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DEVELOPMENT AND EVALUATION OF CURCUMIN- NANOPARTICLE LOADED GEL FOR TOPICAL APPLICATION

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ABSTRACT

Curcumin, a natural polyphenolic compound found in turmeric, is recognized for its notable antioxidant and antimicrobial properties, making it a promising candidate for therapeutic applications. This research explores the preformulation, characterization, and biological activity of curcumin nanoparticles (CrNp) in detail. The study assessed essential flow properties, such as particle size, shape, angle of repose, bulk and tapped densities, Carr's index, and Hausner ratio, through bulk characterization. Physical properties of curcumin nanoparticles, including particle size and zeta potential, were analyzed, and their encapsulation efficiency was quantified using UV-Vis spectrophotometry. A standard curve was developed for precise measurement of curcumin concentration in DMSO. Additionally, curcumin gel formulations were evaluated for their physical characteristics, including stability, pH, viscosity, and spreadability. Biological activity testing demonstrated the antioxidant capabilities of curcumin and its antimicrobial effectiveness against *Staphylococcus aureus* and *Escherichia coli*. An in-vitro release study conducted over 72 hours offered valuable insights into the controlled release profile of curcumin nanoparticles. This comprehensive research underscores the therapeutic potential of curcumin nanoparticles, highlighting their effectiveness in drug delivery systems and antimicrobial treatments. The controlled release behavior observed further enhances the prospects for sustained therapeutic benefits. Overall, this study lays a robust foundation for the development of curcumin-based delivery systems, opening avenues for innovative healthcare solutions.

Keywords: Curcumin, Nanoparticles, Antisolvent method, Poloxamer 188, Antibacterial activity, Anti-inflammatory.

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INTRODUCTION

In recent years, nanotechnology has emerged as a powerful tool in pharmaceutical research, providing revolutionary solutions for drug delivery and enhancing therapeutic efficacy [1]. One of the possible natural substances explored in this study is "Curcumin". Curcumin is a polyphenol obtained from the dried roots of *Curcuma longa*, a perennial plant belonging to the *Zingiberaceae* family [2]. Curcumin is extracted from turmeric, a plant native to the Indian subcontinent and southeast Asia [3]. It has been used in various traditional medical systems, including Siddha, Ayurvedic, and Chinese medicine, for treating a wide range of illnesses. Turmeric finds applications in food, medicine, the

textile industry, nutraceuticals, and as a dietary spice [4]. The rhizome's phytochemical assessment has shown the existence of several significant phytochemical components, including minerals, dietary fibers, proteins, volatile oils, and curcuminoids [5].

In 1815, two scientists named Pelletier and Vogel isolated curcumin for the first time at Harvard College Laboratory [6]. Curcumin's molecular weight is 368.38 g/mol and its chemical formula is C₂₁H₂₀O₆. Its structure was first identified in 1910 [7]. Curcumin exhibits absorption maxima at 240nm⁴. It is a type of polyphenol that is commonly known as diferuloylmethane [8].

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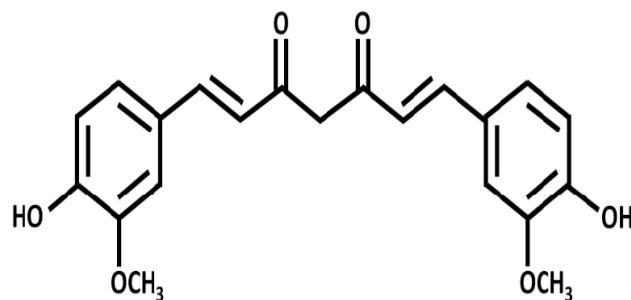


Figure 1: Structure of curcumin.

Diferuloylmethane is classified as a bis- α,β -unsaturated diketone based on its structural composition. This substance exhibits tautomerism between the keto and enol forms. In acidic and neutral environments, the keto form is more common, but the enol form is more stable in alkaline environments. This enol form substance can cross the blood brain barrier (BBB) [9]. Curcumin is a pivotal constituent of the curcuminoid family, distinguished by its unique characteristics. Due to its low molecular weight, curcumin is predominantly soluble in organo-sulphur compound namely, dimethyl sulfoxide (DMSO) and minimally soluble in other organic solvents such as methanol and chloroform. However, it is insoluble in water and ether [10]. Additionally, curcumin remains stable in the stomach's acidic environment [11]. To overcome its poor solubility and enhance bioavailability, various formulations have been developed [12].

Curcuminoids, such as curcumin, are present in various *Curcuma* species. The IUPAC name for curcumin is [1, 7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] [13]. Turmeric also contains a water-soluble peptide called Turmerin, as well as essential oils like zingiberene, turmerones, and atlantones [14]. Turmeric is rich in natural hydrophobic polyphenols. Its active components include approximately 77.0% curcumin (CUR), 17.0% demethoxycurcumin (DMC), and 3.0% bisdemethoxycurcumin (BDMC), along with cyclic curcumin [15]. Among these constituents, curcumin represents the major constituent, while cyclic curcumin serves as the minor component [2]. DMC is another significant constituent with a structural resemblance to curcumin, lacks one of the methoxy groups found in its counterpart [16]. DMC presents itself as a viable option for treating Alzheimer's disease because of its anti-inflammatory, antiproliferative, and anti-cancer characteristics [17]. Bisdemethoxycurcumin (BDMC), which lacks both methoxy groups found in curcumin, is known for its potent antioxidant, anticancer, and antimetastasis properties [18]. Its

efficacy in preventing and treating a variety of ailments is highlighted by research findings. These compounds are all categorized as curcuminoids, and they are associated with various biological processes that contribute to the therapeutic properties of turmeric [15].

