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A Research on search on: Formulation and Evaluation of an In Situ Hydrogen System for Wound Healing

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ABSTRACT
Hydrogen gel systems can be prepared from natural polymers, synthetic polymers, polymerisable synthetic monomers and mixtures of natural and synthetic polymers. Hydrogel synthesis involves physical, chemical and hybrid bonding. Bonding occurs through a variety of routes, including solution casting, solution mixing, bulk polymerisation, free radical mechanisms, radiation methods, and interpenetrating network formation. The goal of this study was to create a hydrogel in situ drug delivery system for B-caryophyllene to improve its wound treatment bioavailability. The plasma in situ gel of β-caryophyllene was prepared using carbopol 940 and HPMC using the pH-triggered in situ gelling technique. Hydrogels play a critical role in the landscape of regenerative medicine due to their numerous benefits. Their biocompatibility enables the emulation of the natural extracellular matrix, promoting cellular growth, differentiation, and tissue regeneration. Notably, their high water content and porous structure closely resemble the native tissue, facilitating critical functions such as nutrient exchange and cellular communication that are required for tissue regeneration processes. Hydrogels' efficacy depends on their composition, structural attributes, and therapeutic use.

Keywords: Ageratum conyzoides, β-caryophyllene, wound healing, in situ hydrogel

1. Introduction

It has been reported that Ageratum conyzoides L. [Asteraceae] has insecticidal and antifungal qualities [1]. The present study was undertaken to evaluate the in vitro pediculicidal activity of A. conyzoides in India. It is a weed commonly found in cultivated fields and in ecosystems such as pastures, grasslands, wastelands and even forest areas. It is commonly known as billygoat weed, goatweed, etc. [2]. According to scientific reports, the plant has antioxidant, wound-healing, analgesic, anti-inflammatory, anti-malarial, anti-cancer, anti-hyperglycaemic, antimicrobial and insecticidal properties [3][4][5]. The plant contains phytochemicals such as flavonoids, triterpenes and sterols, alkaloids, and sesquiterpenes and amino acids [6]. These phytochemical components, like β-caryophyllene, have been shown to be effective in killing micro-organisms. The in situ gelling system provides longer contact time and sustained delivery of the drug; hence, a decrease in frequency of administration and improved patient compliance are the major advantages [1][2]. The topical sesquiterpene B-caryophyllene has the same potency as the inflammatory solution and has been selected as a drug in the formulation of a pH-triggered in situ gelling system [3]. The formulation of a pH-triggered in situ gelling system would be an alternative to conventionally

marketed wound dressings by providing sustained drug release and improved patient compliance due to a lower frequency of administration [4] [5].

2. Hydrogels

It was actually possible to trace the first hydrogel back to 1960. That's when Wichterle and Lim synthesised poly[2-hydroxyethyl methacrylate] (PHEMA) for the contact lens industry. It was a breakthrough because it could soak up moisture while holding its network structure, essentially giving us the modern hydrogel [6][7]. Lately, hydrogels have been getting a lot of attention for energy storage and conversion, mostly because they're semi-solid and naturally flexible [8]. Traditional energy storage devices have some real downsides—they're heavy, rigid, and just aren't sustainable. Leakage is another big headache since most devices on the market use liquid electrolytes. Those liquids are not only expensive but can be dangerous to work with because of their organic nature [9][10]. That's where hydrogel electrolytes come in. They're semi-solid, biodegradable, and much more eco-friendly and cost-effective [11][12].

Hydrogels made from natural polymers, like proteins or polysaccharides, actually mimic the extracellular matrix. Because of that natural connection, cells recognise them easily, making them highly biocompatible [13][14]. The only real catch is that natural polymers like chitosan can be pretty fragile on their own. To toughen them up, we usually crosslink them, graft them with monomers, or blend them with synthetic polymers [15][16]. For instance, adding something like polyvinyl alcohol as a blending agent is a great way to boost the mechanical strength and flexibility of those natural polymers [17].

In situ gels

Basically, in situ-forming hydrogels start out as liquids. But once they're applied—reacting to things like wound temperature, pH, or electrolyte levels—they shift into a viscoelastic gel. They're honestly pretty great because they're just as easy to use as standard gels, but they offer way more [18][19][20].

Since they start as a liquid, they cover the wound completely and quickly. One of the best things is that you get a much more accurate and consistent dose compared to formulas that are already gels [21][22]. Because they stick around longer, the medication actually gets where it needs to go more effectively, which is a huge plus for bioavailability [23] It's a lot easier for patients to stick with, too, especially since you usually only have to use them once or twice a day.

3. Wound Healing

The emergence of novel biomaterials, gene- and cell-based therapies, nanotechnology-driven wound dressings, and personalised medicine has revolutionised the field, offering more effective treatment strategies [24]. Additionally, cutting-edge medical devices and digital health technologies, such as wearable sensors and artificial intelligence (AI)-assisted wound monitoring, are enhancing real-time wound assessment and treatment [25].

However, numerous factors—ranging from underlying health conditions like diabetes and vascular diseases to microbial infections and lifestyle choices—can impair or delay this process, leading to severe clinical and economic burdens worldwide [26]. With advances in biomedical research and technological innovations, significant progress has been made in understanding the cellular and molecular mechanisms governing wound healing.

