Formulation development and characterization of quercetin loaded poly caprolactone nanoparticles for tumors

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Abstract

Cancer is a formidable health obstacle, characterized by its bleak outlook. Considerable scientific investigation has shed light on the capacity to modify the dispersion of anticancer medications at various levels within tissues and cells by enclosing them within submicronic colloidal systems, often known as nanoparticles. This approach is based on the goal of enhancing the therapeutic effectiveness of these medications while minimizing adverse effects on the entire body. Moreover, the theragnostic characteristics of these nanoparticles are widely acknowledged, hence enhancing their therapeutic potential. The current study is centered on exploring the potential anti-tumor effects of quercetin by utilizing its antioxidant capabilities. The quercetin nanoparticles are synthesized with great precision utilizing the nanoprecipitation approach, in which poly(caprolactone) is utilized as the polymer matrix. Following synthesis, the nanoparticles are extracted for further analysis. Further attempts are undertaken to enhance the drug loading process, and the resultant nanoparticles undergo a thorough analysis, including the examination of their morphology using scanning electron microscopy, and the evaluation of drug-polymer interactions using Fourier transform infrared spectroscopy and differential scanning calorimetry. The remarkable efficacy of quercetin's envelopment can be attributed to its lipophilic nature, reaching a maximum of 81%. The utilization of scanning electron microscopy allows for the observation of nanoparticles with varying forms. Conversely, the absence of noticeable interactions in Fourier-transform infrared analysis indicates the stability of poly(caprolactone) nanoparticles loaded with quercetin.

Keywords: nanoparticles, scanning electron microscopy, caprolactone, drug polymer, synthesis, quercetin.

Desenvolvimento de formulações e caracterização de nanopartículas de policaprolactona carregadas de quercetina para tumores

Resumo

O câncer é um formidável obstáculo à saúde, caracterizado pela sua perspectiva sombria. Uma investigação científica considerável lançou luz sobre a capacidade de modificar a dispersão de medicamentos anticancerígenos em vários níveis dentro dos tecidos e células, encerrando-os em sistemas coloidais submicrônicos, frequentemente conhecidos como nanopartículas. Esta abordagem baseia-se no objetivo de aumentar a eficácia terapêutica destes medicamentos e, ao mesmo tempo, minimizar os efeitos adversos em todo o corpo. Além disso, as características teragnósticas destas nanopartículas são amplamente reconhecidas, aumentando assim o seu potencial terapêutico. O presente estudo está centrado na exploração dos potenciais

efeitos antitumorais da quercetina, utilizando suas capacidades antioxidantes. As nanopartículas de quercetina são sintetizadas com grande precisão utilizando a abordagem de nanoprecipitação, na qual a poli(caprolactona) é utilizada como matriz polimérica. Após a síntese, as nanopartículas são extraídas para análise posterior. Outras tentativas são realizadas para melhorar o processo de carregamento do medicamento, e as nanopartículas resultantes passam por uma análise minuciosa, incluindo o exame de sua morfologia usando microscopia eletrônica de varredura e a avaliação das interações droga-polímero usando espectroscopia no infravermelho com transformada de Fourier e calorimetria diferencial de varredura. A notável eficácia do envolvimento da quercetina pode ser atribuída à sua natureza lipofílica, atingindo um máximo de 81%. A utilização da microscopia eletrônica de varredura permite a observação de nanopartículas com formas variadas. Por outro lado, a ausência de interações perceptíveis na análise infravermelha por transformada de Fourier indica a estabilidade das nanopartículas de poli(caprolactona) carregadas com quercetina.

Palavras-chave: nanopartículas, microscopia eletrônica de varredura, caprolactona, polímero droga, síntese, quercetina.

1. Introduction

Cancer represents a category of ailments marked by unbridled cellular proliferation, as cells override growth regulatory mechanisms, manifesting malignancy. This intricate genetic disorder primarily stems from environmental carcinogens inherent in the atmosphere, diet, hydrosphere, and solar radiation. Globally, cancer contributes to one-eighth of all mortalities, underscoring its pervasive impact on human health (Gibellini et al., 2011).

Cancer constitutes a heterogeneous group of over 100 distinct diseases, each characterized by unique risk factors and epidemiological patterns. It originates from various cell types and organs within the human body, marked by unbridled cellular proliferation that exhibits invasive properties, enabling metastasis to distant organs. Notably, cancer is not restricted to humans and animals, as other organisms are also susceptible. These malignant cells possess the capacity to dissociate from the primary tumor mass, enter the circulatory and lymphatic systems, and establish secondary growths in distant anatomical sites, a phenomenon denoted as metastatic dissemination or metastatic disease.

