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Research Article…

Research On: Formulation and Evaluation Wound Healing Nanogel Drug: Quercetin.

Dr. Kiran D. Baviskar[1], Miss. Vaishanvi Sukhdev Wagh[2], Dr. Bharat Jain[3], Dr. Sandip Pawar[4], Dr. Tanvir Shaikh[5]

Department of Pharmaceutics, Smt. Sharadchandrika Suresh Patil College of Pharmacy Chopda

Abstrct:

Topical administration of medications at diseased areas may have the advantage of delivering the drug directly to the site of action. The primary purpose of this work was to Formulation and Evaluation Wound Healing Nanogel of Quercetin. Quercetin is the shows enhanced antioxidant, anti-inflammatory, cardioprotective, antiviral and antibacterial activity and stability.

Wound healing is an important physiological process to maintain the integrity of skin after trauma, either by accident or by intent procedure. The normal wound healing involves three successive but overlapping phases, including hemostasis/inflammatory phase, proliferative phase, and remodeling phase. Wound healing remains a challenging clinical problem and correct, efficient wound management is essential. Much effort has been focused on wound care with an emphasis on new therapeutic approaches and the development of technologies for acute and chronic wound management. Wound healing involves multiple cell populations, the extracellular matrix and the action of soluble mediators such as growth factors and cytokines. Wound is defined as the disruption of cellular and anatomic continuity of a tissue. According to the Wound Healing Society (WHS), wounds are physical injuries that result in an opening or break of skin that causes disturbance in the normal skin anatomy and function.

Key Words: Novel Drug Delivery System, Transdermal drug delivery systems, Wound Healing, Nanogel, Quercetin.

Introduction:

Novel drug delivery system or targeted drug delivery system is a method of delivering medication to a patient in a manner that increases the concentration of the medication in desired parts and reducing the relative concentration of the medication in the remaining tissues. The novel ideas on controlling the pharmacokinetics, pharmacodynamics, nonspecific toxicity, immunogenicity, bio-recognition and efficacy of drugs were provoked) These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bio-conjugate chemistry and molecular biology. The drug's therapeutic index, as measured by its pharmacological response and safety, relies in the access and specific introduction of the drug with its candidate receptor, whilst minimizing its introduction with non –target tissue. The desired differential distribution of drug its targeted delivery would spare the rest of the body and thus significantly reduce the overall toxicity while maintaining its therapeutic benefits.

Novel Drug Delivery Carriers:

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter developed by optimizing drug/polymer concentration and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may

even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties.

- **Types of Novel Drug Delivery Systems:**

The most common types of novel drug delivery carriers are as follows;

- Liposomes
- Nanoparticles
- Microspheres
- Nanogels
- Dendrimers
- Niosomes
- Micelles
- Carbon Nanotubes

Nanogel :

The term "Nanogel" (Nano-Gel) was first introduced to define cross- linked dual- functional networks of a poly-ions and a non-ionic polymer for delivery of polynucleotide. Nanogels composed of nanosize particles formed by physically or chemically cross linked polymer networks that swells in a good solvent. The nanogel systems have proven their potential to deliver drugs in controlled, constant and targetable mode. With the promising field of polymer sciences it has now become predestinated to prepare smart nano-system which can establish effectual for treatment, diagnosing as well as clinical trials progress. Nanogel basically falls in two major categories i.e., Responsive type (Nonresponsive nanogels and Stimuli responsive nanogel) and Linkage type. The linkage type nanogel further sub classified into following subtypes i.e., physical cross-linked, liposomes modified, micellar type, hybrid type and chemically cross-linked nanogel.

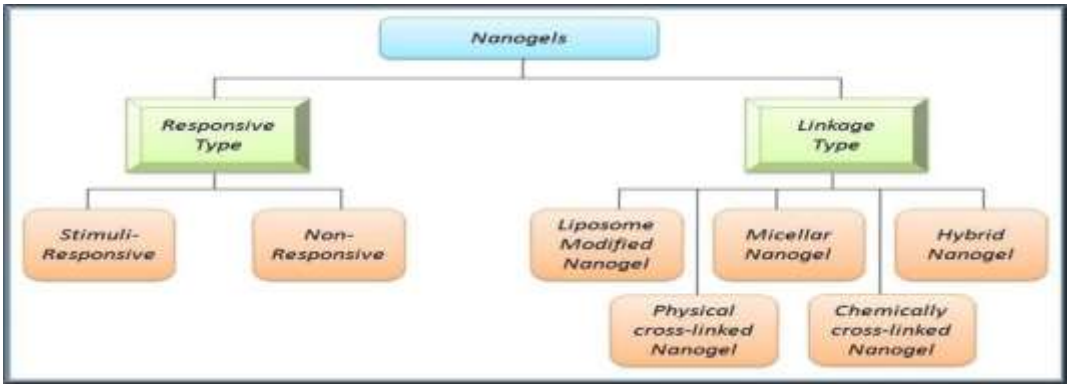


Figure 2: Demonstration of nanogel carrier system.