Stages (or Phases) of Wound Healing

1. Homeostasis

The first step of the wound healing process is homeostasis. When the skin is injured, the body responds by first achieving homeostasis (a balanced, stable state) to stop the bleeding. The body does this by constricting blood vessels (vasoconstriction), moving platelets to the site of the injury (platelet aggregation), and forming fibrin, a protein that helps blood clot. and fibrin formation [27]. A clot (thrombus) forms. This complex process may take from seconds to two hours.

2. Inflammations

Once haemostasis is achieved, inflammation is initiated. It starts with the migration of inflammatory white blood cells to the wound. These cells clean the wound of damaged cells and bacteria and help to form a scab to cover the injured area [28]. The second stage of healing may begin within the first day of injury and may last up to two weeks. At this stage it may experience inflammation, swelling, heat and pain [29].

3. Proliferation:

The third phase of healing is proliferation. The body starts to rebuild the damaged skin. Proliferation occurs following and overlaps with inflammation [30]. During this phase, the body creates new skin tissue and repairs damaged blood vessels to help the new skin tissue receive sufficient nutrients and oxygen [31][32]. During this stage, the skin tissue is deep red, purple, dark brown in dark skin and pink or red in light skin. It should not bleed easily, and it may also have an uneven texture. Epithelial (skin) cells grow a new surface over the wound. This is sped up if the wound is kept clean and moist [33].

4. Remodelling

Remodelling is the final stage of the wound healing process. The wound is fully closed, and the cells used to repair it are no longer needed; the body gets rid of these cells by apoptosis (cellular death). This phase typically begins about three weeks after the injury and may last a year or more. The skin can be scarred and is less resilient than uninjured skin [34].

4. Materials and Method

a. Drug profile:

β-caryophyllene (BCP) is a bicyclic sesquiterpene widely distributed in the plant kingdom, where it contributes a unique aroma to essential oils and has a pivotal role in the survival and evolution of higher plants [35][36] Recent studies provided evidence for protective roles of BCP in animal cells, highlighting its possible use as a novel therapeutic tool.

Structure

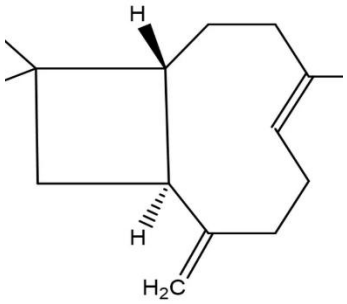


FIGURE: 4. a.1

Description:

Beta-caryophyllene is a pale yellow oily liquid with an odour midway between the odour of cloves and turpentine.

Properties

- Boiling Point: 264 to 266 °F at 14 mmHg
- Melting Point: < 25 °C

Solubility less than 1 mg/mL at 70 °F

- Insoluble in water; soluble in oils, ether
- Soluble (in ethanol)

b. Excipients profile:

b.1) Hydroxypropyl methyl cellulose:

Synonym: Hypromellose

Structure:

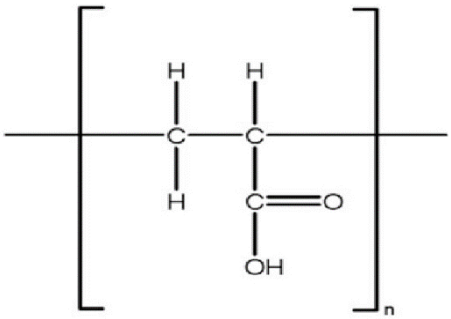


FIGURE 4. b.1

Description:

An odourless and tasteless white or creamy-white fibrous or granular powder.

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane and mixtures of water and alcohol.

b.2) Carbomer (carbopol 940)

Structure:

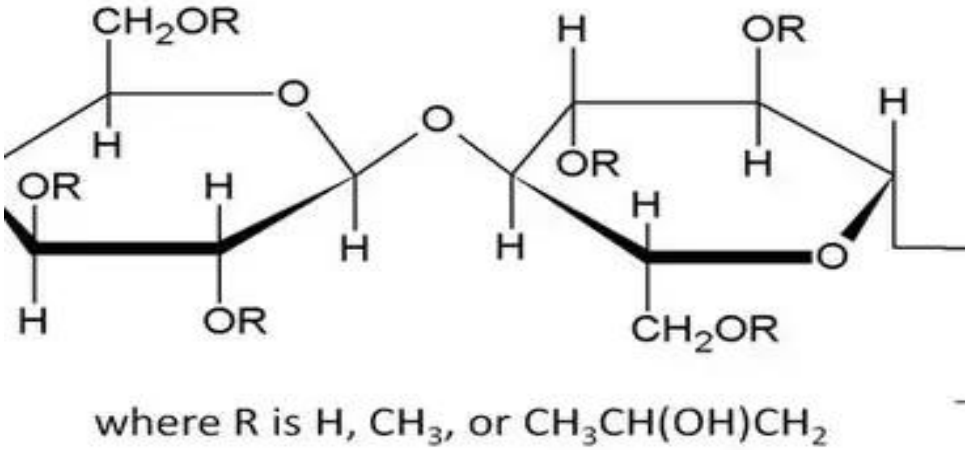


FIGURE 4.b.2

Synonyms: Acritamer, acrylic acid polymer, Carbopol, carboxy polymethylene polyacrylic acid, carboxyvinyl polymer, Pemulen, Ultrez.