Among these, curcumin has garnered significant interest due to its diverse pharmacological properties. These property include anti-inflammatory, antioxidant, anti-aging, and immunomodulatory effects [19]. Additionally, curcumin exhibits anticancer effects [20], wound healing [21], and antimicrobial activities [22].

Antioxidant: Curcumin shows strong antioxidant activity in various in-vitro assays, including DPPH, ABTS, and DMPD radical scavenging, ferric thiocyanate, Fe^{3+} - Fe^{2+} transformation, superoxide anion scavenging, hydrogen peroxide scavenging, and ferrous ion chelation [23].

Wound healing: Curcumin enhances wound healing through multiple mechanisms, including increased expression of transforming growth factor- β 1, modulation of collagen levels, and reduction of reactive oxygen species. It promotes earlier reepithelialization, improved neovascularization, increased cell migration, and higher collagen content in the wound bed [24].

Anti-inflammatory: Curcumin exhibits significant anti-inflammatory activity in both acute and chronic inflammation models, comparable to phenylbutazone in acute tests. Its safety and efficacy have been validated in human trials. Its mechanism of action involves inhibiting various molecules associated with inflammation, including transcription factors, cytokines, protein kinases, and adhesion molecules [25].

Antibacterial activity: Curcumin effectively inhibits periodontopathic bacteria and biofilm formation, inducing bacterial apoptosis-like responses. Combined with Polymyxin B, it broadens antibacterial efficacy. Curcumin-loaded materials show promise for antimicrobial applications. In vivo, curcumin shows therapeutic potential against *Helicobacter pylori* infection, reducing inflammation and gastric damage [24].

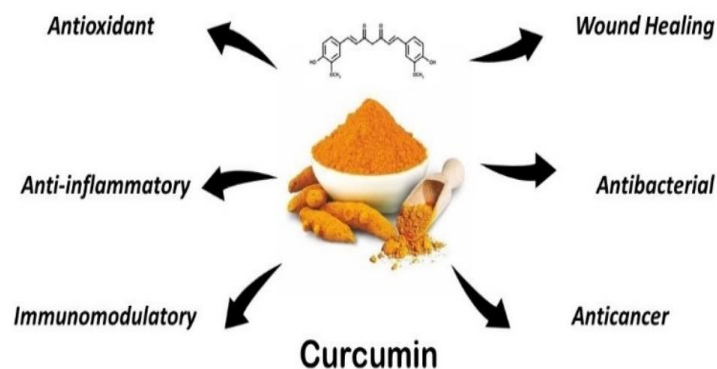


Figure 2: Pharmacological properties of curcumin.

Anticancer activity: Curcumin demonstrates potent anticancer activity, inhibiting angiogenesis and tumor growth in vitro and in vivo. It induces apoptosis in various cancer cells and inhibits proliferation via modulation of transcription factors and growth factor receptors. Curcumin formulations, including nanoparticles, enhance bioavailability and efficacy against prostate cancer cells, showing promising tumor-specific targeting in preclinical models.

Curcumin is categorized as Biopharmaceutics Class II in the pharmaceutical field due to its poor solubility and high permeability [26]. Although it has significant medicinal properties, various formulations have been created to overcome its poor water solubility and limited oral bioavailability [27]. The primary objective is to tackle existing challenges and enhance the therapeutic efficacy of curcumin. A common strategy involves encapsulating curcumin to improve its stability and absorption within the body using nanoscale drug delivery techniques, such as nanocarriers or nanoparticles. In general, these nanoparticle-based methods offer significant advantages, including increased solubility, bioavailability, enhanced circulation, and the ability to overcome physiological barriers [28]. Colloidal systems, especially nanoparticles, effectively deliver small molecules and larger substances like proteins. They enable precise, targeted drug delivery, enhance oral bioavailability, sustain drug effects, solubilize drugs for intravascular delivery, and improve stability against enzymatic degradation.

Conventional dosage forms typically exhibit issues such as high doses with limited bioavailability, instability, susceptibility to the first-pass effect, changes in plasma drug levels, and rapid drug product release [28]. These issues might cause an adverse effect on the shelf life, patient compliance, safety, and efficacy of the product. Novel Drug Delivery Systems (NDDS) integration provide an acceptable solution for these issues [29]. These systems employ innovative techniques and modern

technology. The aim is to deliver active molecules safely and effectively at concentrations that induce the desired pharmacological action [30]. These advanced systems may regulate plasma drug concentrations, therefore extending the duration of desired effects. As a result, as compared to conventional dosage forms, they improve medication performance in terms of safety, effectiveness, and patient adherence. Technological progress has enabled the encapsulation of molecules with defined toxicity profiles in liposomes, nanoparticles, niosomes, phytosomes, etc. [31].

