidenced by the peak shift, changes in the FWHM peak width, and overlapping of several main functional groups successfully separated using the deconvolution technique.

3.8 Thermal Analysis with Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) Months 0, 8 and 9 XRD

The XRD results showing amorphous powder, characterised by a less clear diffraction pattern or no sharp peaks, can be caused by several factors. Pectin, maltodextrin, and $CaCl_2$ are naturally amorphous and do not have a regular crystalline structure; in addition, it could be because pectin is a very complex or large molecule that may not form a regular crystal structure, so it appears amorphous in XRD (Rivas et al., 2021). Pectin is a huge and complex molecule. Large and complex molecules have difficulty arranging in regular patterns, such as those found in crystals (Corpinot et al., 2019). Therefore, pectin tends to form an amorphous structure, which lacks the long-range order necessary for crystal formation. Pectin and maltodextrin are polymers, meaning they comprise long chains of repeating molecular units. Polymers often form an amorphous structure because their long chains can undergo various interactions, making it difficult to line up in a regular pattern like a crystal. There are many hydrogen bonds and other complex intermolecular interactions. This data makes it difficult for these molecules to form regular crystalline structures.

In general, amorphous materials do not have the symmetry or long-range order that crystals do. Amorphous structures tend to have a random distribution of atomic positions, which results in scattered diffraction patterns, and this is what is shown in the XRD results. $CaCl_2$ at room temperature is usually found in crystalline form, but it can become amorphous under certain conditions, such as excessive hydration or in mixtures with other compounds (Du et al., 2018). This can occur due to the disruption of the formation of a regular crystal lattice, causing the material to lose its crystalline structure. Thus, the amorphous nature of pectin, maltodextrin, and $CaCl_2$ in XRD can be caused by the complexity of the molecules and physical properties of these materials that do not support the formation of a regular crystalline structure. The results of the XRD test are shown in Figure 7.

Another factor influencing this is the size of the microspheres from FA to FJ, which may not be large enough to form a crystal structure that XRD can detect. If the microspheres are too small, they may not be large enough to form a crystal structure that XRD can detect. XRD is a technique used to determine the crystal structure of a material by analysing the X-ray diffraction pattern reflected by the crystal. However, for XRD to detect crystals, the material must have crystalline domains that are large enough, generally above 5 nm. If the particles are too small or amorphous, the resulting diffraction signal may be too weak or not formed, so XRD cannot detect them. Suppose the particle size is in the nanometre scale, especially below 2-3 nm. In that case, the crystallinity may not provide a clear diffraction pattern, and the material will appear amorphous in XRD analysis. At 2θ values of around 11, 13, and 27, quercetin showed a crystalline pattern, but this changed when formulated into FA, FB, FC, FD, FE, FF, FG, FH, FI and FJ microsphere formulations, where the crystalline form of quercetin was no longer visible. These data indicate that quercetin is dispersed in the microsphere system. The same pattern is also found in microspheres made from commercial orange and apple peel pectin, where both have amorphous patterns with the same intensity patterns.

OA75 pectin has the highest absorption intensity of more than 420 cps at 2θ 22, with a semi-crystalline structure at 2θ 17 with an intensity of less than 420 cps. CA75 pectin has the highest intensity of 420 cps at 2θ 22 with a semi-crystalline structure at 2θ 17 with a value of 420 cps. At the same time, AA75 pectin has the highest absorption intensity of 420 cps at $2\ \theta 22$ with a relatively strong semi-crystalline structure at 2θ 17 with an intensity value of more than 420 cps. It can be concluded that the three types of red dragon fruit skin pectin have the same XRD profile, with almost the same intensity, with the highest peak at 2θ 22.

Commercial orange peel pectin (PCP) also has an amorphous XRD profile but with a higher intensity of more than 740 cps at 2θ 22. At the same time, commercial apple pectin (PAP) has an absorption intensity of 630 cps at 2θ 22 with a semi-crystalline structure at 2θ 25, 32 and 37. From the XRD test results, three pectins from red dragon fruit peel and two commercial pectins have the same XRD pattern and profile, namely amorphous with the highest absorption intensity at 2θ 22. Minor differences are found in several pectin with a weak semi-crystalline structure at several 2θ values. The differences in the semi-crystalline structure are due to differences in the purity of the pectin produced and the influence of differences in the source of the extracted pectin material.

The 10 microparticle formulas were then subjected to a stability test for 9 months by storing them at a temperature of 40± 2°C and RH 75±5%, and their XRD profiles were tested at months 0, 8, and 9. The results of the XRD microspheres at months 0,8, and 9 are shown in Figure 8.

DSC All types of pectin extracted from red dragon fruit skin, namely OA75, CA75, and AA75, and commercial pectin PCP and PAP experienced 3 phases of the same thermal changes: vaporization, small crystallization, and decomposition. In the temperature range of 60°C to 70°C, all types of red dragon fruit skin pectin experienced the vaporization stage, namely the evaporation of water content in the microsphere sample due to heating the sample. The same thing also occurs in commercial pectin from orange and apple peels. The results of the DSC test are shown in Figure 9.

This vaporization event occurred in the FA to FJ microsphere preparations at the same temperature range. This result shows that the pectin content in the microsphere preparation can still absorb moisture from the environment, even though it has been formulated as a microsphere. Small crystallisation events occurred at different ambient temperature ranges for the three red dragon fruit skin pectin types produced. In OA75 pectin, small crystallisation occurred at a temperature of 235.11°C with a ΔH value of -15.96 J/g. CA75 pectin crystallised at a temperature of 207.78°C with a ΔH value of -12.26. At the same time, AA75 pectin crystallised at a temperature of 253.03°C with a ΔH value of -12.26 J/g. Pectin can absorb and store water. Suppose bound water is released during DSC testing. This process does not permanently damage pectin, but changes in hydration properties can affect the physical stability of microspheres during storage; this release can be seen as a small exothermic peak. When the three types of red dragon fruit skin pectin were formulated into microspheres, the crystallisation event did not appear again due to the ionic gelation process involving pectin and $CaCl_2$ used (Putri et al., 2025). Likewise, the profile of DSC quercetin also changed and formed a different thermal pattern when forming microspheres. Quercetin experienced dispersion, which caused changes in its thermal pattern when tested using DSC. When pectin OA75, CA75, and AA75 were formulated into microspheres, the resulting DSC pattern slightly changed to vaporisation, glass transition, and decomposition events. In the FA and FB formulas using OA75 pectin, the FA vaporisation temperature value is shown at a temperature of 60.13°C with a ΔH value of 226.11 J/g, while in FB, it is at a temperature