- **Transdermal drug delivery systems (TDDS)**

are topically applied "patches" intended to convey a therapeutically active drug across skin at controlled rate for systemic effect. The major obstacle for transdermal drug delivery is the low diffusion rate of drugs across the relatively impermeable, outermost skin layer, the stratum corneum. Besides, the intercellular lipid region, the major pathway for lipophilic drugs, has a diffusion path length of about 500mm which is much longer than the thickness of stratum corneum (20 mm).

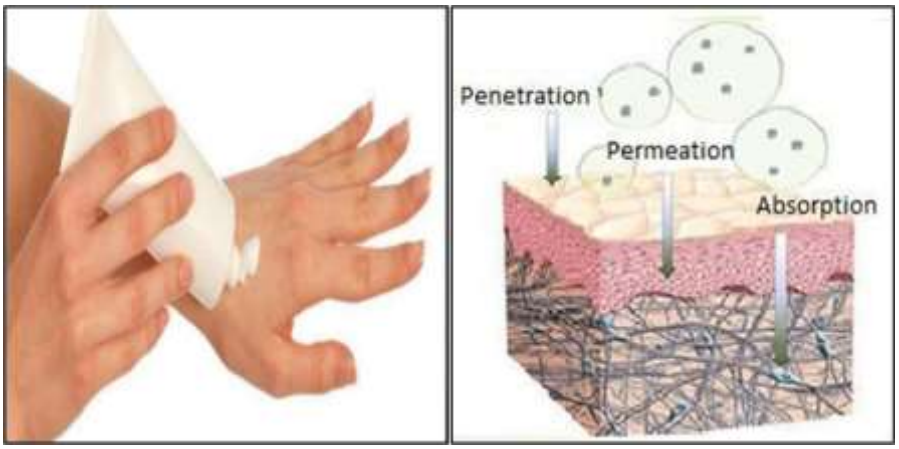


Figure 4 : Demonstration of transdermal drug delivery system

- **Topical drug delivery System:**

Topical drug delivery means the application of drug to skin for localized effect. The skin is one of the most widespread and freely available structures of the human body. It contains dead keratinized cells called corneocytes. For the permeation of drug to this barrier many technologies and systems have been investigated and one of the most promising techniques is the vesicular carrier for drug delivery through the skin. Novel drug delivery carriers have great potential for dermal delivery. The lipidic and nonlipidic vesicular systems like liposome, transfersome, ethosome, and niosome are used to overcome the problem associated with topical conventional formulation In 1985, niosomes were studied as an alternative to liposome because they offer some benefits over liposome such as being more stable, nontoxic, and economic due to low cost of nonionic surfactant as compared to phospholipids which are prone to oxidation.

Advantages of topical drug delivery system:

1. It avoids first pass metabolism.
2. Expedient and easy to apply.
3. Lowers the total drug administration.
4. Improving physiological and pharmacological response.
5. Improve patient acceptance.
6. Self-medication is possible.

Anatomy and Physiology of Skin and barrier properties:

Skin is one of the largest organ, separates the most stable internal environment from the most unstable external environment. Skin compose of epidermis, dermis and subcutis, each plays a fundamental role of maintaining chemical balance and protection of skin from microorganisms, dust and varied climatic conditions.

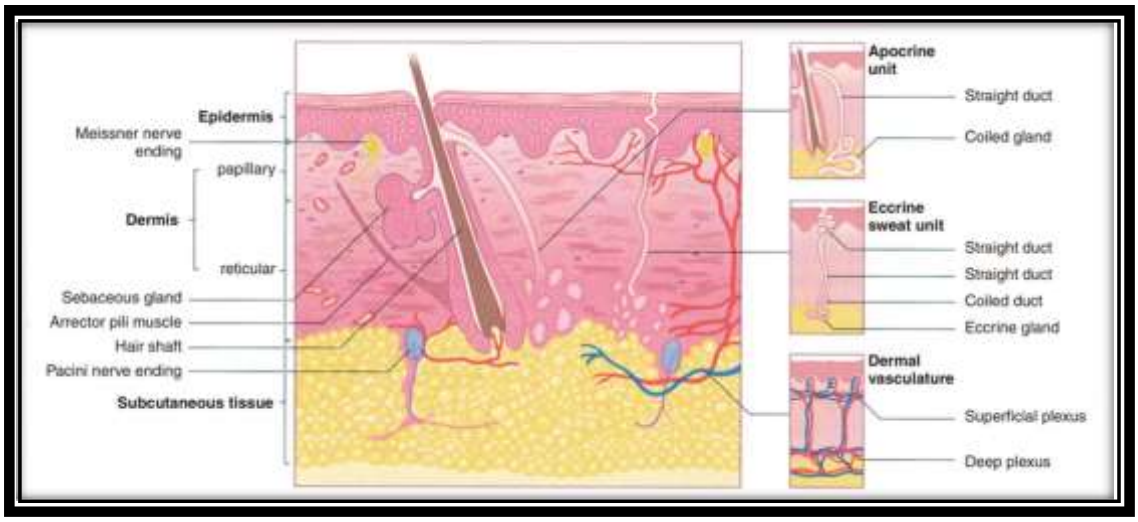


Figure 5: Cross-Section of Human Skin

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital functions, including protection against external physical, chemical, and biologic assailants, as well as prevention of excess water loss from the body and a role in thermoregulation.