Nanoparticles are now of interest due to their potential health and environmental benefits, diverse applications, and the challenge of quantifying and characterizing them. Nanoparticle (NP) research has focused on developing tissue-targeted delivery strategies for the active form of curcumin over the last 8-10 years [32]. Drugs are either dissolved, entrapped, encapsulated, or linked to the matrix of these colloidal structures, known as nanoparticles, which are made of synthetic or semi-synthetic polymers. Typically, they are between one to one hundred nanometers in size. The term "nanoparticle" refers to both nanospheres and nanocapsules. This term originates from the prefix "nano," derived from the ancient Greek word "νᾶνος" via the Latin "nanus," meaning very small [33]. Curcumin-loaded nanoparticles have been shown in several studies to be an effective therapy for a variety of conditions. A variety of curcumin NPs are being developed to increase stability and bioavailability, such as polymer NPs, solid lipid NPs, polymer micelles, polymer conjugates, nanocrystals, nanogels, liposomes, nano- or micro-emulsions and self-assembly [34]. An intravenous injection of phospholipid vesicles or lipid-nanospheres containing liposomes and curcumin is one possible route of administration [35].

The major goal of this study was to use antisolvent crystallization to synthesize curcumin nanoparticles containing poloxamer. The hypothesis influencing this study was that incorporating curcumin into

nanoparticles would significantly improve its bioavailability [36]. The main reason for curcumin's low bioavailability is its limited solubility and rapid breakdown in the body [37]. As we know that, curcumin is categorized as Biopharmaceutics Class II in the pharmaceutical field due to its poor solubility and high permeability [26]. According to this categorization, over 40% of pharmaceuticals in the pipeline have characteristics with Class II (low solubility–high permeability) or Class IV (low solubility–low permeability) drugs. The above categories of drugs have limited bioavailability due to their slower rates of dissolution and poor solubility. Over recent decades, extensive research has concentrated on a variety of strategies for formulating drugs, aiming to enhance the dissolution rates of these complex compounds [38].

This issue is currently being addressed through the exploration of two key approaches: enhancing curcumin's solubility and shielding it from breakdown. A modern approach in recent times includes creating nanoparticles/microparticles for drugs like curcumin. This method focuses on decreasing particle size, leading to an increased surface area-to-volume ratio. Consequently, this improves the solubility and dissolution rates of molecules with low water solubility, such as curcumin, ultimately enhancing their bioavailability [39]. Curcumin, as a member of Biopharmaceutics Class II, may benefit from these advanced formulation processes, which might lead to advancements in both drug delivery and therapeutic efficacy [26].

There are two primary methods to produce nanoparticles: bottom-up and top-down [40]. Top-down techniques, particularly milling and high-pressure homogenization (HPH), are often used in the pharmaceutical field. Despite their effectiveness, these methods have drawbacks, including high energy input and prolonged processing times. In contrast, the bottom-up strategy, particularly antisolvent crystallization, offers a simple and cost-effective approach. Nanoparticles are formed by combining a solubilized drug in an organic solvent with an antisolvent, often water. This method requires no

expensive equipment, has a short processing time, and allows particle engineering [41, 42].

The anti-solvent precipitation method is also known as de-solvation. It involves reducing the quality of the solvent to induce precipitation of a solute (active ingredient). Supersaturation is achieved by introducing a non-solvent, leading to the precipitation of solutes [43]. The careful selection of solvents and anti-solvents is deemed essential, considering the characteristics of biopolymers or compounds used. The procedure includes steps such as supersaturation generation, nucleation initiation, crystal growth promotion, and coagulation induction [44].

The first stage, supersaturation, occurs when the equilibrium saturation concentration is exceeded by the solute concentration, inducing nucleation. Nanoparticle properties like size, crystallinity, and morphology are influenced by supersaturation conditions. Smaller particle sizes can result from higher supersaturation, but at very high concentrations, an increase in size is observed due to agglomeration [45]. Solvent polarity, surface tension, and system viscosity influence the process. Growth through condensation involves adding molecules to particle surfaces, while growth through coagulation occurs when particles adhere to each other. Ostwald ripening, influenced by solute solubility and concentration gradients, can change particle sizes over time. Particle coagulation is driven by attractive interactions, such as van der Waals or hydrophobic attraction, dominating repulsive interactions. Repulsive interactions can be introduced by stabilizing agents like surfactants to prevent coagulation [44].

The final step involves removing the solvent and anti-solvent phases [46]. Various methods, including freeze-drying, may be employed, but care must be taken to maintain particle integrity and prevent undesired chemical reactions. Particle stability during drying can be enhanced by excipients like lactose or polymers. In short, the anti-solvent precipitation method is a multi-stage process crucial for controlling nanoparticle properties, and careful consideration of factors such as solvent selection and drying techniques is essential for successful nanoparticle production [47].

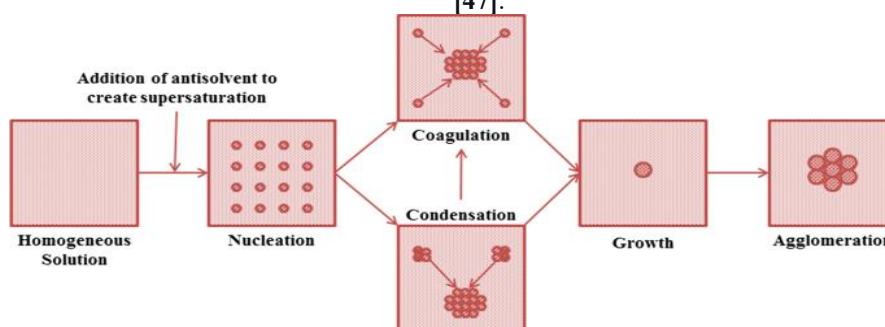


Figure 3: Antisolvent precipitation method stages.