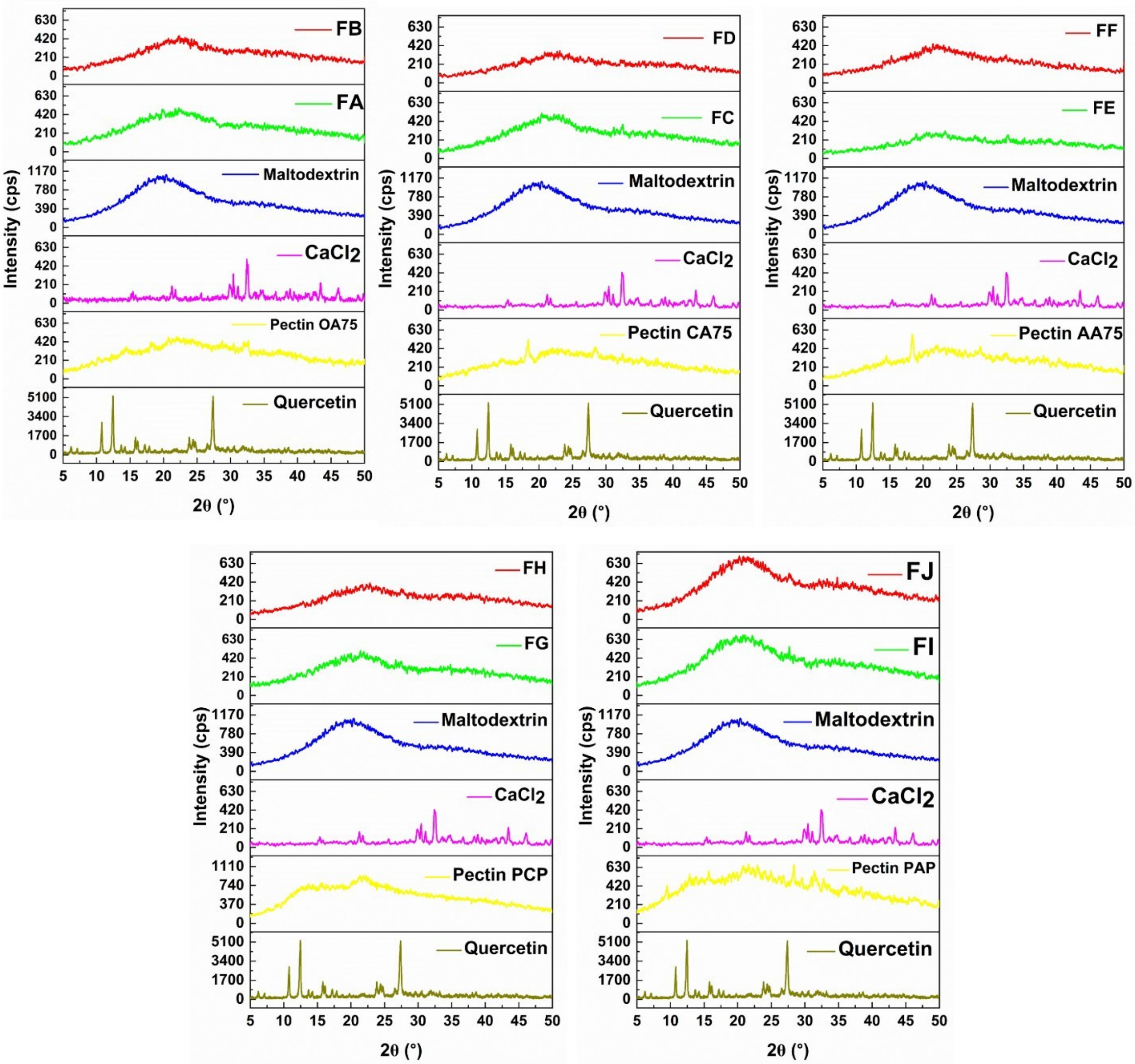


Figure 7. XRD Test Results of Dragon Fruit Skin Quercetin-Pectin Microspheres Compared with Commercial Quercetin-Pectin Microspheres

of 67.44°C with a ΔH value of 168.86 J/g. These values are not much different from the vaporisation value of pure OA75 pectin, which occurs at a peak temperature of 65.10°C with a ΔH value of 197.16 J/g.

The concentration of pectin affects the peak vaporization temperature and the resulting ΔH value, where a concentration of 1.5% produces a higher peak temperature and ΔH value than a concentration of 1% pectin in the formulation. These data show that the ability to bind water content in pectin will increase if the concentration of pectin used in the microsphere formulation is increased. The ΔH glass transition value produced from FA microspheres is at a peak temperature of 212.37°C, 99.01 J/g, and from FB microspheres at a peak temperature of 204.33°C, 116.92 J/g. These results indicate that increasing the concentration of OA75 pectin does not cause any effect on the change in the ΔH glass transition produced, where a concentration of 1% in FA and a concentration of 1.5% in FB do not affect the change in the ΔH glass transition value. In the decomposition parameters, FA decomposition data was obtained at 231.28°C and in FB at a temperature of 223.22°C. The decomposition temperature data explains that FA and FB microspheres will only experience physical and chemical changes after being heated at temperatures above 200°C. The value of ΔH glass transition is an important parameter to observe be-