- **Wounds:**

Wound is defined as the disruption of cellular and anatomic continuity of a tissue. According to the Wound Healing Society (WHS), wounds are physical injuries that result in an opening or break of skin that causes disturbance in the normal skin anatomy and function. They result in the loss of continuity of epithelium with or without the loss of underlying connective tissue. This includes injury of underlying tissues / organs caused by surgery, a blow, a cut, chemicals, heat/cold, friction / shear force, pressure or as a result of disease. Wound may arise due to physical, chemical, microbial agents, thermal or immunological damage to the tissue.

- **Classification of Wounds:**

There is no definite method of classifying wounds. There are many different types of wounds ranging from mild to severe to potntially fatal.

1. Based on anatomical site:

Wounds can be referred by their anatomical site, e.g. abdominal or axillary wound.

2. Based on the basis of physiology of wound healing:

Wounds are popularly categorized by their level of chronicity as either an acute or a chronic wound.

- **Acute Wounds Acute:**

wound is a tissue injury that normally precedes through an orderly and timely reparative process that result in sustained restoration of anatomic and functional integrity. Acute wounds are usually caused by cuts or surgical incisions and complete the wound healing process within the expected time frame.

- **Chronic Wounds:**

Chronic wounds are wounds that have failed to progress through the normal stages of healing and therefore enter a state of pathologic inflammation. Chronic wounds either require a prolonged time to heal or recur frequently. Local infection, hypoxia, trauma, foreign bodies

and systemic problems such as diabetes mellitus, malnutrition, immune deficiency or medications are the most frequent causes of chronic wounds.

- **Factors Affecting Wound Healing:**

Wound healing is a normal biological process in the human body. Many factors can adversely affect this process and lead to improper and impaired wound healing. Understanding of these systemic and local factors and their influence on wound healing is essential for better therapeutic opportunity for wound treatment.

- **Systemic factors**

1. Nutrition:

Several macro and micro nutrients play a vital role in wound healing.

- **Macronutrients:**

Relevant macronutrients include proteins, carbohydrates, fats and water. Protein is essential for collagen and protein synthesis on wound site. A state of malnutrition may provide an inadequate amount of protein and this can decrease the rate of collagen synthesis, wound tensile strength or increased chance of infection.25,26 Carbohydrate aids cell proliferation and phagocytic activity of leucocytes to prepare wounds for fibroplasia and its deficiency decreases resistance to infection and impairs collagen synthesis.

- **Micronutrients**;

Relevant micronutrients include vitamins A, B-complex, C, E and K and minerals such as copper, iron and zinc.

2. Medication:

Many drugs are known to impair wound healing. Chemotherapeutic agents used in cancer are the largest group well known to delay wound repair. Systemic glucocorticoids interfere with normal healing process by reducing collagen synthesis and fibroblast proliferation.

- **Phases of Wound Healing:**

Wound healing involves a complex interaction between epidermal and dermal cells, the extra cellular matrix, controlled angiogenesis and plasma-derived proteins, all coordinated by an array of cytokines and growth factors. This dynamic process is classically divided into four overlapping phases such as Hemostasis, Inflammation, Proliferation and Remodeling.

1. Hemostasis:

Hemostasis occurs immediately after initial injury. Platelet is the key cell responsible for this function, in which body forms a clot to prevent further bleeding. The coagulation cascade is activated through extrinsic and intrinsic pathways, leading to platelet aggregation and clot formation in order to limit blood loss. As blood spills into the site of injury, the blood components and platelets come in contact with exposed collagen and other extracellular matrix components. This contact, triggers the release of clotting factors from the platelets and the formation of a blood clot composed of fibronectin, fibrin, vitronectin and thrombospondin.35-37 The blood clot and platelets trapped within it are not only important for haemostasis, as the clot also provides a provisional matrix for cell migration in the subsequent phases of haemostatic and inflammatory phases.

2. The Inflammatory Phase:

The humoral and cellular inflammatory phase follows two separate phases, an early inflammatory phase and a late inflammatory phase. Early inflammatory phase It activates the complement cascade and initiates molecular events, leading to infiltration of the wound site by neutrophils, whose main function is phagocytosis in order to destroy and remove bacteria, foreign particles and damaged tissue. The neutrophils begin to be attracted to the wound site within 24 - 36 h of injury by various chemoattractive agents including TGF-β, complement components such as C3a and C5a, formyl methionyl peptides produced by bacteria and platelet products.