In recent years, polymers have revolutionized our daily lives, particularly in biological applications. The integration of pharmaceutical and polymeric sciences has significantly advanced the development of Novel Drug Delivery Systems (NDDSs) [48]. The introduction of the first polymer-based NDDSs demonstrated scientists' interest in creating new biodegradable polymers through synthesis or design [49]. Over time, further advancement in technology led to the development of the Polymeric Hydrogel System. Polymers consist of long chains that are linked by materials with varying molecular weights. These chains contain a variety of functional groups. They are considered as the backbone of DDSs [50]. Research on polymers has made it easier for scientists to create novel techniques and instruments that both increase the efficacy and lessen the adverse effects of medical treatments. Polymers are crucial because they serve as binders and stabilizers in DDSs, as well as controlling the rate at which drugs are released [51]. Poloxamers are also called Pluronics. They are synthetic polymers made up of three-block co-polymers of polyethylene oxide and polypropylene oxide. They are amphiphilic in nature because they include both hydrophilic and hydrophobic groups [52].

The presence of an alkaline catalysts, potassium hydroxide or sodium hydroxide, led to the composition of poloxamers of different co-polymers through the sequential addition of monomers i.e., propylene oxide and ethylene oxide, resulting in varying Hydrophilic and Lipophilic Balance (HLB) values. They were earlier developed for the industrial purposes but they find the application in medical field as well [53]. These are non-ionic surface active blocks dissolve in the water [54]. Poloxamer with 80% ethylene oxide is commonly used to increase drug solubility in solid dispersions [55].

The most commonly used poloxamers are poloxamer-188 and poloxamer-407. The first commercially available poloxamer is Poloxamer-188. It is known for its safety in medical and clinical applications [56]. Poloxamers were initially utilized for various pharmaceutical applications. They were first employed as an emulsifier in 1957 in Lipomul I.V., primarily for patients experiencing difficulties in digesting food [57]. They are generally non-toxic and non-irritating, making them suitable for use as wetting agents in ointments and suppositories [58]. Poloxamer-188 has a molecular weight of approximately 8.4 kD (kilodaltons) and is 80% hydrophilic. Compounds or materials with molecular weights exceeding 5000 daltons are typically unable to cross the blood-brain barrier. However, when injected into the peritoneum, poloxamer-188 can penetrate the

blood-brain barrier and be eliminated unchanged from the body via the kidneys [56].

Poloxamers are used to increase the solubility, bioavailability, and dissolution of poorly water-soluble drugs such as ibuprofen [59]. Poloxamer-188, known for its low melting point and surfactant properties, is extensively employed in the preparation of solid dispersion particles [55]. It is also used to prevent protein degradation in required formulations. However, at elevated temperatures, both poloxamer-188 and poloxamer-407 may undergo degradation due to auto-oxidation and chain cleavage [60]. In the preparation of curcumin nanoparticles, poloxamer 188 serves as a stabilizer, effectively enhancing the formulation's stability, solubility, and dissolution of curcumin [61].

MATERIALS AND METHODOLOGY

Materials

Curcumin (Extraction), Dimethyl sulfoxide (I.K. Enterprises), and Poloxamer 188 (China) were obtained as gift. Carbapol (China), Hydroxypropyl Methylcellulose (Merck Chemicals), Triethanolamine (J.K. Enterprises), Propylene Glycol (AD Chemicals), and Glycerin (Oleocorp Pakistan Ltd) were all of analytical grade. Measuring cylinder, beaker, syringes, pipette, sucker, stirrer and microspatula. Sonicator (LAB-O-MED Italiano), analytical balance (Bante Instruments), and magnetic stirrer.

METHODOLOGY

Extraction of the Curcumin

The extraction of curcumin from dried rhizomes of *Curcuma longa* involves several sequential steps. Firstly, the rhizomes are dried at 50°C for 2 hours and then milled to a fine powder using a sieve of 40 mesh. The powdered rhizomes are subjected to solvent extraction in a Soxhlet apparatus using 95 % ethanol as the solvent. The extraction process occurs for 4 hours at 60 °C, followed by cooling to room temperature. The resulting solution is filtered through Whatman filter paper #1 to remove any insoluble impurities. Subsequently, the filtrate is concentrated using a rotary evaporator. The concentrated solution is then dried at 40 °C until a constant weight is achieved, indicating the complete removal of solvent. Finally, the dried curcumin extract is obtained and ready for further analysis [62].

Preparation of Curcumin Nanoparticles

The procedure for preparing curcumin-loaded nanoparticles began by weighing the appropriate amount of poloxamer 188 and dissolving it in deionized water kept in a sonicator for 10 minutes, creating a polymer solution. Meanwhile, curcumin was weighed and dissolved in DMSO at the desired concentration, forming the drug solution. The drug solution was then gradually added drop by drop to the poloxamer solution under continuous mixing on a hotplate to ensure proper mixing. The resulting

mixture was sonicated for an additional 10 minutes to ensure a clear solution devoid of any solid particles. Subsequently, the formulation was placed on a hot plate stirrer for approximately 20 minutes to allow for the evaporation of the organic solvent DMSO. Once the solvent was removed, the curcumin-loaded nanoparticles were ready for further characterization [63].