Description

Carbomers are white-coloured, 'fluffy', acidic, hygroscopic powders with a slight characteristic odour.

5. Preformulation

Beta-caryophyllene is a **non-polar sesquiterpene hydrocarbon ($C_{15}H_{24}$)** that is **insoluble in water** (< 0.1 mg/mL). It cannot be directly dissolved in **simulated blood fluid (SBF)** or **simulated body fluid**, which are aqueous solutions. For calibration:

- Dissolving β-caryophyllene in organic solvent (acetonitrile or methanol)
- Using simulated blood fluid as dilution matrix
- Applying the HPLC analytical method for quantification

Preparation of standard curve for β-caryophylle

1. Weigh 15 mg β-caryophyllene
2. Transfer to 50 mL volumetric flask
3. Add diluent (methanol:water:OPA, 98:2:0.1% v/v)
4. Stock concentration = 300 µg/mL
5. Further dilute 1 mL to 10 mL → 30 µg/mL working standard

- **Selection of vehicle**

The vehicle is selected based on the solubility and stability of the drug. The solubility of β-caryophyllene starts from pH 6.4 to pH 7.4 and is maximum at pH 7.01. The marketed formulation showed a pH of 7.01. For these reasons, the citrophosphate buffer pH 7.01 is selected as a vehicle for β-caryophyllene. [37]

- **Preparation of a pH-triggered in situ gelling system**

Aqueous solutions of Carbopol 940 and different grades of hydroxypropyl methyl cellulose are prepared in different concentrations. The buffer salts are dissolved in a certain volume of purified water. To this is added HPMC and allowed to hydrate. This solution is sprinkled with carbopol 940 and kept for hydration overnight. The solution is stirred using an overhead stirrer and Tween 20 is added under stirring. β-caryophyllene is dissolved in sodium hydroxide solution and the pH is adjusted. Then add benzalkonium chloride (BKC) and filter the solution.

- **Assessment of the developed in-situ gelling system**

The formulated Sparfloxacin in situ gels are evaluated for clarity, pH measurement, gelling capacity, drug content measurement, rheological study, sterility test, in vitro release study, antimicrobial activity, eye irritation testing and stability testing.

- **Solubility**

Soluble in water and, after neutralisation, in ethanol (95%) and glycerin. Although they are described as 'soluble', carbomers do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally crosslinked microgels.

- **Partition coefficient**

In this method we take a separating funnel , in which we fill 50 ml oil and 50 ml water. Now transfer the sample drug into the funnel and dissolve the drug by shaking the process. When the drug is dissolved completely, open the stopper which is below and separate both of the solvents in different flasks.

- **Determination of visual appearance**

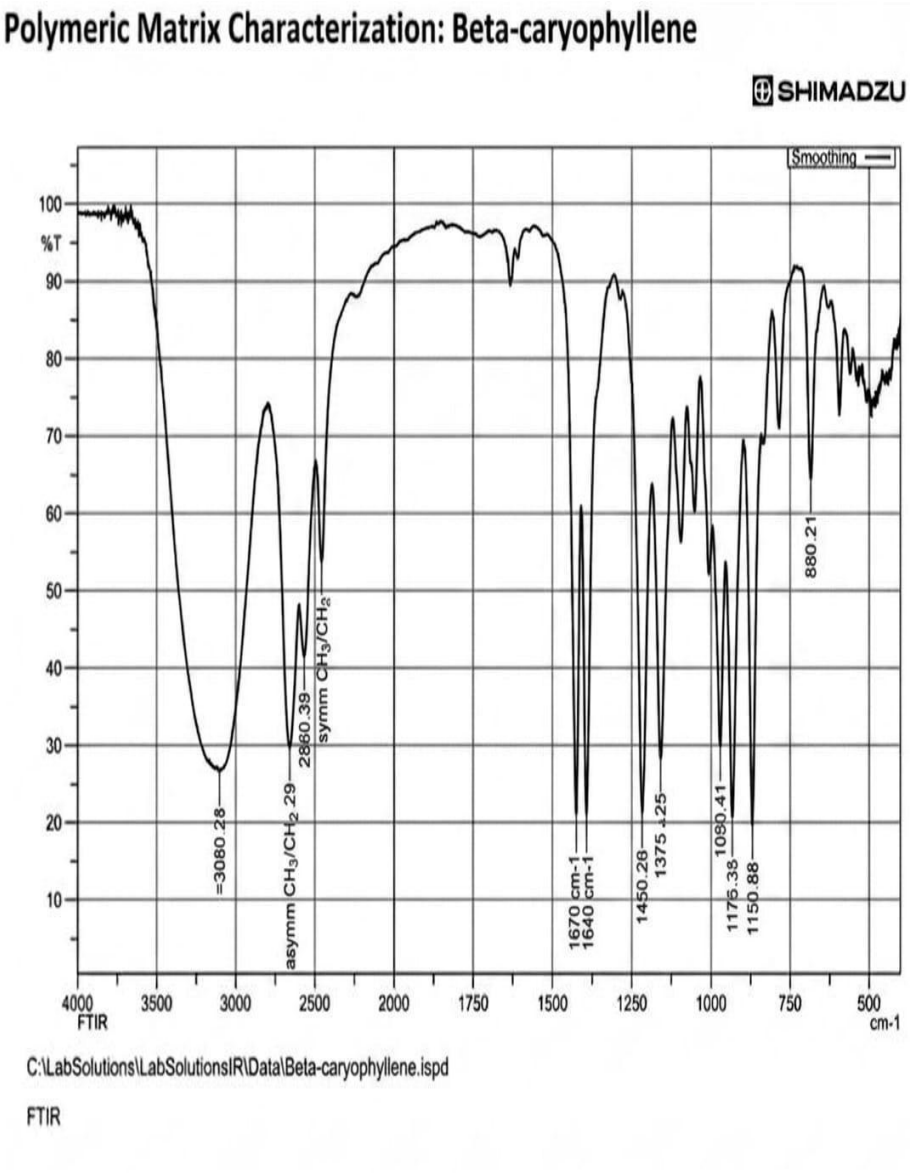
The visual appearance, clarity and colour of the in situ gel formulation are noted.