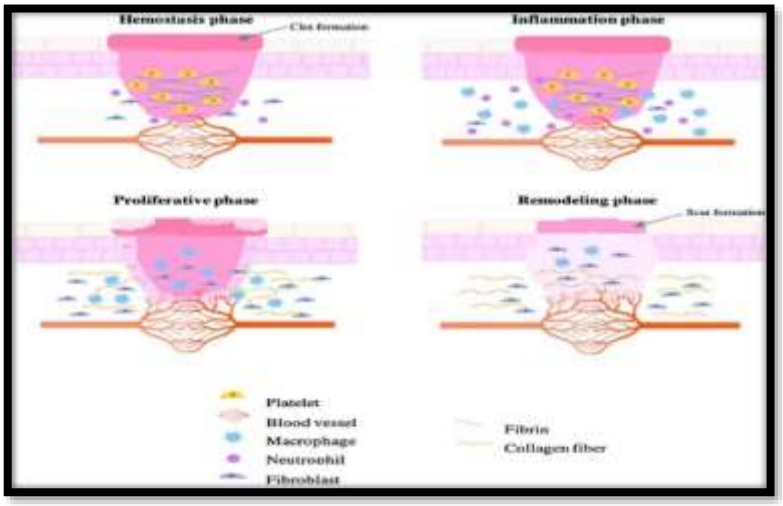


Figure. 6: Phases of wound healing

- **DRUG PROFILE:**

1. QUERCETIN:

- **Chemical Structure:**

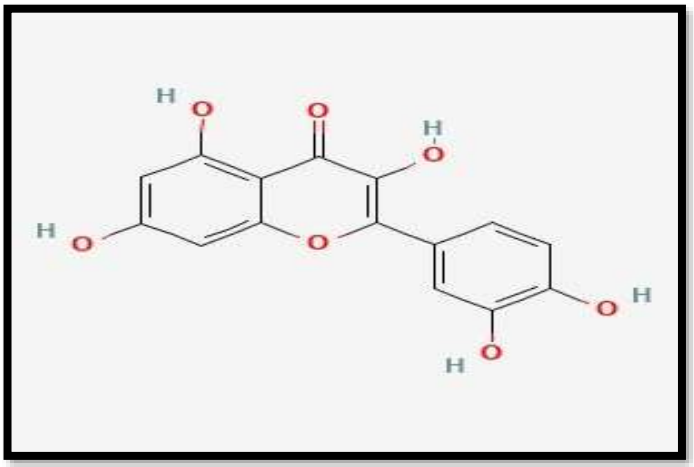


Figure 7: Structure of Quercetin

- **Molecular formula:** C15H10O7

- **Molecular weight:** 302.23 g/mol

- **Category:** Quercetin is a potent antioxidant that helps neutralize free radicals, reducing oxidative stress and preventing cellular damage.

- **Absorption, Distribution and Excretion:** After oral administration of a single dose of 4 g quercetin to four male and two female volunteers, neither quercetin nor its conjugates was detected in the blood or urine during the first 24 hr; 53% of the dose was recovered in the feces within 72 hr. After a single intravenous injection of 100 mg quercetin to six volunteers, the blood plasma levels declined biphasically, with half-lives of 8.8 min and 2.4 hr; protein binding exceeded 98%. In the urine, 0.65% of the intravenous dose was excreted as unchanged quercetin and 7.4% as a conjugate within 9 hr; no further excretion occurred up to 24 hr

- **Mechanism of action:** Quercetin is a specific quinone reductase 2 (QR2) inhibitor, an enzyme (along with the human QR1 homolog) which catalyzes metabolism of toxic quinolines. Inhibition of QR2 in plasmodium may potentially cause lethal oxidative stress. The inhibition of antioxidant activity in plasmodium may contribute to killing the malaria causing parasites.

➢ **Pharmacological Classification:**

Quercetin is a natural flavonoid found in many fruits and vegetables, and it has a wide range of pharmacological properties. Here are some key points about its pharmacology:

1. **Antioxidant:** Quercetin is a potent antioxidant that helps neutralize free radicals, reducing oxidative stress and preventing cellular damag.

2. **Anti-inflammatory:** It has strong anti-inflammatory effects, which can help reduce inflammation and pain in various conditions.

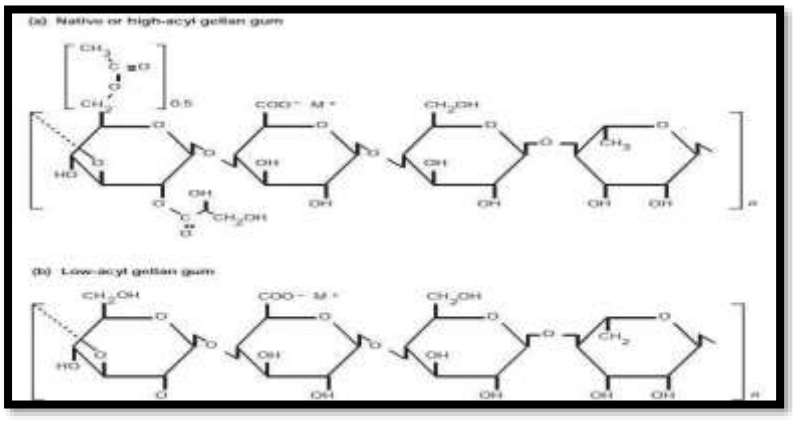
3. **Cardioprotective:** Quercetin has been shown to have cardioprotective properties, helping to lower blood pressure, reduce cholesterol levels, and improve overall heart health.