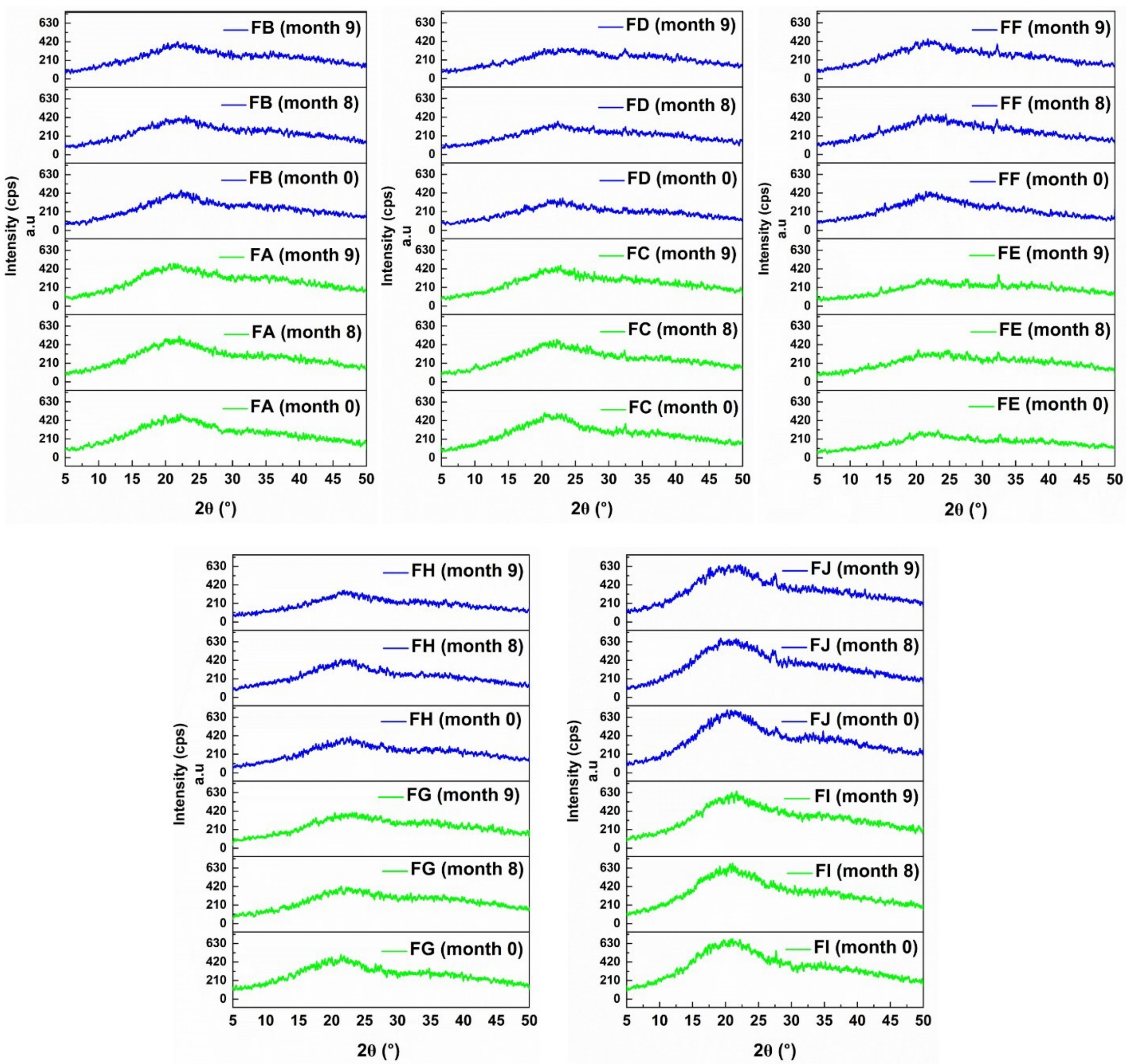


Figure 8. XRD of Red Dragon Fruit Skin Quercetin-Pectin Microspheres Compared with Commercial Quercetin-Pectin Microspheres at Month 0,8 and 9

cause it shows the energy required for changes in the material structure of quercetin-pectin microspheres. Suppose the value of ΔH glass transition remains constant for a particular time. In that case, the microsphere structure is stable and does not experience significant changes, especially against degradation events, recrystallization, or other chemical interactions. To observe the thermal stability, the microspheres were stored in a climatic chamber at a temperature of 40°C with an RH value of 75% and retested after being stored for 9 months (Rao, 2020)

In the FC and FD formulas using CA75 pectin, the FC vaporization temperature value was produced at a temperature of 65.69°C with a ΔH value of 154.47 J/g, while in FD at a temperature of 63.65°C with a ΔH value of 158.97 J/g. These values are not much different from the vaporization value of pure CA75 pectin, which occurs at a peak temperature of 67.82°C with a ΔH value of 231.67 J/g. In the vaporization data of the FC and FD formula groups using CA75 pectin, there were no significant changes in the temperature and vaporization values produced, and the resulting microspheres had a peak vaporization temperature value and a ΔH value that were smaller than the CA75 pectin used. These results indicate the effectiveness of the microsphere manufacturing process, especially during the drying process, using a freeze dryer to obtain microspheres with a low moisture content value. Meanwhile, from the parameter value ΔH in the glass transition phase, the value of FC microspheres at a peak temperature of 216.24°C