Nanoparticles, employed as drug delivery vehicles, encompass sub-micron entities measuring between 3 to 200 nanometers. They can be fabricated from a diverse array of materials, including polymers (polymeric nanoparticles, micelles, or dendrimers), lipids (liposomes), viral components (viral nanoparticles), and organometallic compounds or carbon nanotubes. Quercetin (Q), a flavonoid belonging to the flavonol class, is the aglycone configuration of several flavonoid glycosides, such as rutin and quercitrin, which are commonly present in citrus fruits, buckwheat, and onions. Quercetin gives rise to glycosides, namely quercitrin, and rutin, through associations with rhamnose and rutinose, respectively (Stratton et al., 2009).

Quercetin, classified under IARC group 3 denoting no substantiated evidence of carcinogenicity in humans, exhibits potent antioxidant properties and is postulated to possess natural anti-cancer and anti-inflammatory attributes. It has been advocated for its potential efficacy against a wide spectrum of diseases. The primary objective of the current investigation is to develop an innovative nanoparticle formulation for cancer treatment.

This endeavor entails the formulation of nanoparticles employing polycaprolactone (PCL) as the polymer to achieve sustained release characteristics and involves the optimization and subsequent characterization of Quercetin (Q) loaded nanoparticles (Sumer; Gao, 2008). The overarching aim of this research is to devise Q-loaded polycaprolactone nanoparticles, to enhance their therapeutic efficacy for anti-cancer activity.

2. Materials and Methods

2.1 Analytical reagents

Quercetin dihydrate and poly caprolactone samples were sourced from Sigma Aldrich, while Polyvinyl alcohol, Gelatin, Acetone, Tween 80, and Span 80 were obtained from Himedia. Dichloromethane and Poloxamer-188, along with ethanol, were procured from Hayman.

2.2 Preparation of PCL nanoparticles

In this procedure, nanoparticles were fabricated using the solvent evaporation method. Initially, a measured

amount of poloxamer-188 was introduced into double-distilled water under magnetic stirring. The solution was then held at a temperature range of 50-60 °C, while PCL was dissolved in acetone with gentle sonication (Chen et al., 2013). Subsequently, the organic solution was introduced into the aqueous solution in a gradual manner using a micro pipette to facilitate the dispersion of the organic solution. Upon the addition of PCL to the aqueous solution, a discernible bluish tinge emerged, signifying the initiation of nanoparticle formation. This mixture was subjected to continuous stirring for approximately 2 h, maintaining the same temperature. The resulting nanoparticles were then separated through low-pressure centrifugation exceeding 10,000 rpm. The collected sediment was subsequently subjected to lyophilization, yielding the final nanoparticle product.

2.3 Top of form

Preparation of quercetin loaded PCL Nanoparticles: The production of Quercetin-loaded PCL nanoparticles, as detailed in (Table 1), mirrors the procedure for empty nanoparticles, with the incorporation of the drug into the organic solution containing PCL. Subsequently, the resulting Quercetin nanoparticles were isolated via low-pressure centrifugation at 10,000 rpm (Rather; Bhagat, 2020). Various formulations of Quercetin-loaded PCL nanoparticles were prepared.

2.4 Evaluation of quercetin loaded PCL nano-particles

2.4.1 Particle size

The confirmation of nanoparticle formation involved the collection of the nanosuspension generated post-addition of the organic phase to the aqueous phase and subsequent stirring. The nanoparticle samples, following lyophilization, were subjected to particle size analysis, utilizing Malvern Zeta Sizer to ascertain their size characteristics (Guan et al., 2016).

2.4.2 Polydispersity index

Polydispersity index is done for both nanosuspension both before and after lyophilization (Cabral; Baptista, 2014). Polydispersity (nonuniform size distribution) was calculated by using the following formula:

$$\text{Polydispersity} = (D\ 0.9 - D\ 0.1)/D\ 0.5$$

Where: D 0.9, D 0.5, and D 0.1 represent particle diameters determined at the 90th, 50th, and 10th percentiles of undersized particles, respectively. A high polydispersity index value serves as an indicator of non-uniformity, enabling the characterization of nanoparticles as either monodisperse, homogeneous, or heterogeneous systems (Jiang et al., 2019).