4. **Antiviral and Antibacterial:** It exhibits antiviral and antibacterial activities, making it useful in
fighting infections.

➢ **EXCIPIENT PROFILE:**

1. GELRITE :

- **Name:** Gellan Gum
- **Formula Weight:** Approximately 500,000
- **Functional Uses:** Thickener, gelling agent, stabilizer.



- **Mol. Structure:**

Figure 8: Gelrite Chemical Structure

2. 2. Polyoxyethylene Sorbitan Fatty Acid Esters (Tween 20, 40, 60, 80);

- **Name:** Polyoxyethylene Sorbitan Fatty Acid Esters.
- **Chemical Name:** Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 80
- **Molecular Formula: Polysorbate 20-** C58H114O26 1128, **Polysorbate 40-** C62H122O26 1284
  Polysorbate 60- C64H126O26 1312, **Polysorbate 80-** C64H124O26 1310.
- **Mol.wt: Polysorbate 20-** 1128, **Polysorbate 40-** 1284, **Polysorbate 60-** 1312, **Polysorbate 80-** 1310.

3. Transcuto:

- **Name:** Transcutol
- **Chemical Name:** 2-(2-ethoxyethoxy) ethanol
- **Molecular Formula:** C6H14O3
- **Molecular weight:** 134.18
- **Mol. Structure:**

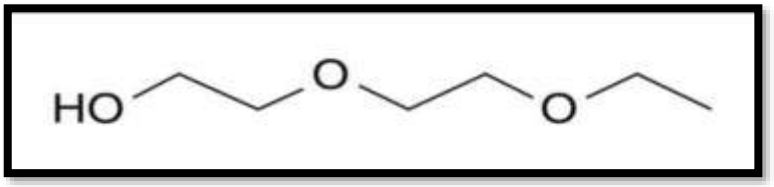


Figure 9: Transcutol Chemical Structure

- **MATERIALS AND METHODS:**

MATERIALS & EQUIPMENT USED:

Table 1: Materials used

S.r No	Name
1	Quercetin
2	Polysorbate 20
3	Polysorbate 80
4	GELRITE (Gellan Gum)
5	Methanol
6	DMSO
7	Triethanolamine
8	Propylene Glycol
9	Ethanol
10	Sodium Hydroxide
11	Glycerin
12	Sodium Chloride
13	Potassium phosphate monobasic
14	Sodium phosphate dibasic

Table 2: Equipments used

S. No	Instruments
1	Microgram Electronic balance
2	UV-Vis Double beam Spectrophotometer
3	Diffusion test Apparatus
4	Hot Air Oven
5	FTIR
6	Differential Scanning Calorimetry DSC Q20

- **PREPARATION OF STOCK & BUFFER SOLUTIONS**

1. Hydrochloric acid buffer pH1.2: 50ml of 0.2M potassium chloride and 85ml of 0.2 M HCl were taken in a 200 ml volumetric flask and made up to the volume with water.

2. Phosphate buffer pH 6.8: Dissolve 60.5 g of disodium hydrogen phosphate and 46 g of potassium dihydrogen phosphate in water add 100 ml of 0.02 M disodium edetate and 20 mg of mercuric chloride and dilute with water to produce 1000ml.
3. Phosphate buffer pH 7.4: 50 ml of 0.2 M potassium dihydrogen phosphate and 39.1 ml of 0.2 M NaOH were taken in a 200 ml volumetric flask and made up to the volume with water.
4. Sodium hydroxide solution (0.2 M): Accurately weighed 8.0 gm of sodium hydroxide was dissolved in 1000 ml of distilled water.
5. Potassium dihydrogen phosphate (0.2 M): Accurately weighed 27.218 gm of potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water.
6. Potassium chloride (0.2 M): Accurately weighed 14.91 gm of potassium chloride was dissolved in 1000 ml of distilled water.

➢ SOLID STATE CHARACTERIZATION OF DRUG:

1. Fourier Transfer Infrared Spectroscopy:

Drug was mixed with Potassium Bromide in a ratio of 9:1 which was triturated and blended evenly. The mixture was further compressed into pellets on a motorized pellet press at pressure of 15 ton. The prepared pellets were then scanned over range of 4000 – 400 cm-1 to get the IR spectra. Functional group determination was studied visually by interpreting the peaks observed. The FTIR experiment was conducted on FTIR- 8400S apparatus.

2. Differential Scanning Calorimetry:

Drug was hermitically sealed in perforated aluminum pan using crimper and heated at constant rate of 10°C/min over the temperature ranges of 30-300°C at 20mL/min nitrogen purging on a Mettler Toledo DSC apparatus.

3. Melting Point Determination:

Capillary Method was employed for Melting Point Determination. Drug was filled in a one end sealed capillary tube and was placed in a Liquid Paraffin bath in a Thiele's Tube. Upon visual inspection, temperature on which the solid starts turning into a liquid was noted down.