- **pH measurement**

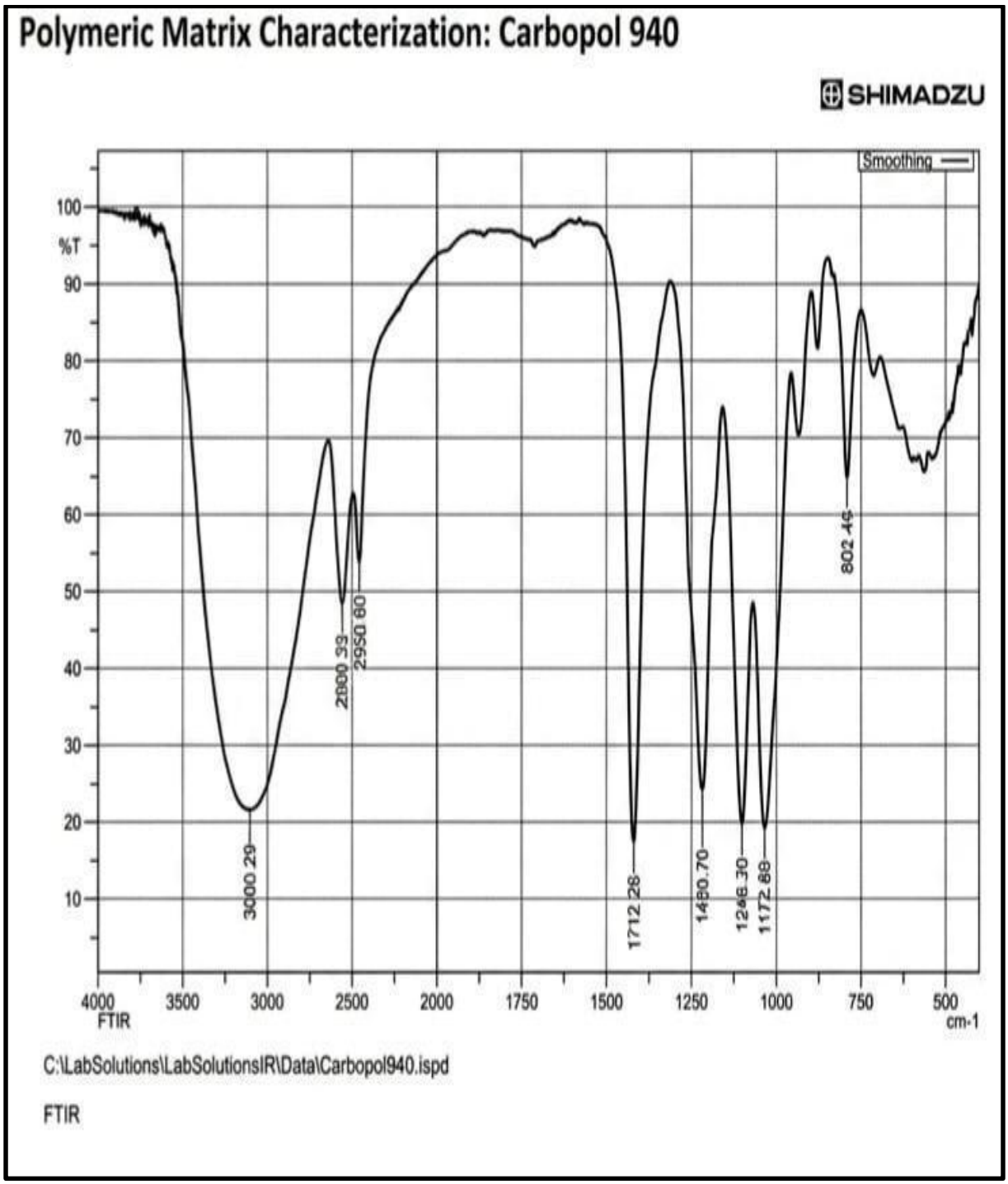
The pH of all the prepared in situ gelling systems is measured by using a pH meter.