Curcumin Nanoparticle Gel-based Preparation

The prepared curcumin nanoparticle (CrNp) was used by weighing the required amounts of carbopol and hydroxypropyl methylcellulose (HPMC) and incorporate them into the CrNp lyophilized powder. Thoroughly mixed the excipients into the formulation and allow the solution to stand for 4 hours to ensure accurate component integration. Subsequently, add triethanolamine, propylene glycol, and glycerin one by one into the solution, mixing the formulation after each addition of excipient. Upon completion, the CrNp gel is fully prepared and ready for further utilization or characterization [64].

Optimization of CrNP

The formulation method was optimized by Box Behnken design of expert. The independent factors were Drug concentration (mg), Polymer concentration (Poloxamer mg) and Sonication time (min) and dependent factors were particle size and % entrapment efficiency.

CHARACTERIZATION

Bulk Characterization

Flow Property

In its purest form, curcumin is present as a bright yellow-orange powder. Particle size and shape, angle of repose, bulk and tapped densities, Carr's index, and Hausner ratio are some of the factors that might affect its flow properties [65].

Particle Size and Shape

The particle size distribution and shape of curcumin particles can significantly affect their flow properties. Generally, smaller particles of curcumin with spherical shapes exhibit superior flowability in comparison to larger particles that are irregularly shaped [65].

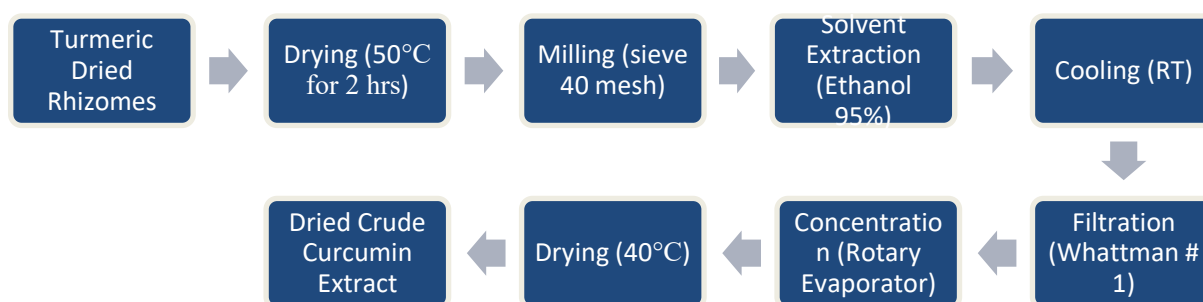


Figure 4: Flowchart of curcumin extraction from turmeric rhizomes.

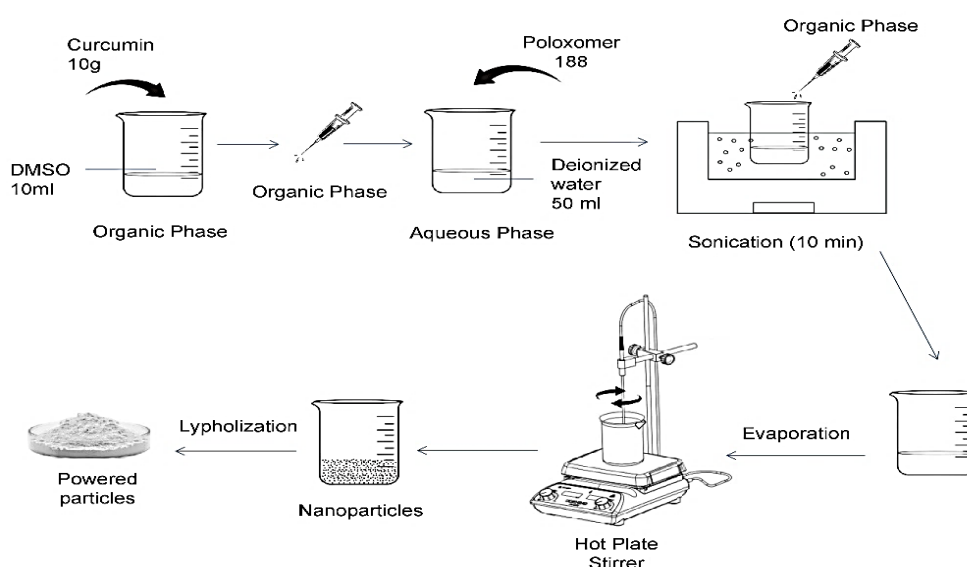


Figure 5: Formulation of curcumin nanoparticles.

Table 1: Formulation factor and responses for optimization by Box-Behnken design.

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A: Drug	B: Poloxamer 188	C: Sonication Time	EE	PS
		mg	mg	min	%	nm
2	1	6	3	15	40	387
12	2	5	5	20	84	112
7	3	4	4	20	84	110
5	4	4	4	10	76	154
14	5	5	4	15	45	374
10	6	5	5	10	70	323
11	7	5	3	20	48	349
4	8	6	5	15	34	441
3	9	4	5	15	38	401
6	10	6	4	10	31	421
15	11	5	4	15	49	372
1	12	4	3	15	32	406
8	13	6	4	20	41	379
9	14	5	3	10	32	410
13	15	5	4	15	48	365

Factors

Factor	Name	Units	Type	Sub Type	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	Drug	mg	Numeric	Continuous	4.00	6.00	-1 ↔ 4.00	+1 ↔ 6.00	5.00	0.7559
B	Poloxamer 188	mg	Numeric	Continuous	3.00	5.00	-1 ↔ 3.00	+1 ↔ 5.00	4.00	0.7559
C	Sonication Time	min	Numeric	Continuous	10.00	20.00	-1 ↔ 10.00	+1 ↔ 20.00	15.00	3.78