➢ DRUG-EXCIPIENTS INCOMPATIBILITY STUDIES:

Fourier Transfer Infrared Spectroscopy:

The Fourier Transform – Infrared (FT-IR) spectroscopy has numerous application in Pharmaceutical field. It is widely used in determination of identification of known and unknown compound. Apart from this it can also be used in evaluating the drug interaction. During formulation the active ingredient are used mixed with various excipients to give proper shape and appearance. Sometimes it happens after mixing the active ingredients with excipient, it produces incompatibility due to drug excipient interaction. Drug was mixed with all excipients in equal proportion forming a physical mixture were all compressed as a KBr pellet respectively for each sample at a ratio of 9:1. The prepared pellets were then scanned over range of 4000 – 400 cm-1 to get the IR spectra.

➢ ANALYTICAL METHOD DEVELOPMENT

- **Determination of ƛmax for Quercetin:** 10 mg drug was suspended in 100 ml methanol to prepare a stock solution and 10ppm sample was taken out and studied for its UV Spectra photometrically.
- **Preparation of Stock Solution:** Accurately weighed 10 mg of Quercetin was transferred to a 100 ml volumetric flask, dissolved in 10 ml Methanol by shaking manually for 10 min. The volume was adjusted with the same up to the mark to give the final strength, i.e.100 µg/ml.

➢ FORMULATION OF QUERCETIN NANOGEL:

Formulation Code	Quercetin (%)	GELRITE (%)	Tween 20:80 (%)	Diluent to make 100%
F1	5	10	10	Q.S
F2	5	20	10	Q.S
F3	5	10	20	Q.S
F4	5	20	20	Q.S
F5	5	7.92893	15	Q.S
F6	5	22.0711	15	Q.S
F7	5	15	7.92893	Q.S
F8	5	15	22.0711	Q.S
F9	5	15	15	Q.S

Table 3: Formulation Table for Quercetin Nanogel

The Quercetin Nanogel was synthesized with the aid of Gelrite as a polymer. Accurately weighed 5 mg of Quercetin SLNs and variable concentration of GELRITE was dissolved in 1% v/v methanol followed by the drop wise addition of Tween 20:80 (1:1) at the rate of 2 ml/min with constant stirring for 3 h by using magnetic stirrer at 1000 rpm. pH was adjusted by gel Triethanalamine(0.05%). The mixture was allowed to achieve room temperature which resulted in gel formation.

➢ CHARACTERIZATION OF QUERCETIN NANOGEL:

a. Mean Particle size:
The MPS were determined by PCS with a Malvern Zetasizer (Nano ZS 90, Malvern ltd., UK). The measurement using PCS is based on the light scattering phenomena in which the statistical intensity fluctuations of the scattered light from the particles in the measuring cell are measured. Prior to the measurements, all samples were diluted with double distilled water to produce a suitable scattering intensity. The z-average and PDI values were obtained at an angle of 90° using disposable polystyrene cells having 10 mm diameter cells at 25°C, which were equilibrating for 120 seconds.

b. Production yield: The production yield of nanogel formulation were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of nanogel**. Production Yield = Practical/ Theoretical Yield * 100**

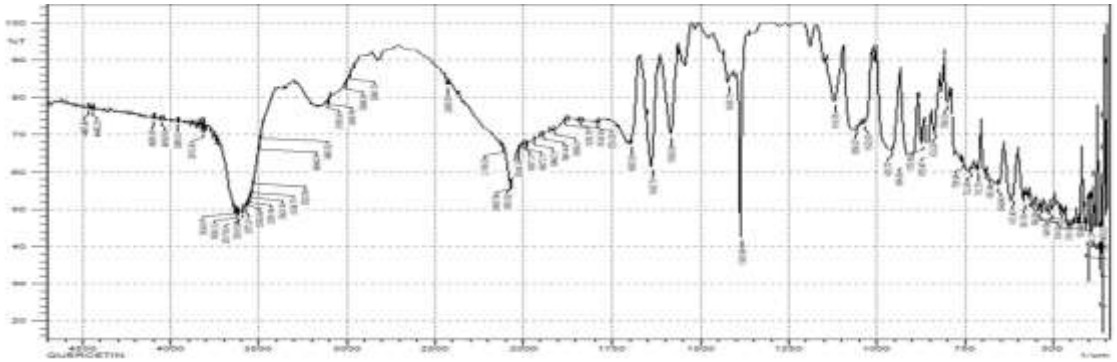
c. Entrapment Efficiency and Drug loading: Percent Entrapment efficiency (EE) is defined as the percentage of drug incorporated into the polymeric nanogel relative to the total drug added. It specifies how much percent of drug is included in the particles and how much percent of free drug are still present in the dispersion medium. For this both, Quercetin SLNs and NG were centrifuge at 45,000 rpm for 35 min ; 1.0 mL of the supernatant collected after centrifugation was diluted with 3.0 mL of DMSO and methanol and then make up volume up to 10 ml in 10ml volumetric flask and measured spectrophotometrically at 354 nm using UV-Visible spectrophotometer. Entrapment efficiency (%)= (Total amount of drug- un-entrapped drug)/(Total amount of drug) x 100 Drug loading (%)= (Actual amount drug in nanogel)/(Total amount of drug) x 100.