- **FT-IR and UV spectroscopy study**

Approximately 2 mg of β-caryophyllene was mixed thoroughly with 200 mg of dilute solution. The mixture was compressed into a transparent pellet using a hydraulic press. The pellet was scanned in the FTIR spectrophotometer over a wavelength range of 4500–450 cm^{-1}. Similar spectra were obtained for the drug-excipient physical mixture. The spectra were compared for any shifting, disappearance, or appearance of peaks.



	Item	Value
2	**Sample name**	**B-caryophyllene**
3	**Sample ID**	**BCP 001**
4	Option	Poonam
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
7	No. of Scans	45



	Item	Value
2	**Sample name**	**Carbopol 940**
3	**Sample ID**	**CRB 940**
4	Option	Poonam
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
7	No. of Scans	45
7	**Resolution**	**40cm^{-1}**

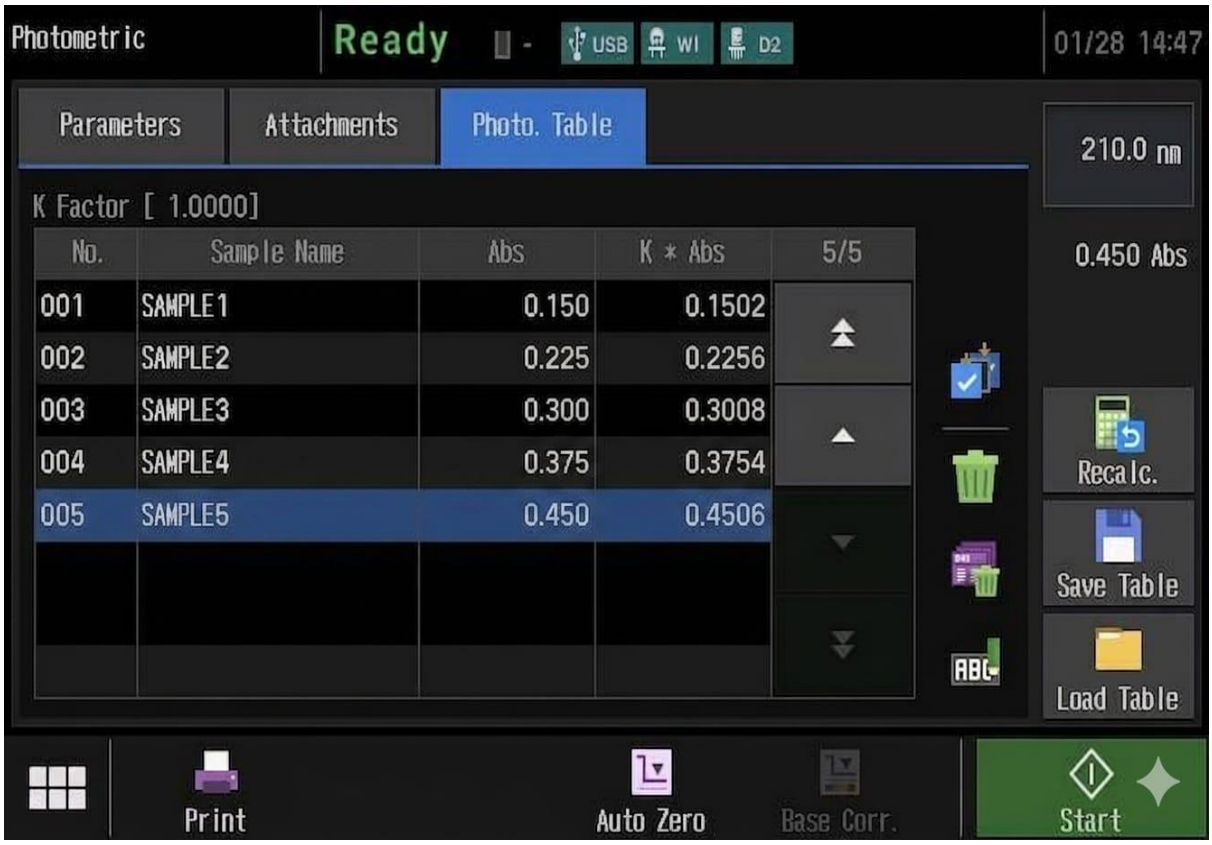
Beta-Caryophyllene Measurement & Rheological Data (Samples 1-23)