2.5 Drug loading and encapsulation efficiency

For drug loading and encapsulation efficiency assessment, precisely 1 mg of nanoparticles was weighed and placed in 2 mL *Eppendorf* tubes. Subsequently, these samples were subjected to vortex mixing with 200 µL of dichloromethane for 5 min. To precipitate the PCL component, which is insoluble, 1800 µL of ethanol was introduced, and the mixture was vortexed for an additional 10 min. The UV-*Vis* spectrophotometer was then employed to measure the absorbances of the samples at 370 nm, enabling the quantification of quercetin content within the nanoparticles (Zhang et al., 2022). These values are then used for calculating the % drug loading (DL) and entrapment efficiency (EE) using the formulae.

$$\%\ \text{Drug loading} = (\text{Weight of Quercetin in Nanoparticles})/(\text{Weight of nanoparticles}) \times 100$$

$$\%\ \text{Entrapment Efficiency} = (\%\ \text{Drug loading})/(\%\ \text{Theoratical loading}) \times 100$$

2.5.1 *In-vitro* release studies

In this, an accurately weighed quantity of nanoparticles is taken into a pretreated dialysis membrane. A small quantity of buffer is added into the dialysis bag along with nanoparticles and suspended in PBS at 37 ± 1 ºC.

Subsequently, aliquots of the samples were periodically withdrawn, with an equivalent volume of PBS added to preserve sink conditions. The absorbances of the collected aliquots were measured at 370 nm using a UV-*Vis* spectrophotometer to monitor the release profile (Ezzati et al., 2020).

2.5.2 Scanning electron microscopy

Scanning electron microscopy (SEM) serves as a valuable tool for the physical examination of nanoparticle morphological attributes. This method is particularly useful for assessing microsphere shape and surface characteristics, facilitating correlations with other determined properties, including surface area and bulk density. To conduct SEM analysis, nanoparticles were gently deposited onto one surface of an adhesive stub. Subsequently, a conductive gold coating was applied to the stub, enabling qualitative scrutiny of nanoparticle morphology through SEM examination (Kashif et al., 2023).

2.6 Drug

2.6.1 Excipient interaction and Polymorphism studies

2.6.1.1 Fourier transform infrared spectral (FT-IR) analysis

FT-IR spectra provide comprehensive information regarding the positions and intensities of absorptions within the IR spectrum, aiding in the evaluation of potential chemical interactions between the drug and various excipients in the formulation. Analysis was carried out using the pressed pellet technique with KBr, encompassing the examination of drug, polymer, empty nanoparticles, and drug-loaded nanoparticles, with their respective spectra recorded for comparative analysis (Zaman et al., 2024).

3. Results and Discussion

3.1 Refinement of the preparation methodology for quercetin (Q) loaded poly caprolactone (PCL) nanoparticles

Formulation N1 was created utilizing the emulsion method, where an emulsion was generated and stabilized through surfactants. The procedure involved the combination of an organic solution composed of polycaprolactone, span-80, and quercetin with an aqueous solution containing Tween-80 as a stabilizing agent. In contrast, formulation N2 was prepared using the nanoprecipitation method, incorporating distinct stabilizers.

This approach entailed the introduction of an organic solution containing polycaprolactone and quercetin into an aqueous phase, facilitated by the presence of various stabilizing agents. The formed nanoparticles in both formulations are then centrifuged at 10,000 rpm at 40 ºC and then lyophilized. In this, the nanoparticles in the N1 formulation failed to recover because of the surfactants which formed a slurry but in the N2 formulation, the nanoparticles are recovered. So, the nanoprecipitation method is best suited for the formation of quercetin nanoparticles using PCL as a polymer. Therefore, further optimization of stabilizers in the nanoprecipitation method was done.

3.2 Optimization of stabilizers in nano precipitation method

3.2.1 Characterization of nanosuspensions

In this different stabilizer gelatin, polyvinyl alcohol, and poloxamer-188 of similar concentration are used in the nanoprecipitation method. The formed nanosuspensions were then stirred for 2 h and then analyzed for particle size and zeta potential. The particle size analysis of the nanoparticle suspension using gelatin, polyvinyl alcohol, and poloxamer-188 i.e., n3, n4, n5 respectively. The zeta potentials of the formulations are also measured. From reports the particle sizes and zeta potentials of gelatin, PVA stabilizers are better compared to that of poloxamer-188. For these suspensions, the polydispersity indexes are also measured to determine the uniformity of nanoparticles. The dispersity index of poloxamer-188 was found to be lesser than the other two indicating higher uniformity of particles (Table 1).