➢ RESULT AND DISCUSSION:

➢ SOLID STATE CHARACTERIZATION OF DRUG:

1. Fourier Transfer Infrared Spectroscopy: Fourier transformed infrared spectra of Quercetin was taken by using the KBr disk method. physical nature of quercetin, GELRITE shown in Figure. The quercetin FTIR spectra clearly showed all of the characteristic peaks. Thus, all the drug's properties remained largely unchanged, and quercetin was effectively incorporated into the gel formulation.

Figure 11: FTIR spectra of Quercetin



2. Differential Scanning Calorimetry:

DSC thermograms of pure quercetin, physical mixture of quercetin, GELRITE. Sharp endothermic peaks at 270.67ºC were visible on the thermal graph of pure quercetin, signifying the compound's melting point The physical mixture Thermogram was nearly identical to that of pure Quercetin and showed an endothermic peak at 2700 67C.

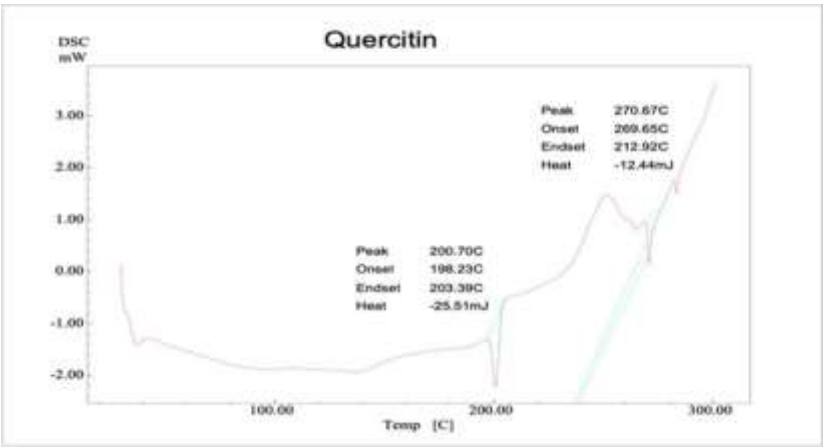


Figure 12 : Overlay of DSC Thermogram of Quercetin, Physical mixture

3. **Melting Point Determination:** Melting point of Quercetin was found by glass capillary method to be 245- 256 0C. The observed melting point of Quercetin was confirmed with the standard melting point of Quercetin.

➢ **DRUG-EXCIPIENTS INCOMPATIBILITY STUDIES:**

1. Fourier Transfer Infrared Spectroscopy:

Identification of any possible incompatibilities between the drug and excipients is major task to be achieved through preformulation and compatibility studies. Compatibility studies deal with understanding of any physicochemical interactions of drug and excipients. Development of a robust and effective formulation necessitates careful selection of the excipients that maintain the quality, safety, efficacy and stability of the drug product. FTIR is a widely used technique to evaluate any incompatibilities between the drug and excipients. The FTIR spectroscopic analysis of the pure drug and lipid physical mixture measures changes in the frequency and bandwidth of interacting groups during any physicochemical interactions.

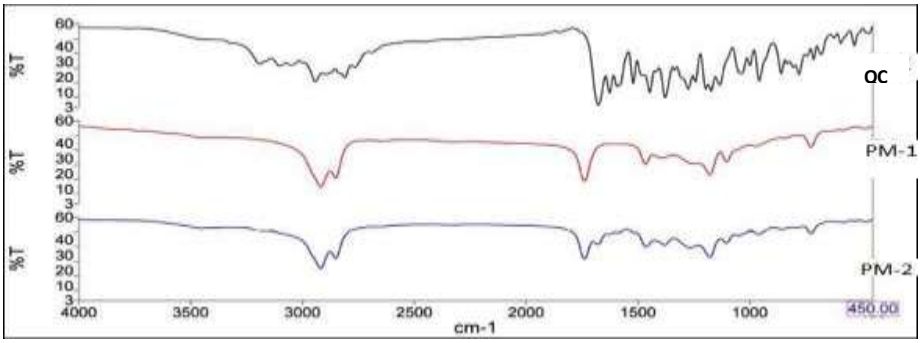


Figure 13: FTIR Spectra of Quercetin and their Physical Mixture

➢ ANALYTICAL METHOD DEVELOPMENT

1. **Determination of ƛmax for QUERCETIN:** The solution of Quercetin in methanol was found to exhibit maximum absorption at 354 nm after scanning on the UV-Vis spectrophotometer which was reported as λmax in the literature. Thus the procured drug sample of Quercetin complies with the reference spectra.