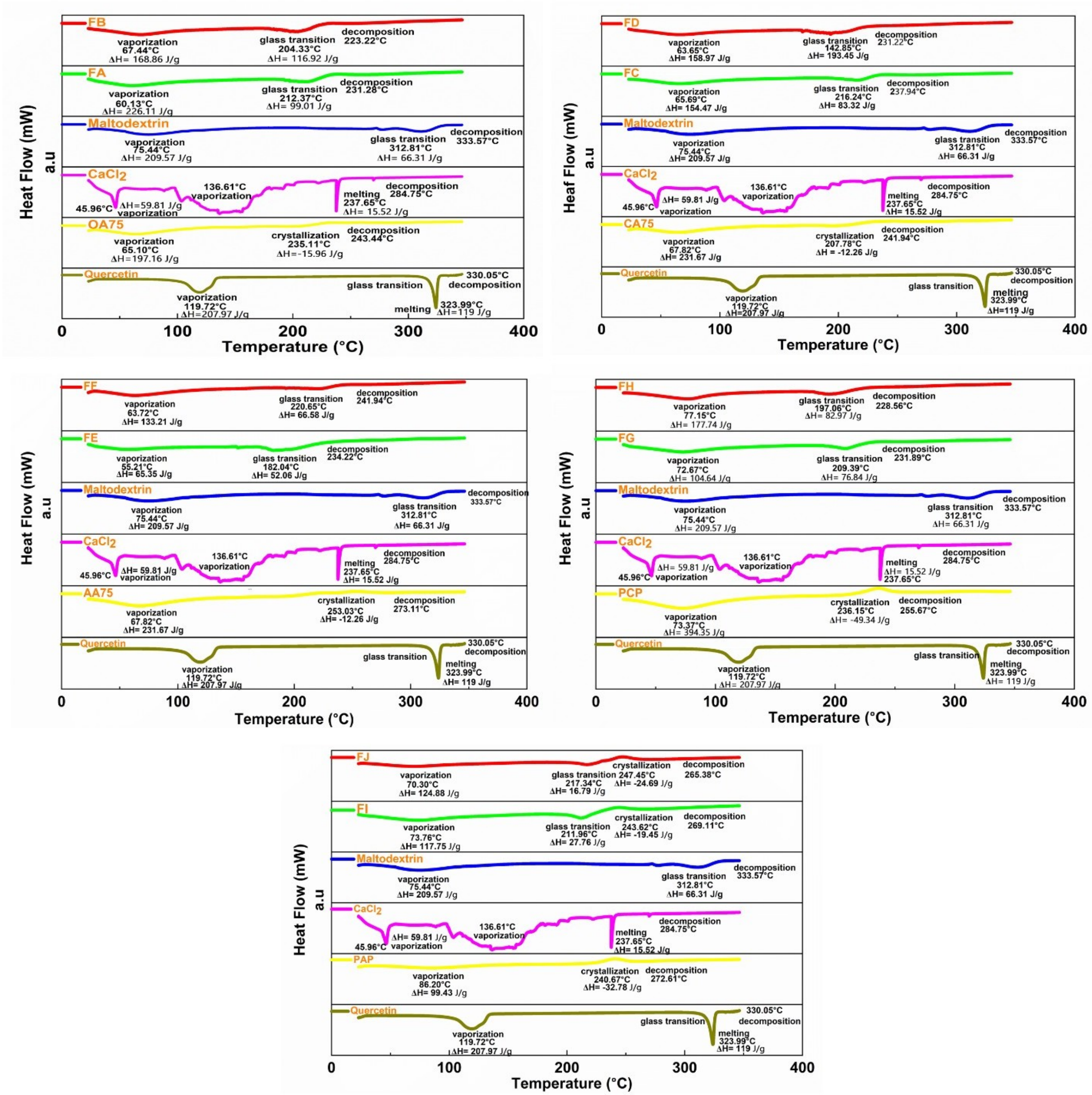


Figure 9. DSC of Red Dragon Fruit Skin Quercetin-Pectin Microspheres Compared with Commercial Quercetin-Pectin Microspheres

with a ΔH value of 83.32 J/g was obtained, while the value of FD microspheres at a peak temperature of 142.85°C with a ΔH value of 193.45 J/g. These results indicate thermal instability due to a decrease in peak temperature and a very high change in ΔH value with the increasing concentration of CA75 pectin. The decomposition process of the microspheres in FC occurs at 237.94°C, and the value is not very different from the peak temperature of FD decomposition at a temperature of 231.22°C. In the FE and FF formulas using AA75 pectin, the vaporization temperature value of FE was produced at a temperature of 55.21°C with a ΔH value of 65.35 J/g, while in FF at a temperature of 63.72°C with a ΔH value of 133.21 J/g, compared to the value in AA75 pectin of 67.82°C with a ΔH value of 231.67 J/g.

The vaporization pattern in FE and FF microspheres is similar to FC and FD microspheres. The ΔH glass transition value of FE at a peak temperature of 182.04°C is 52.06 J/g, and FF at a peak temperature of 220.65°C with a ΔH glass transition value of 66.58 J/g. There is an increase in the ΔH glass transition value with increasing concentration of AA75 pectin used in the quercetin-pectin microsphere formulation. The decomposition phase occurs at 234.22°C for FE and 220.65°C for FF. The decomposition event occurs at almost the same temperature in the six microspheres made from FA and FB using OA75 pectin, FC and FD using CA75 pectin, and FE and FF using AA75 pectin. Increasing the concentration of pectin used from 1% to 1.5% also does not affect changes in decomposition temperature. This data indicates that the thermal stability of the ingredients in the formula is relatively similar, and there is no significant interaction between ingredients that affect thermal stability. The component with the highest content in the formula determines the decomposition temperature. If all formulas use the same type and quality of pectin, the decomposition temperature will be similar. Quercetin may not significantly affect decomposition temperature if it only functions as an active ingredient in small amounts. The almost same decomposition temperature in various microsphere formulas indicates that the main ingredients' formula components, manufacturing process, and thermal stability tend to be uniform. This result is a positive indicator of the thermal stability of the formulation using red dragon fruit skin pectin with various types of acids used for its extraction process (Carrillo-Martinez et al., 2024).

The ΔH glass transition value needs to be tested through testing for a long enough duration with extreme conditions that can describe the degradation profile and thermal changes of the resulting microspheres. This study tested the stability of the ΔH glass transition value after 9 months of storage in a climatic chamber at 40°C with RH 75%. Glass transition indicates changes in the amorphous structure in microspheres. ΔH glass transition reflects the energy required to pass from the amorphous phase to a more plastic condition. If ΔH decreases from 0 to 9 months, the microspheres experience a decrease in energy in the amorphous matrix, which may indicate physical degradation such as crystallisation or loss of plasticity. These changes can affect the ability of the microspheres to retain quercetin and their release properties. If ΔH glass transition increases significantly after storage in the eighth month, this could indicate partial crystallisation or a change in the amorphous structure to become more regular. Crystallisation can affect the ability to release drugs because active ingredients in crystalline form are more difficult to dissolve than in amorphous form. Testing the ΔH glass transition indicates whether the formulation is still in a stable amorphous phase or has begun to show structural instability. Storage at a high temperature of 40°C and high humidity of 75% RH is an accelerated condition designed to accelerate the degradation of the microspheres. Testing at 0 and 9 months allows a direct evaluation of how well the microspheres maintain their thermal stability under stressful conditions. If the ΔH glass transition remains stable from 0 to 9 months, the microsphere formulation has good physical stability, even under extreme storage conditions. FG, FH, FI, and FJ microspheres made using commercial pectin showed the same pattern as red dragon fruit skin pectin. This data indicates that dragon fruit skin pectin has the same thermal stability as commercial pectin used for comparison. The comparative results of the DSC test at 0, 8, and 9 months are shown in Figure 10.