Angle of Repose

The greatest angle formed between the horizontal surface and the slope of the material heap when poured onto a flat surface is called Angle of repose. A standard funnel was positioned 40 mm above a flat surface, where a sheet of millimeter paper was laid. 5 grams of turmeric powder were carefully poured into the funnel without any disruption or movement. The funnel remained stationary while being blocked by a dry finger. The powder flowed freely to form a cone-shaped pile on the millimeter paper. The angle of repose was determined using the cone's height (h) in centimeters and the radius (r) of the cone's base in centimeters, calculated as follows [65].

$$\theta = \tan^{-1}\left(\frac{\text{height}}{\text{radius}}\right) \quad [65]$$

Bulk and Tapped Density

Both bulk and tapped density are important parameters of curcumin powder. Firstly, Bulk

density refers to the mass of a powder divided by its bulk volume, including the void spaces between particles. It's measured by filling a cylindrical container with a known volume with the powder and weighing it [66].

$$\text{Bulk Density} = \frac{\text{Weight of curcumin powder}}{\text{Volume of curcumin powder}} \quad [66]$$

While Tapped density is the maximum density achievable by tapping a container containing the powder until little further volume change occurs. It gives an indication of how closely packed the particles can become under applied stress [66].

$$\text{Tapped Density} = \frac{\text{Weight of curcumin powder}}{\text{Minimum volume occupied after tapping}} \quad [66]$$

Carr's index & Hausner Ratio

The powder flow qualities are represented by the Hausner ratio (HR) and Carr's index (CI). Both were calculated by measuring the bulk and tapped

densities of 5 g of powder in a 25 mL measuring cylinder. The density values were then used to compute the compressibility index and Hausner ratio as follows [67].

The CI is a measure of the powder's ability to decrease in volume under pressure. It is determined using the following formula

$$\text{Carr's index (CI)} = 100 \times \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \quad [68]$$

The ratio of tapped density to bulk density is used to calculate the Hausner ratio (HR), which shows the powder's flowability

$$\text{Hausner ratio (HR)} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \quad [68]$$

Sieve Analysis

One technique for separating powder particles according to size is powder sieve analysis [69]. In this investigation, the Pharmacopoeia Hungarica VII (Ph. Hg. VII) requirements were followed in order to manually evaluate the particle size distribution of turmeric using conventional test sieves. In this study, the particle size distribution of turmeric was manually examined using conventional test sieves following the recommendations specified in the Pharmacopoeia Hungarica VII. 30g ground turmeric powder was sieved for 5 minutes, and the amounts of powder retained and passed through each sieve were recorded. The particle-size distribution was then obtained by calculating and expressing the retained masses of powders on the sieves as percentages [65].

Solubility Analysis

Curcumin is a polyphenolic compound found in turmeric that exhibits limited solubility in water. However, curcumin readily dissolves in organic solvents dimethyl sulfoxide (DMSO) and slightly dissolves in methanol due to their non-polar nature [70]. In this procedure, 2mg of curcumin powder is dissolved in 2ml of DMSO until completely dissolved in the organic solvent. Similarly, 2mg of curcumin are dissolved in 2ml of methanol. The solubility of curcumin in each solvent is then compared [65].

Particle size & Zeta potential Analysis

The analysis of particle size was conducted by using a method where a 2 mL formulation was prepared specifically for this purpose. A nanozetasizer was employed to measure the particle size of a formulation obtained via antisolvent evaporation. Subsequently, measurements were performed in triplicate, and zeta potential were calculated [61].

Entrapment Efficiency (E.E)

The entrapment efficiency (E.E) of curcumin nanoparticles was determined by dissolving the nanoparticles in 1 ml of DMSO and measuring the absorbance at 425 nm using a UV-Vis

spectrophotometer. A standard calibration curve of curcumin in DMSO was used to estimate the curcumin concentration. The EE was calculated using the formula

$$\%EE = \frac{\text{Total amount of Curcumin-Free Curcumin}}{\text{Total amount of Curcumin}} \times 100 \quad [71]$$

Standard Curve Analysis

Standard curve analysis is used to characterize curcumin in DMSO. This is done by preparing a 10 mg stock solution in 10 mL of DMSO, which is then diluted five times. Absorbance at 425 nm is measured using a double-beam spectrophotometer for each dilution and a blank solution. A calibration curve is constructed by plotting the concentration of curcumin against its corresponding absorbance values, obtained from the dilutions. Linear regression analysis is performed on the data to generate the equation of the calibration curve, facilitating the determination of curcumin concentration in unknown samples based on their absorbance readings at 425 nm. Quality control ensures the accuracy of the quantitative analysis [72].

$$y = mx + b \quad [72]$$

Where **m** is slope of straight line and **b** is the y-intercept.

Characterization of Curcumin (CrNp) Gel

Physical Appearance (Color, Clarity, Surface Texture)

The prepared gel was visually evaluated for its color, transparency, uniformity, and overall appearance. These evaluations were conducted to ensure that the gel met the desired quality standards [73].

Stability Studies

After preparation, the gel was stored at room temperature (40°C) for one month, with observations made on days 1, 15, and 30. The stability of the gel was evaluated by examining its appearance over this period [73].

pH Analysis

A pH meter was used to determine the pH of the gel's 1% aqueous solution. 100 mL of distilled water was used to dissolve one gram of gel per meter, which was then stored for two hours. The pH of each formulation was measured three times, and the average was determined [73].