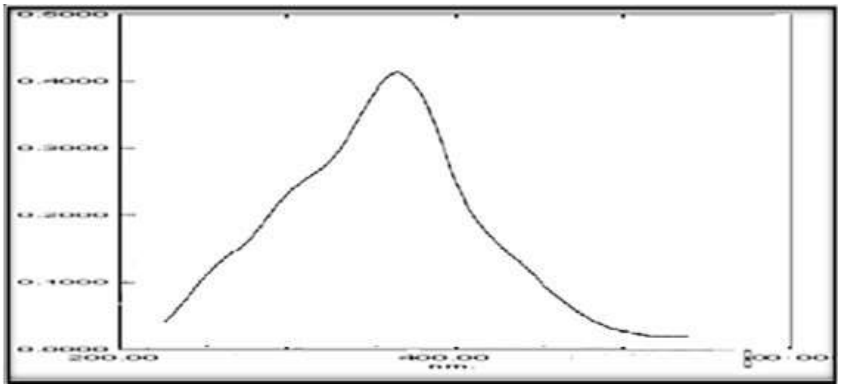


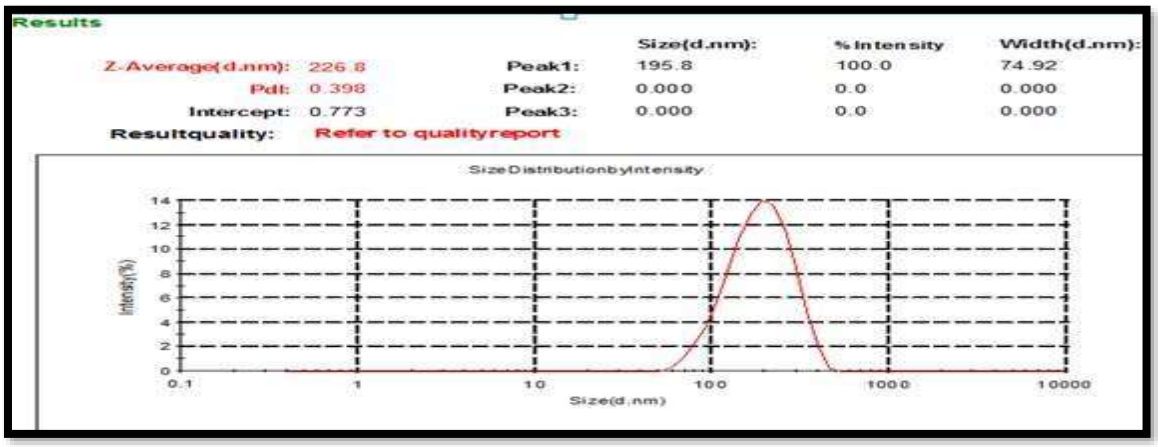
Figure 14: UV spectrum of Quercetin in Methanol

➢ CHARACTERIZATION OF QUERCETIN NANOGEL:

Selection of suitable Quercetin for further preparation of Nanogel:
Formula F1 was selected as the most optimized formula for preparation of Nanogel. This decision was based upon the Entrapment Efficiency results (99.98 %) for F1

a. Mean Particle size: The particle size and PDI the drug free NG was found to be 201nm and 0.3 respectively. After then drug loading partical size of Quercetin loaded NG was increase 226 nm there was no significant change in PDI. Partical size of NG a crucial factor because it determines the rate and extent of drug release as well as drug absorption. The smaller droplet size provides a larger interfacial surface area for drug absorption. The particles having average diameter up to 300 nm could be easily transported Parental route. In addition, it was suggested that the smaller droplet size permit a faster release rate. Also, it has been reported that the smaller particle size may lead to more rapid absorption and improve the bioavailability.

Figure 14: Particle size analysis of Optimized Formulation of Quercetin NG



- **Production yield, Entrapment Efficiency and Drug loading:**

Formulation Code	Production yield (%)	Entrapment Efficiency (%)	Drug loading (%)
F1	77.2	98.7	7.3
F2	69.8	99.8	6.5
F3	74.6	89.0	7.7
F4	79.0	95.4	5.8
F5	72.1	99.9	7.4
F6	74.2	100.8	8.2
F7	78.0	94.3	9.5
F8	73.2	89.1	8.3
F9	70.0	91.1	7.1

Table 4: Results

- **Accelerated stability study:**

Stability parameter	Test period			
	0 Days	**30 Days**	**60 Days**	**90 Days**
MPS (nm)	226.2 ± 0.027	227.2 ± 1.80	229.9 ± 0.03	230.1 ±0.013
PDI	0.3 ± 0.19	0.3 ± 0.53	0.3 ± 0.57	0.3 ± 0.96
% EE	96.66 ± 1.18	94.02 ± 0.02	90.98 ± 1.05	87.01 ± 1.35

Table 5: Stability studies

From stability studies, it was observed that particle size was slightly increased from 226.2 ± 0.027 nm to 227 ± 1.80 nm and % EE was decreased to 87.01 ± 1.35 % during storage. Additionally, there was not much change in PDI means, initially it was 0.189 ± 0.89 and changed to 0.262 ± 1.045. Minimum loss of % EE indicates that the drug was retained within the matrix carriers during the stability period and minimum loss of drug was occurred. The obtained results revealed that there was no significant change in the MPS, PDI and % EE indicating that they were found to be stable at 25 ± 2°C, 60 ± 5% RH for a total period of 3 months.

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