In FA microspheres, there was a decrease in the ΔH glass transition value from 99.01 J/g in month 0 to 90.13 J/g after being stored for 8 months in a climatic chamber at a temperature of 40°C with RH 75%. There was a decrease in the ΔH glass transition value of 8.97% in FA microspheres, so there is a potential for 8.97% of the FA microspheres to experience thermal degradation and have implications for the release of quercetin. In the FB microsphere formula using a higher concentration of OA75 red dragon fruit skin pectin by 0.5%, there was a decrease in the ΔH glass transition value from 116.92 J/g to 106.97 J/g or 8.51%. This result means a potential degradation of 8.51% of FB microspheres within a storage period of 8 months. In OA75 red dragon fruit skin pectin, when the concentration of the formulation was increased by 0.5% from 1% to 1.5%, it produced the same pattern, namely a decrease in the ΔH glass transition value after being stored for 8 months at a temperature of 40°C with RH 75%. FA and FB microsphere formulas using OA75 pectin have a degradation potential of less than 9%. These results show that OA75 red dragon fruit skin pectin can relatively well protect the structure and stability of quercetin-pectin microspheres. In FC microspheres using 1% CA75 red dragon fruit skin pectin after being stored for 8 months, there was a change in ΔH glass transition from 116.92 J/g to 106.97 J/g or a decrease of only 3.37%. These data indicate that FC microspheres only have the potential to degrade by 3.37% or are pretty small during storage at extreme temperatures and RH for 8 months. Different results occur when the concentration of CA75 pectin is increased from 1% to 1.5%, as seen in the FD formulation, where there is a decrease in the ΔH glass transition value from 142.85 J/g to 98.86 J/g or a reduction of 30.79%. The value decrease is significant because it is more than 30%. These results indicate that pectin extracted from red dragon fruit skin using citric acid, when formulated into microspheres with a concentration of 1.5%, results in significant degradation potential. In AA75 pectin, when formulated in FE and FF microspheres, it resulted in a massive increase in ΔH glass transition. There was a change in FE from 52.06 J/g to 103.79 J/g after being stored for 8 months, or a rise of 99.37%. In FF microspheres, there was also an increase from the original 66.58 J/g to 111.74 J/g, or 67.83%. The surge in ΔH of 99.37% in FE microspheres indicates that physical restructuring and stabilisation occurred

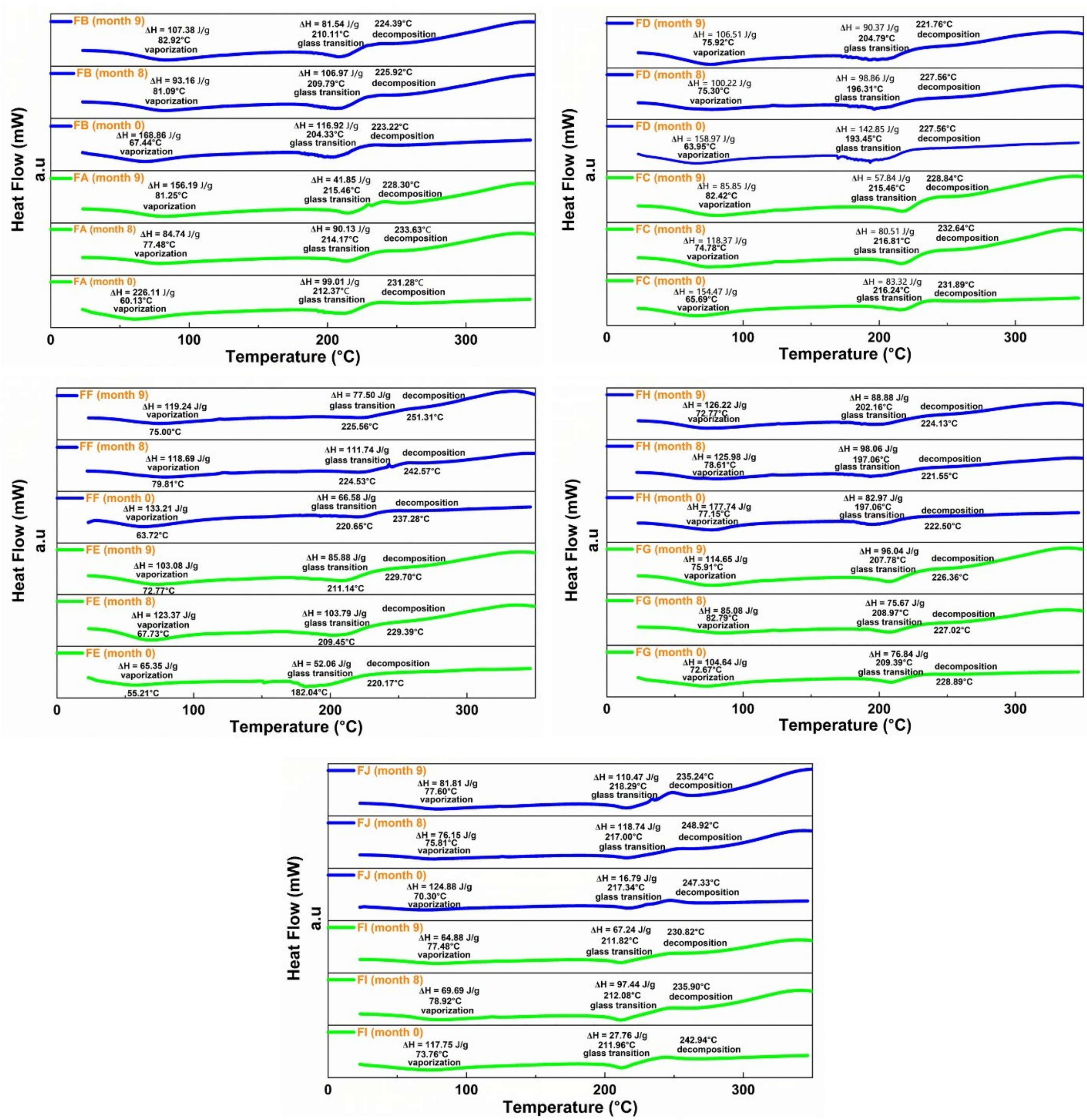


Figure 10. Comparison of DSC Of Red Dragon Fruit Skin Quercetin-Pectin Microspheres Compared with Commercial Quercetin-Pectin Microspheres at Month 0,8 and 9

more significantly in this formulation.