Table 1. Evaluation of nanoparticle formulations.

Formulation Code	Polydispersity index	% drug loading

n1	0.64	---
n2	0.15	---
n3	0.69	---
N4	1	68%
N5	1	75.6%
N6	1	84%
N7	1	80.3%

Source: Authors, 2023.

3.2.2 Optimization of centrifugation rpm for recovery of product

The nanosuspensions are then centrifuged at 10,000 rpm and 18,000 rpm for N4 and N5 formulations respectively. The formulations are then evaluated for particle size and zeta potentials. It has shown that 18,000 rpm for centrifugation produced nanoparticles of much uniform size because of the higher rpm that collects the smaller-sized nanoparticles. This also further enhanced the (%) yield of nanoparticles. This polydispersity index in indicates the homogeneous distribution of nanoparticles in the suspensions when measured for particle size.

The formed nanoparticles are then centrifuged and lyophilized at 540 ºC and 1 pas pressure for 3 days for the removal of aqueous solution. The dried nanoparticles are recovered and observed. The nanoparticles formed by using PVA, gelatin stabilizers have formed film-like structures failing to recover the nanoparticles. The nanoparticles of poloxamer-188 are powdery and are recovered properly. Therefore, the choice of the stabilizer, Poloxamer-188, was made for the formulation of quercetin nanoparticles utilizing the nanoprecipitation technique. The formed nanoparticles also easily got redispersed in water.

3.2.3 Optimization of drug loading

In N5 formulation initially 2.5 mg of quercetin was loaded into PCL nanoparticles (1:20). Then the nanoparticles were then evaluated for entrapment efficiency. The formulations N6, and N7 are then loaded with a higher % of Quercetin. The formulation N6 was loaded with 5mg (2:50) of quercetin into the PCL nanoparticles and evaluated. The formulation N7 was also loaded with a higher amount of quercetin (3:50) and then evaluated. The entrapment efficiency of the N6 formulation was found to be 84% and so it is then used for further studies. The N6 formulation was then evaluated for drug excipient interaction and polymorphism characterization.

3.2.4 *In vitro* release studies

Formulation F6 was chosen for in vitro release studies based on its particle size and entrapment efficiency. Quercetin release profiles were assessed in a pH 7.4 phosphate buffer saline (PBS) solution at 37 °C the drug release profiles in the formulation (N6) initially showed burst release for 24 h and then a constant release was observed. The initial burst release of quercetin, may be attributed to the heterogeneous distribution of quercetin within the nanoparticles. Quercetin entities that exhibit loose surface association or are embedded within the surface layer contribute to the observed burst release, as detailed in (Table 2).

Table 2. *In-vitro* drug release of quercetin from nanoparticles.

Time (h)	**Abs**	**Conc. (µg mL^{-1})**	**Vol of SF (ml)**	**Conc. of SF (µg)**	**Conc. in TV (µg)**	**Cumulative Concentration (µg)**	**Quercetin release (%)**
0	0	0	2	0	0	0	0
0.25	0	0	2	0	0	0	0

0.5	0	0	2	0	0	0	0
1	0.0061	0.123232	2	0.246465	4.929292929	4.929293	1.040264415
1.5	0.0016	0.032323	2	0.064646	1.292929293	1.539394	0.324869461
2	0.0036	0.072727	2	0.145455	2.909090909	3.220202	0.679582573
4	0.0132	0.266667	2	0.533333	10.66666667	11.12323	2.347416339
7	0.0105	0.212121	2	0.424242	8.484848485	9.474747	1.999524633
10	0.0158	0.319192	2	0.638384	12.76767677	14.18182	2.992891882
19	0.0276	0.557576	2	1.115152	22.3030303	24.35556	5.13992942
24	0.0374	0.755556	2	1.511111	30.22222222	33.3899	7.046512396
30	0.0818	1.652525	4	6.610101	66.1010101	70.7798	14.93717378
42	0.1372	2.771717	4	11.08687	110.8686869	122.1576	25.77979862
54	0.1638	3.309091	4	13.23636	132.3636364	154.7394	32.65577587
66	0.1676	3.385859	4	13.54343	135.4343434	171.0465	36.09717519
90	0.2263	4.571717	4	18.28687	182.8686869	232.0242	48.96575761
114	0.2022	4.084848	4	16.33939	163.3939394	230.8364	48.71507094
174	0.1874	3.785859	4	15.14343	151.4343434	235.2162	49.63937145
234	0.1774	3.583838	4	14.33535	143.3535354	242.2788	51.12984866
294	0.1662	3.357576	4	13.4303	134.3030303	247.5636	52.24514854

Source: Authors, 2023.