Viscosity

In the assessment of rheological properties, the curcumin gel sample was transferred into a beaker and subjected to rotational testing at 10 rpm using a Brookfield viscometer at a controlled temperature of 25–27°C [73].

Spreadability

One gram of the curcumin gel was evenly distributed between two glass slides in order to test the gel's spreadability. The gel was covered with a pre-weighed plate, then incremental weights were added gradually until the gel stopped spreading.

The cumulative weight applied and the time taken for gel diffusion was recorded separately. The spreadability of the gel was then calculated using the formula [74].

$$\text{Spreadability} = \frac{(\text{Mass} \times \text{Length})}{\text{Time}} \quad [74]$$

Biological Activity

Antioxidant Activity

An in vitro antioxidant activity was performed using two controls. One was the negative control, ascorbic acid, which doesn't undergo oxidation, while the other was the positive control, DPPH, 2,2-diphenyl-1-picrylhydrazyl, a dark purple substance, which undergoes complete oxidation. Both controls were prepared as 0.02% solutions using methanol as solvent, i.e., 0.02 g of ascorbic acid and DPPH in 100 ml of methanol, separately. A 2 mL solution of ascorbic acid was prepared and labelled as test sample 1. A 6 ml solution of DPPH was prepared, from which 2 ml was labelled as test sample 2. A curcumin formulation (1 mg/ml) was diluted to 100 µg/ml and 10 µg/ml. Test samples 3 and 4 were prepared by adding 0.1 ml of these dilutions to 1.9 ml of DPPH solution. Absorbance at 517 nm was measured after 1 and 2 hours. Test samples 3 and 4 changed from dark purple to light pink, indicating curcumin's antioxidant activity [61].

Antimicrobial Activity

The antibacterial activity of the nanocurcumin formulation against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* bacteria was assessed by in vitro antibacterial assays. The technique employed for this purpose was the disc diffusion method. After evenly swiping the swab over the plate's surface three times, the Petri plates were rotated by around 60° to introduce the corresponding bacteria into the agar plates. Finally, the periphery of the agar surface was swabbed. Sterile filter paper discs, each 7 mm in size, were placed at an equal distance on the agar plates. The discs were soaked in the nanocurcumin formulation for a certain time interval and then placed onto the agar surface. A 24-hour incubation period was then observed for the plates at 37°C. The inhibition zones were observed and measured using a scale in millimeters. The tests were repeated three times to minimize errors [75].

Invitro Release Study

In order to perform the drug release studies, 0.5 mL of from the curcumin nanoparticle loaded gel was placed in a dialysis bag molecular weight cut-off of 3000 Dalton and submerged in 50 mL of pH 5.5 phosphate-buffered saline (PBS) in a beaker. The solution was constantly stirred at 25 °C. Samples were taken at time intervals (1, 2, 4, 6 hours) over 48 hours, with each sample averaging 1 ml. A UV-visible spectrophotometer set at 425 nm was used to measure the amount of curcumin released. The total percentage release was calculated [76].

RESULTS AND DISCUSSIONS

Flow Properties

The flow properties of curcumin, a vibrant yellow-orange powder, were evaluated through various parameters including particle size and shape, angle of repose, bulk and tapped densities, Carr's index, and Hausner's ratio.

Particle Size and Shape was observed that smaller and spherical particles of curcumin exhibited good flowability as compared to larger and irregular shaped particles. The angle of repose for the powder was found to be 29.24°, indicating a favorable flowability according to standardized criteria. This value was obtained using the formula

$$\theta = \tan^{-1} (h/r)$$

where h is the cone's height (1.4 cm) and r is its base's radius (2.5 cm). Moreover, the bulk density of the curcumin powder was calculated to be 0.625 g/ml, while the tapped density was found to be 0.689 g/ml. This indicates that the powder has a tendency to pack more densely under tapping conditions compared to its bulk state.

While the Carr's index (CI) is a measure of the flow properties of a powdered material. A low value of CI indicates favorable flowability, while a high value suggests poor flow properties. In this study, the CI of curcumin was found to be 9.28%, which indicates excellent flow properties. Similarly, the Hausner's ratio (HR) is another indicator of powder flowability. The Hausner's ratio of curcumin was calculated to be 1.1024, further corroborating its excellent flowability. These results suggest that curcumin possesses favorable flow properties. These results collectively affirm that curcumin exhibits highly favorable flow properties, which can be attributed to its particle size, shape, and other physical characteristics [77].

Solubility Analysis

Curcumin exhibits significantly greater solubility in dimethyl sulfoxide (DMSO) compared to methanol. When 2 mg of curcumin powder was dissolved in 2 mL of DMSO, the compound readily dissolved, indicating its high solubility in this organic solvent. Conversely, when the same amount of curcumin was dissolved in methanol under identical conditions, only slight dissolution was observed. This discrepancy in solubility can be attributed to the non-polar nature of DMSO, which facilitates the dissolution of the hydrophobic curcumin molecules more effectively than the relatively polar methanol.