In FF microspheres, the increase in ΔH of 67.83% indicates a more moderate change. This result could be due to a more stable initial structure. The rise in ΔH in FE and FF microspheres indicates that microspheres made using pectin extracted using acetic acid are more thermally and kinetically stable during storage, which can extend shelf life. A more stable amorphous structure can slow down the release of quercetin from the microsphere matrix, which can affect its release profile and bioavailability. The release of quercetin will be much slower if the microspheres are made using AA75 pectin than OA75 and CA75 pectin. The lower EE DL values also confirm this result than the FA, FB, FC, and FD formulas, which are possible by the structure of the FE and FF microspheres, which bind quercetin very strongly, as well as the in vitro quercetin release test for 600 minutes, where the FE and FF formulas have a smaller release profile than FA, FB, FC, and FD. If the test and in vitro quercetin release test are extended again, the highest quercetin release will be produced in the FE and FF microspheres. In addition, it is also possible that the best protection against gastric acid will be achieved compared to FA, FB, FC, and FD microspheres.

3.9 In Vitro Release

The in vitro release results are shown in Figure 8. Based on the data, the lowest release value of FF microspheres was 65.59±7.27%, and the highest FA formula was 89.19±4.40%. The release test results in FA microspheres were 89.19±4.40% and were statistically significantly different ($p<0.05$) from the other formula. These results indicate that the type of organic acid solvent used in the extraction produces a different quality of pectin from other types of acid used, and the concentration of pectin used also affects the speed of quercetin release in the microsphere system. In this case, oxalic acid provides a better pectin profile than citric acid and acetic acid. The in vitro release test of quercetin-pectin microspheres is shown in Figure 11.

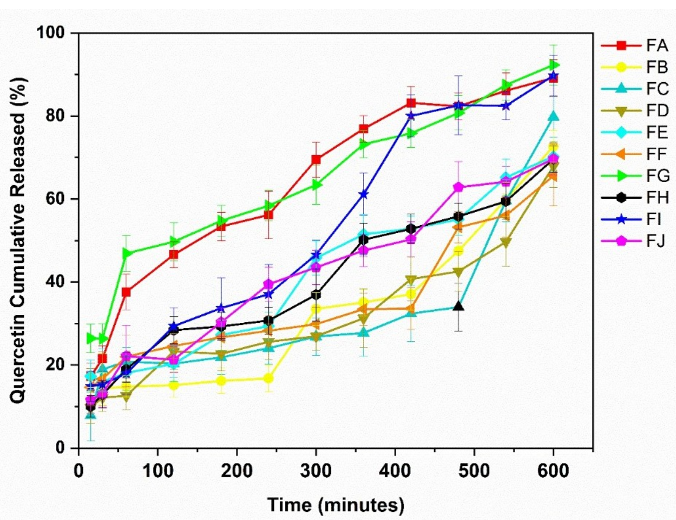


Figure 11. In Vitro Release Test of Quercetin-Pectin Microspheres

Previous studies have shown that the methoxyl content, galacturonic acid content, and degree of esterification of OA75 pectin have profiles that are not significantly different from commercial pectin (Kurniawan et al., 2024b). The value of the 10-hour release test on all microsphere formulas from FA to FF was obtained from the data. The percentage of microspheres made using pectin with a concentration of 1% produced a higher value than those made using pectin with a concentration of 1.5%. The results of the in vitro release test of microspheres showed that the concentration of pectin polymer 1.5% was slower in releasing the active substance quercetin, indicating that the difference in concentration affects the release power of quercetin. The concentration of pectin polymer used in the microsphere formulation can affect the in vitro release of encapsulated active substances. With increasing pectin concentration, the layer formed around the active substance becomes thicker, inhibiting the diffusion of active substances from the microencapsulation, thereby slowing down the in vitro release. Higher pectin concentrations usually produce denser matrices. A denser matrix can slow down the rate of release of active substances because the passage of molecules through the matrix becomes more difficult. Pectin can swell when exposed to liquids. If the concentration is higher, the swelling rate can increase, affecting the release of the active substance either by slowing it down or speeding it up, depending on the in vitro environmental conditions, such as pH and the presence of specific ions. Increasing the concentration of pectin can provide a more controlled and gradual release of the active substance, which is desired in some applications, such as prolonged drug release. In general, the effect of pectin concentration on in vitro release depends on many factors, including the physicochemical properties of the encapsulated active substance, the microencapsulation method used, and the environmental conditions during the in vitro release test. About the release test, pectin at a concentration of 1.5% has the potential to be developed into a sustained-release microsphere preparation that can release a certain amount of quercetin slowly over a specific time, but this needs to be confirmed by the duration of the quercetin release test in microspheres with a longer duration.

Based on the results of linear regression analysis of the logarithmic transformation of the FA to FJ microsphere release data, the Korsmeyer-Peppas model release kinetics were obtained. The n value in the $0.45 < n < 0.89$ range indicates that the release mechanism follows anomalous transport or non-Fickian diffusion, which means that the release of quercetin from the pectin microsphere matrix is controlled by the diffusion process and influenced by the polymer chain relaxation process, matrix development, or polymer erosion. Thus, the release of quercetin in the FA to FJ microsphere system occurs through a combined mechanism between diffusion from the matrix and changes in the physical structure of pectin during the release process. this result is in line with the nature of pectin as a hydrophilic polymer that can absorb water, expand, and undergo partial degradation in the release medium environment.

The dissolution test in phosphate buffer media, pH 7.4, aims to simulate physiological conditions in the small intestine, where the pH tends to be neutral to slightly alkaline. Under these conditions, pectin as a microsphere-forming matrix tends to dissolve or swell faster because its carboxylate groups undergo ionization. This ionization increases the hydrophilicity and water penetration into the matrix, thereby accelerating the release of quercetin through a combination of diffusion and matrix relaxation mechanisms. The resulting exponent value of >0.45 from the Korsmeyer-Peppas model confirms that the release occurs through anomalous transport, which is often observed in hydrophilic polymer systems at neutral pH. Therefore, the quercetin-pectin microsphere formulation can be used as a drug delivery system targeted to the intestine, with the ability to maintain the stability of active ingredients from degradation at a more acidic gastric pH.