3.3 Surface morphology

Nanoparticles prepared with Poloxamer-188 as the stabilizer were subjected to centrifugation at 18,000 rpm and subsequent lyophilization (Figure 1). Analysis of these nanoparticles via SEM revealed a morphological diversity, with the presence of spherical and rod-shaped structures, indicating a heterogeneous surface morphology.

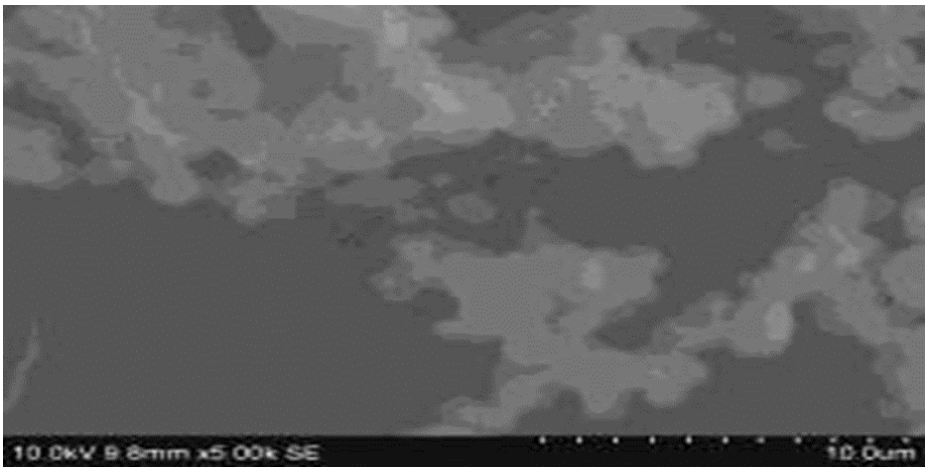

Figure 1. Morphology of surface of empty PCL nanoparticles. Source: Authors, 2023.

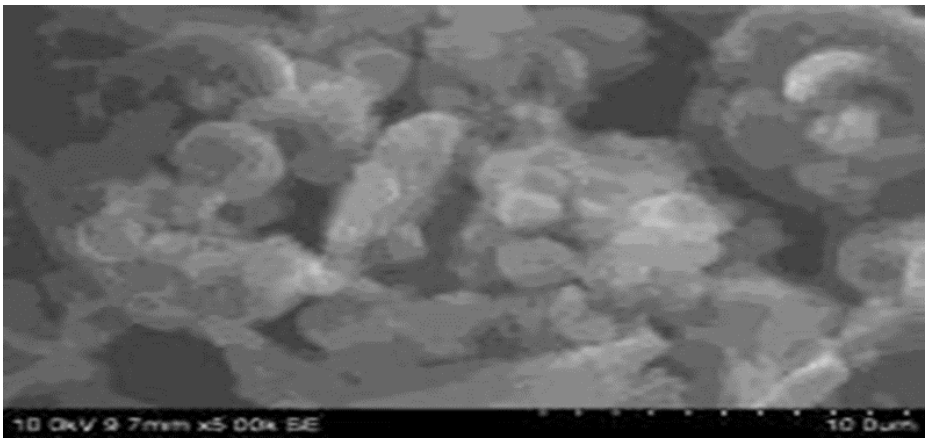

Figure 2. Morphology of surface of Q loaded PCL nanoparticle. Source: Authors, 2023.

3.4 Characterization of drug excipient interaction and polymorphism

3.4.1 FT-IR spectra

The optimized formulation, N6, was subjected to characterization through FT-IR spectra to affirm the chemical stability of quercetin within the nanoparticles. The FT-IR spectra of quercetin, PCL, empty PCL nanoparticles, and quercetin-loaded PCL nanoparticles were presented in Figures 3, 4, 5, 6 and 7 , respectively. Quercetin exhibited distinctive features in the form of aromatic bending and stretching signals around 1100 and 1600 cm^{-1}, with phenolic -OH bending evident around 1200 and 1400 cm^{-1}. PCL FT-IR spectra revealed notable peaks at 1730 and 3440 cm^{-1}, corresponding to -CO (stretching) and -OH (bending) groups, alongside C-H bond-related peaks at 2868 and 2947 cm^{-1}.