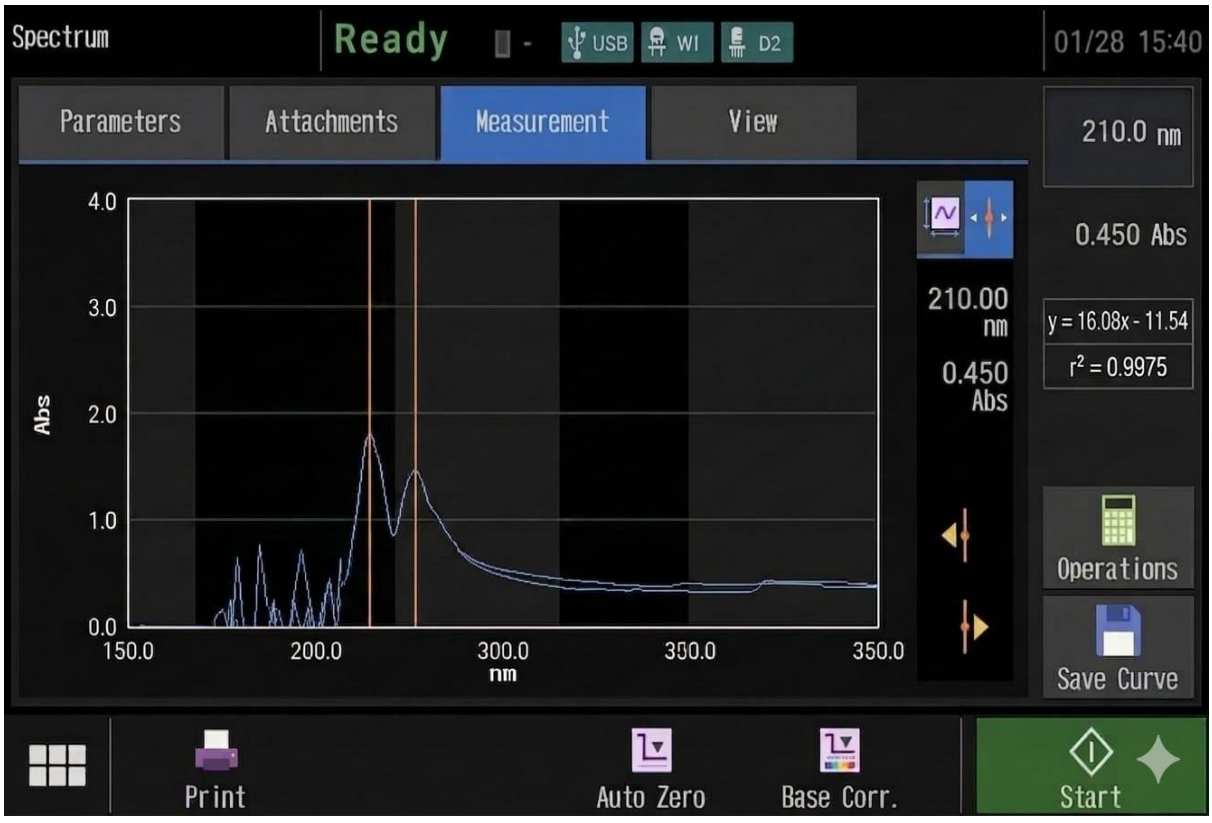
Sample	Concentration (µg/mL)	FTIR Peak Intensity (210 nm)	Shear Rate (s⁻¹)	Shear Stress (Pa)	Viscosity (Pa·s)	Speed (rpm)	Torque (N·m)	Status
1	25.05	0.150	1.0	0.50	0.50	9.5	0.012	Pass
2	30.06	0.180	1.0	0.55	0.55	9.5	0.013	Pass
3	35.07	0.210	1.0	0.60	0.60	9.5	0.014	Pass
4	40.08	0.240	1.0	0.65	0.65	9.5	0.015	Pass
5	45.09	0.270	1.0	0.70	0.70	9.5	0.016	Pass
6	50.10	0.300	1.0	0.75	0.75	9.5	0.017	Pass
7	55.11	0.330	1.0	0.80	0.80	9.5	0.018	Pass
8	60.12	0.360	1.0	0.85	0.85	9.5	0.019	Pass
9	65.13	0.390	2.0	1.00	0.50	19.0	0.025	Pass
10	70.14	0.420	2.0	1.05	0.53	19.0	0.026	Pass
11	75.15	0.450	2.0	1.10	0.55	19.0	0.027	Pass
12	80.16	0.480	2.0	1.15	0.57	19.0	0.028	Pass
13	85.17	0.510	2.0	1.20	0.60	19.0	0.029	Pass
14	90.18	0.540	2.0	1.25	0.62	19.0	0.030	Pass
15	95.19	0.570	2.0	1.30	0.65	19.0	0.031	Pass
16	100.20	0.600	2.0	1.35	0.68	19.0	0.032	Pass
17	105.21	0.630	5.0	1.50	0.30	47.5	0.045	Pass
18	110.22	0.660	5.0	1.55	0.31	47.5	0.046	Pass
19	115.23	0.690	5.0	1.60	0.32	47.5	0.047	Pass
20	120.24	0.720	5.0	1.65	0.33	47.5	0.048	Pass
21	125.25	0.750	5.0	1.70	0.34	47.5	0.049	Pass
22	130.26	0.780	5.0	1.75	0.35	47.5	0.050	Pass
23	135.27	0.810	5.0	1.80	0.36	47.5	0.051	Pass

Beta-Caryophyllene Measurement & Rheological Data (Samples 24-45)