3.10 Stability Study

Stability tests were conducted in a climatic chamber at 40±2°C, RH 75±5% for 90 days. The stability test results on EE and DL values are shown in Figures 11 and 12. There was a decrease in DL and EE values with increasing duration of stability tests in all formulas, but it was not statistically significant (p>0.05). Over time, encapsulated drugs may undergo chemical or physical degradation. Chemical degradation, such as hydrolysis, oxidation, or photodegradation, can cause a decrease in the amount of drug that is still active in the system and will reduce the drug loading value because some of the medicines that were encapsulated initially have been damaged or decomposed. During the storage process, encapsulated drugs can be slowly released from the polymer matrix, especially if the matrix experiences changes in properties, such as softening or cracking. This drug release will reduce the amount of drug remaining in the matrix, ultimately reducing encapsulation efficiency (Adepu et al., 2021). Figure 12 shows the change in EE values during the stability test.

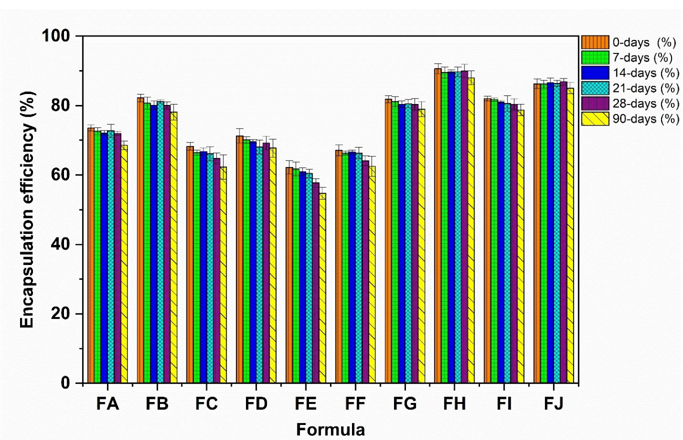


Figure 12. Stability Test Results on EE

Pectin polymers used for encapsulation may undergo physical or chemical changes during storage, such as reticulation, cross-linking, degradation, or swelling. These changes may affect the polymer's ability to retain the drug, causing drug release or damage to the encapsulation matrix (Said et al., 2023). In some systems, the drug may migrate from the interior of the polymer matrix to the surface over time. Once it reaches the surface, the drug may be more susceptible to degradation or released from the matrix, reducing drug loading and encapsulation efficiency. Storage conditions, such as temperature and humidity, can affect the stability of both the drug and the polymer matrix. High temperatures can accelerate chemical degradation and drug release, while moisture can cause the polymer matrix's hydration and affect the encapsulation's structure and integrity (Nalini et al., 2022).

Long-term interactions between drugs and polymers can cause undesirable changes in the encapsulation system. For example, the drug can interact with the polymer and cause degradation of the drug and the polymer or cause the formation of by-products that affect the system's stability. The encapsulated drug can sometimes crystallise or precipitate within the polymer matrix over time. This can reduce the encapsulation efficiency because the drug is no longer evenly dispersed in the polymer and can more easily be released from the system. Overall, the decrease in drug loading and encapsulation efficiency during stability testing results from drug degradation, changes in the polymer matrix, drug release, and environmental factors such as temperature and humidity. These processes decrease the amount of drug encapsulated correctly in the system, thereby reducing the product's overall efficacy (Moschona, 2018). Figure 13 shows the change in DL values during the stability test.

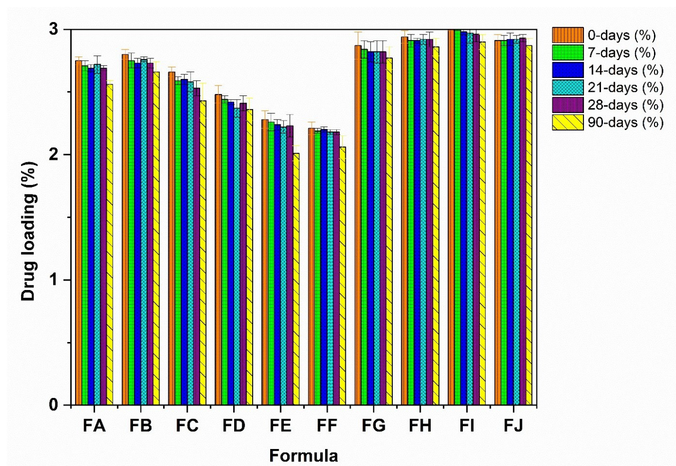


Figure 13. Stability Test Results on DL

Over time, the test material may absorb moisture from the surrounding air, especially if stored in an environment with high relative humidity. This is a common cause of increased moisture content, especially if the material is hygroscopic. The polymer or matrix used in the drug system may undergo physical or chemical changes during storage, such as softening or degradation, which may increase the material's ability to absorb and retain water. For example, cracks or pores formed in the polymer matrix may increase the surface area available for water absorption (Yu et al., 2019). Some excipients in formulations may degrade or change structure during storage, increasing the material's capacity to absorb moisture. These materials may become more susceptible to moisture absorption over time. Maltodextrin is a hygroscopic carbohydrate, meaning it can absorb and hold moisture from the air. When used as a cryoprotectant in formulations, maltodextrin can draw water from its environment, especially under high relative humidity conditions (Lourenço et al., 2020). During storage, especially in long-term stability tests, maltodextrin contained in the product can absorb moisture from the surrounding air and cause an increase in the moisture content in the product, as maltodextrin continues to draw water from its environment over time. Maltodextrin protects the active ingredient during the freeze-drying (lyophilisation) process. However, after drying, the maltodextrin remaining in the product can be a significant source of moisture absorption, contributing to increased moisture content.

Due to its hygroscopic nature, maltodextrin can bind water molecules, which causes an increase in moisture in the product and can affect the stability of the product, especially if the product is sensitive to humidity, causing a decrease in quality and biological activity or even accelerating the degradation of water-sensitive components. Maltodextrin can help maintain moisture at a certain level in the product to prevent damage during storage. However, if the humidity is too high, overhydration can occur, which causes an increase in moisture content beyond the desired limit. Overall, the use of maltodextrin as a cryoprotectant, although helpful in protecting active ingredients during the drying process, also has the consequence of increasing moisture content during storage due to its hygroscopic nature, so it must be considered in the formulation and storage conditions to ensure long-term product stability. If the active ingredient or other components are released from the polymer matrix or degrade, they may open up the material's structure, allowing more water to be absorbed. Fluctuations in storage conditions, such as temperature or relative humidity changes, can affect moisture content. An increased relative humidity in the storage environment can cause the material to absorb more water. Water can migrate from one component to another in systems consisting of multiple components over time and can increase moisture content in a particular component or the entire system. Overall, the increase in moisture content during stability testing results from interactions between the material and its environment, changes in the material structure, and the hygroscopic nature of the material that allows water to be absorbed from the air. This data is an essential indicator in assessing product stability because excessive moisture content can affect the quality, stability, and effectiveness of quercetin microspheres made using pectin polymers.