The FT-IR analysis of empty PCL nanoparticles showcased characteristic peaks akin to plain PCL. In the FT-IR spectrum of quercetin-loaded PCL nanoparticles, additional peaks attributed to quercetin within the blend matrix were observed. Some quercetin bands exhibited low prominence in the drug-loaded nanoparticles, as they closely mirrored those of placebo nanoparticles and occurred at nearly identical wavenumbers. This spectral analysis confirmed the stability of quercetin in the PCL blend and also validated the polymer's stability under the processing conditions applied in this study.

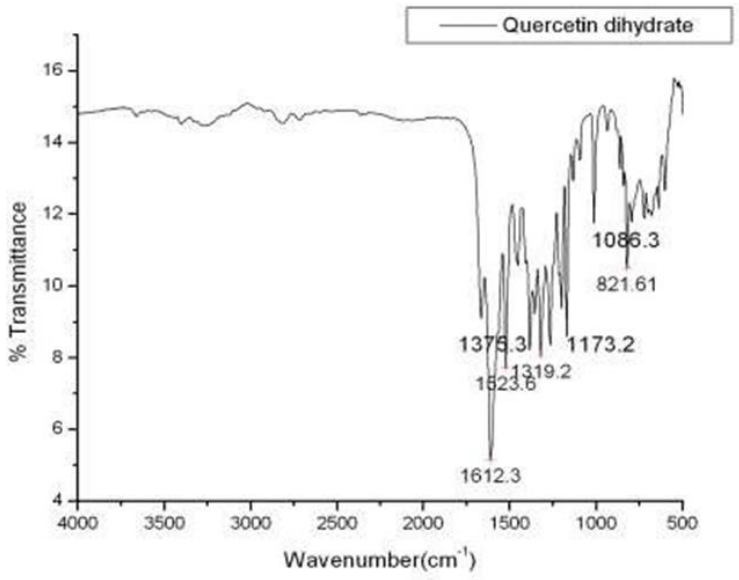

Figure 3. FT-IR spectra of quercetin dihydrate. Source: Authors, 2023.

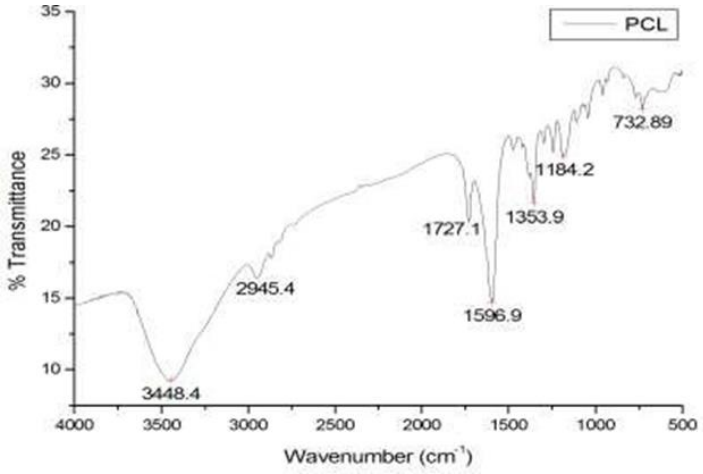

Figure 4. FT-IR spectra of poly caprolactone. Source: Authors, 2023.

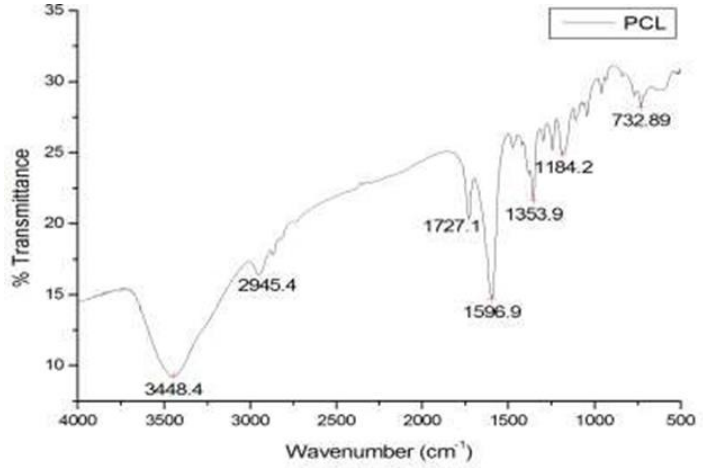

Figure 5. FT-IR spectra of poly caprolactone. Source: Authors, 2023.