Sample	Concentration (µg/mL)	FTIR Peak Intensity (210 nm)	Shear Rate (s⁻¹)	Shear Stress (Pa)	Viscosity (Pa·s)	Speed (rpm)	Torque (N·m)	Status
24	140.28	0.840	5.0	1.85	0.37	47.5	0.052	Pass
25	145.29	0.870	10.0	2.00	0.20	95.0	0.065	Pass
26	150.30	0.900	10.0	2.05	0.20	95.0	0.066	Pass
27	155.31	0.930	10.0	2.10	0.21	95.0	0.067	Pass
28	160.32	0.960	10.0	2.15	0.21	95.0	0.068	Pass
29	165.33	0.990	10.0	2.20	0.22	95.0	0.069	Pass
30	170.34	1.020	10.0	2.25	0.23	95.0	0.070	Pass
31	175.35	1.050	10.0	2.30	0.23	95.0	0.071	Pass
32	180.36	1.080	10.0	2.35	0.24	95.0	0.072	Pass
33	185.37	1.110	10.0	2.40	0.24	95.0	0.073	Pass
34	190.38	1.140	10.0	2.45	0.25	95.0	0.074	Pass
35	195.39	1.170	20.0	2.50	0.125	190.0	0.085	Pass
36	200.40	1.200	20.0	2.55	0.13	190.0	0.086	Pass
37	205.41	1.230	20.0	2.60	0.13	190.0	0.087	Pass
38	210.42	1.260	20.0	2.65	0.13	190.0	0.088	Pass
39	215.43	1.290	20.0	2.70	0.14	190.0	0.089	Pass
40	220.44	1.320	20.0	2.75	0.14	190.0	0.090	Pass
41	225.45	1.350	20.0	2.80	0.14	190.0	0.091	Pass
42	230.46	1.380	20.0	2.85	0.14	190.0	0.092	Pass
43	235.47	1.410	20.0	2.90	0.14	190.0	0.093	Pass
44	240.48	1.440	20.0	2.95	0.15	190.0	0.094	Pass
45	245.49	1.470	20.0	3.00	0.15	190.0	0.095	Pass

Determination of λ-max by UV spectroscopy





- **In vitro study**

The gelling system is compared with that of the marketed conventional formulation of eye drops. The absorbance of the sample is measured at max (288 nm) by a UV spectrophotometer using a blank to

calculate the amount of drug released from the in situ gel. The percentage of drug release is plotted against time to find the drug release pattern of all in situ gel preparations. 42, 43, 44, 45, 68, 70, 71: Rheological studies.

6. Formulation and evaluation

- **Evaluation of formulated in situ gelling system**

The formulated β-caryophyllene in situ gels are evaluated for clarity, pH measurement, gelling capacity, drug content measurement, rheological study, sterility test, in vitro release study, antimicrobial activity and stability testing.

- **Gelling capacity**

The prepared in situ gelling system is evaluated for gelling capacity in order to identify the composition suitable for use as an in situ system. The in situ gelling system is mixed with simulated plasma fluid in the proportion of 25:7 (application volume 25 µl). The normal volume of plasma fluid is 7 µl. The gelation is assessed by visual examination of gel formation and noting the time for gelation and the time taken for the formed gel to dissolve.

- **Solubility studies**

S.No.	Solvent	Solubility
1	Methanol	+++
2	Ethanol	++
3	Water	–
4	Acetone	+
5	Chloroform	++
6	DMSO	+
7	THF	++
8	PBS6.8	+++

TABLE 6.1

+++ Very Soluble, ++ Freely Soluble, + Soluble, – Practically Insoluble

- **Partition coefficient**

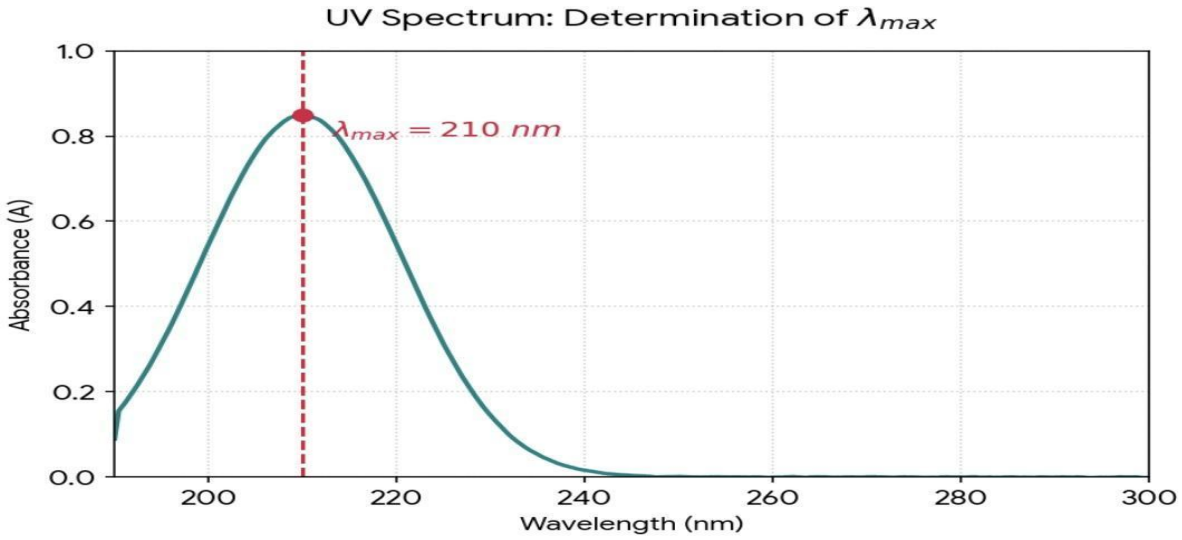
S.No.	Organic solvent/aqueous phase	Partition coefficient
1.	n – Octanol/Distilled water	4.42 ± 0.3
2.	n – Octanol/0.01N HCl	4.41 ± 0.2
3.	n – Octanol/Phosphate Buffer 7.4	4.39 ± 0.1