3.11 Digestion Resistance and Cytotoxicity Test on HeLa Cancer Cells and Vero Cells using MTT Assay

The IC_{50} test results showed that the FF formulation had the highest cytotoxic activity with an IC_{50} value of 48.22 μg/mL against HeLa cells and a Selectivity Index (SI) value of 75.01, indicating a highly selective antitumor potential. Formulas FJ and FB also showed high SI values of 72.50 and 52.36, respectively, although their IC_{50} values were greater than those of FF. Meanwhile, the FC and pure quercetin formulas showed high IC_{50} values and low SI, making them less effective and selective. The results of the cytotoxicity test are shown in Table 4.

The results of pure quercetin incubation in a simulated digestive tract medium showed that this compound was unstable when exposed to artificial gastric acid solution (pH 1.2) and artificial intestinal solution (pH 7.4). Incubation for 2 hours in each medium showed the possibility of degradation of the active compound, which is thought to occur through hydrolysis and oxidation mechanisms, especially in the gastric phase with extreme pH conditions. This result aligns with findings that report that quercetin is unstable in an acidic environment and is easily degraded, reducing its biological activity (Zhou et al., 2016). In the artificial intestinal phase, although the environmental pH is more neutral and relatively supports the stability of quercetin, there is still the potential for degradation due to oxidative reactions or interactions with environmental components such as bile salts and digestive enzymes. Quercetin can undergo structural transformation at neutral to alkaline pH, which has an impact on its bioactivity (Rao, 2020). This condition causes quercetin in its pure form to have difficulty maintaining its active structure during its journey through the digestive tract, so its pharmacological effectiveness, including cytotoxic activity against cancer cells, can decrease. Therefore, a delivery system is needed to protect quercetin from such damage.

In this study, quercetin-pectin microsphere formulation was developed to improve quercetin's stability and bioavailability. Pectin, as a natural polymer, can form a matrix that can withstand quercetin degradation in an acidic environment and allows controlled release in the intestine. Thus, using pectin-based microspheres has the potential to increase the effectiveness of quercetin in oral pharmaceutical applications.

Based on the GPC results, pectin from dragon fruit peel, especially AA75, has a high average molecular weight (Mw) and an extensive polydispersity index (PDI), indicating a complex and heterogeneous polymer structure. This contributes to forming a denser and tighter microparticle matrix, thus supporting a more controlled release of quercetin. The slow and sustained release allows quercetin to remain active longer in the cancer cell environment, ultimately enhancing the cytotoxic effect and selectivity against HeLa cells.

The exponent value n of the Korsmeyer–Peppas model was used to identify the drug release mechanism. The n value between 0.5 and 0.6, as in the FJ, FI, FC, and FH formulas, indicated an anomalous transport release mechanism: a combination of diffusion and polymer matrix relaxation. This mechanism supports a more stable and controlled release of quercetin. Although the FF formula has an n value of 0.4504, which is classified as Fickian diffusion, it still showed the highest activity and selectivity, which the dense matrix structure can explain due to the characteristics of AA75 pectin with high Mw.

Table 4. Cytotoxicity Test Results

Formula	IC_{50} HeLa Cell (μ/ml)	IC_{50} Vero Cell (μ/ml)	Selectivity Index (S1)
FA	304.47 ± 4.27	4372.17 ± 232.28	14.36
FB	106.6 ± 7.38	5581.85 ± 602.34	52.36
FC	1295.75 ± 11.02	9259.86 ± 537.62	7.15
FD	471.67 ± 6.17	6475.95 ± 519.66	13.73
FE	194.81 ± 38.75	7134.57 ± 705.71	36.62
FF	48.22 ± 3.9	3617.19 ± 61.32	75.01
FG	457.45 ± 20.92	9505.43 ± 595.89	20.78
FH	392.99 ± 13.47	8387.43 ± 556.22	21.34
FI	168.52 ± 16.04	8002.89 ± 335.57	47.49
FJ	67.03 ± 4.26	4859.86 ± 210.79	72.50
Quercetin	5400.72 ± 736.47	34152.65 ± 1646.5	6.32

Based on the research results, pure quercetin showed low cytotoxic effectiveness against cervical cancer cells (HeLa) compared to quercetin microparticle formulations combined with various pectin. The IC_{50} value of pure quercetin was 5400.72 μg/mL, and the Selectivity Index (SI) was 6.32, indicating non-selective anticancer activity and potential toxicity to normal cells (Vero). Some of the significant drawbacks of pure quercetin identified in this study include low solubility and bioavailability, non-selective distribution, and the absence of a controlled release system that results in quercetin not being able to reach an optimal effective concentration in the target cell environment. In addition, pure quercetin also lacks protection against enzymatic degradation or extreme pH environments, which could potentially reduce the stability and duration of the compound in the body.

These results emphasize the importance of developing a natural polymer-based delivery system, such as pectin, in enhancing the pharmacological efficacy of quercetin. Thus, encapsulation of quercetin into a pectin microparticle matrix has been shown to improve stability, control drug release, and strengthen selectivity toward cancer cells. Therefore, it can be concluded that the interaction between pectin characteristics, drug release mechanisms, and penetration ability to cancer cells greatly influences the effectiveness and selectivity of quercetin microparticle formulation. FF microsphere is the most promising candidate for developing effective and safe anticancer preparations.

4. CONCLUSIONS

Red dragon fruit skin (*Hylocereus polyrhizus*) contains high levels of pectin, which shows potential as a natural polymer for drug microencapsulation. This study compared red dragon fruit skin pectin extracted using oxalic, citric, and acetic acids with commercial apple and orange pectins in the formulation of quercetin microspheres via ionic gelation. Various evaluations included physical characterization, in vitro drug release, thermal stability, and cytotoxicity activity on HeLa cancer cells. Results indicated that FF microspheres had the highest encapsulation efficiency, controlled drug release through non-Fickian diffusion, excellent stability, and the most potent cytotoxic effect with high selectivity toward cancer cells. In conclusion, red dragon fruit skin pectin demonstrates strong potential as a natural polymer for drug microencapsulation systems.

5. ACKNOWLEDGMENT

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