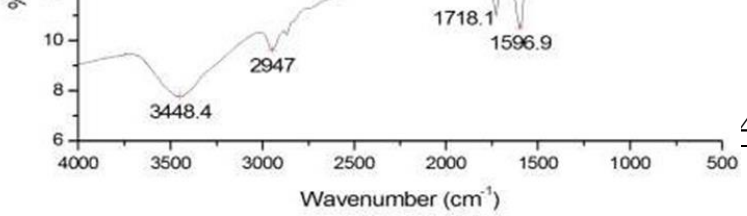

Figure 6. FT-IR spectra of empty polycaprolactone nanoparticles. Source: Authors, 2023.

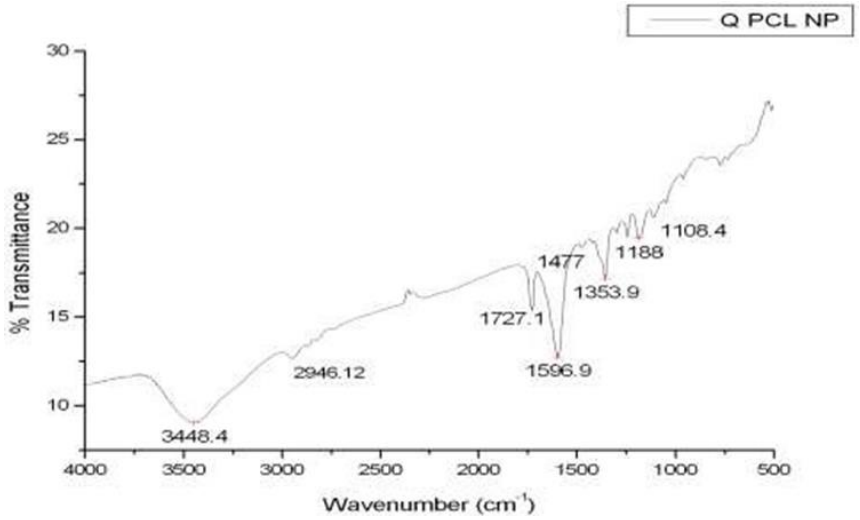

Figure 7. FT-IR spectra of Q loaded polycaprolactone nanoparticles. Source: Authors, 2023.

4. Conclusions

In this study we have prepared the Quercetin nanoparticles for sustained release to show anti-tumor effect are designed and optimized. The nanoparticles prepared by the nanoprecipitation method showed product recovery. The stabilizers gelatin, PVA, and poloxamer-188 used during the formulation are then optimized. The nanoparticles formed using poloxamer- 188 as stabilizer are found well lyophilized. These nanoparticles were then evaluated for drug loading efficiency and a higher drug loading formulation (N6) was found. This optimized formulation is then characterized and reported.

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6. Authors' Contributions

Muhammad Kashif: Conceived and designed the study, supervised the research, and contributed to data analysis and interpretation. *Murad Ali*: Performed experiments related to the synthesis and characterization of polymeric nanoparticles, including the encapsulation of quercetin. *Bushra*: Contributed to the experimental work, particularly in the formulation and optimization of polymeric nanoparticles. *Saira Naz*: Participated in the synthesis and characterization of nanoparticles, including the assessment of their drug release profiles. *Jalal Amir*: Provided valuable insights into the theoretical aspects of drug delivery systems and helped in the literature review. *Shafaq Murad*: Contributed to data analysis and manuscript preparation. *Muhammad Atif*: Contributed to the discussion section and helped in concluding. *Osama Ali Khattak*: Provided valuable input in the interpretation of results. *Saif Ullah*: Participated in data analysis and helped in drafting the methodology section. *Seeqal Aleena*: Assisted in manuscript writing and revisions. *Naqash Khan*: Contributed to the in vitro experiments, including cell culture and cytotoxicity assessments. *Muhammad Younis Khan*: Provided oversight, guidance, and critical input at all stages of the research. Played a key role in manuscript preparation and revision.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Not applicable.

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