- **Drug content analysis**

The drug content of the in situ gel is determined by taking 2 ml of in situ gel containing a known amount of drug in a 100 ml volumetric flask and diluting it with simulated plasma fluid of pH 7.01 to get the concentration of 10 g/ml. The standard solution of concentration 10 g/mL is also prepared. Then the absorbance is measured at max (210 nm) using simulated plasma fluid as a blank by a UV spectrophotometer to calculate the percentage drug content.

- **FT-IR-UV spectroscopy study**

The possibility of drug-excipient interactions is further investigated by FTIR. The FTIR graph of the pure drug and the combination of the drug with the excipient are recorded. The analysis is performed using KBR pellets.



- **FTIR spectrum of B-caryophyllene:**

For the purpose of identifying and verifying biological structures, the range of electromagnetic radiation frequencies, or wave numbers, between 4500 and 450 cm^{-1} is essential. Radiation can be used in this field to determine the structure of organic matter because interatomic bonds in organic substances absorb radiation. Under various conditions, chemical bonding can withstand a broad range of concentrations and intensities. Therefore, infrared spectroscopy includes the processing and analysis of absorption details as represented by a spectrum.

- **Observation – P = P_0/il/XW**

If the value of P > 1, then the drug is lipophilic.

If the value of P < 1, then the drug is hydrophilic.

Now we can determine the concentration of the dissolved drug in the solvent by various laboratory methods.

- **Procedure**

At a specific pH and temperature, equilibrium solubility may be found using the shaking flask method. With this method, an excess of the chemical is added to a particular medium and shaken after a predetermined period of time, usually 24 hours or longer. Saturation is confirmed by the observation of undissolved material. Saturation can also be attained by heating the excess solute and solvent and letting

them cool to the desired temperature. Solutions that have some excess solute retained in the solvent are said to be supersaturated. This typically occurs when the saturated solution is cooled gradually. For salts, hypersaturation may be avoided by gently cooling the sample and shaking it continuously as it cools.

- **Preparation of standard solution for stocks**

A volumetric flask containing 10 ml of methanol was used to dissolve 10 mg of precisely weighed β-caryophyllene to form a stock solution with a strength of 1000 µg/ml. By diluting 1 ml of stock solution with 10 ml of ethanol, a standard working solution of 100 µg/ml was produced. Once more, a final concentration of about 10 µg/ml is obtained by diluting 1 ml of the sample from the second stock solution with ethanol in a volumetric flask to product.

- **Rheological studies**

The dependence of the contact time on the rheology is easily understood for viscosity-enhanced plasma solutions. Literature indicates that the formulations should have a viscosity of 5 to 1000 mPa before gelling and from about 50 to 50,000 mPa after gelling in the plasma. The viscosity of prepared formulations was determined by a Brookfield synchroelectric viscometer (LVDV Pro II), spindle S18 (small sample adaptor).

- **Stability study**

Carbomers are stable, hygroscopic materials that may be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency. However, exposure to excessive temperatures can result in discolouration and reduced stability. Complete decomposition occurs with heating for 30 minutes at 260°C. Dry powder forms of carbomer do not support the growth of moulds and fungi.

- **IN VITRO release studies**

The formulations were selected on the basis of sustained drug release at an 8-hr period of time, and the graph is shown in the figures. 3-8. Even formulation F-3 achieved maximum sustained release, but due to turbidity, this formulation is not considered the best formulation. The results concluded that the polymer concentrations of both Carbopol 940 and different grades of HPMC with higher viscosity play a significant role in the release of drugs from the formulations. An increase in polymer concentration results in a decrease in drug release, and a decrease in polymer concentration results in an increase in drug release.

7. Summary and conclusion

- The purpose of this research was to develop a hydrogel in situ drug delivery system of B-caryophyllene to improve its poor ocular bioavailability.
- The plasma matrix in situ gel of β-caryophyllene was prepared by using carbopol 940 and HPMC by the pH-triggered in situ gelling technique.
- Hydrogels occupy a fundamental role in the landscape of regenerative medicine owing to their multifaceted advantages.
- Their propensity for biocompatibility allows for the emulation of the natural extracellular matrix, fostering an environment conducive to cellular growth, differentiation, and tissue regeneration.
- Notably, their high water content and porous structure closely mirror the native tissue milieu, facilitating crucial functions like nutrient exchange and cellular communication vital for tissue regeneration processes. The efficacy of hydrogels can be contingent upon variables such as their composition, structural attributes, and particular therapeutic use.

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