Particle Size Distribution & Zeta Potential Analysis

The particle size analysis of the curcumin nanoparticles (CrNp) revealed two distinct peaks. The first peak was observed at 12.81 nm, while the second peak was at 112 nm. Both of these values fall within the normal expected range of 1 to 200

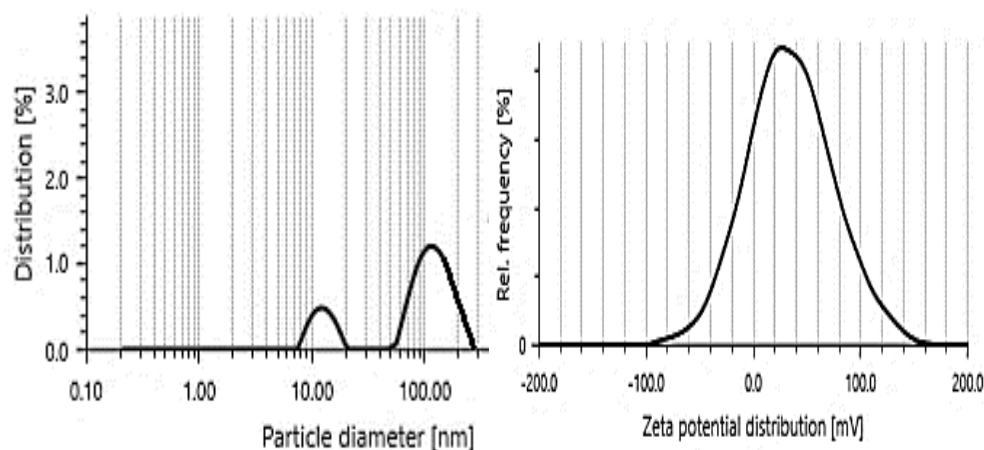


Figure 6: Particle size and zeta potential graphical presentation.

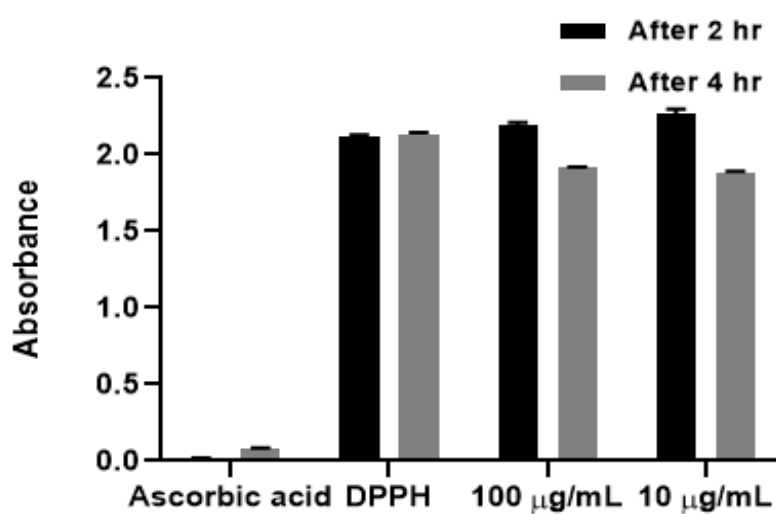


Figure 7: Antioxidant activity graph.

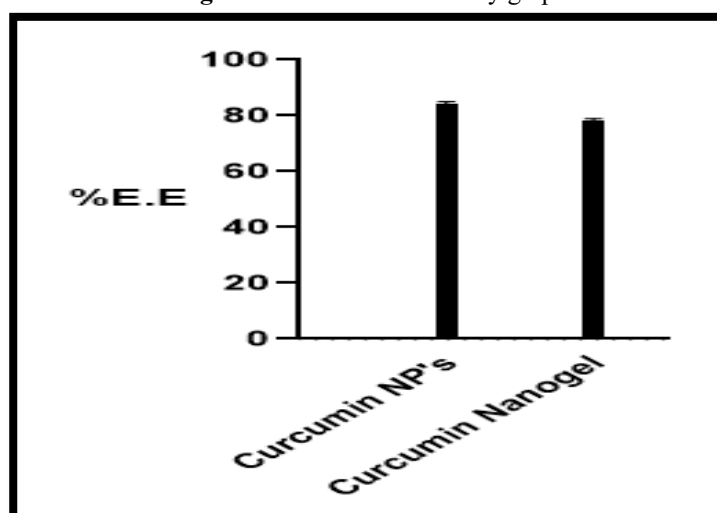


Figure 8: Stability studies of CrNp.

nm for nanoparticle size, indicating that the CrNp are appropriately sized for potential biomedical applications. The zeta potential of the CrNp was

measured to be -0.1 mV, which is within the normal range of -10 mV to +10 mV. Zeta potential is an important parameter as it provided insight into

the stability of colloidal dispersions. A zeta potential close to zero, such as -0.1 mV, suggests that the CrNp might have low electrostatic repulsion, which can lead to aggregation over time.

Entrapment Efficiency

Loading efficiency was calculated for three samples of curcumin loaded in nanoparticles at a concentration of 1 mg/ml. The loading efficiencies for the three samples were found to be 84.05 %, 84.34 %, and 83.91 %. The entrapment efficiency (E.E) of curcumin nanoparticles demonstrated a high loading capacity, with values ranging from 84.34 % to 83.91 %. This falls within the optimal range of less than 90 %, indicating successful entrapment of curcumin within the nanoparticles [78].

Standard Curve Analysis

Standard Curve Analysis characterized curcumin in DMSO. A calibration curve relating concentration to absorbance at 425 nm was constructed, showing a strong linear relationship $R^2 = 0.9883$. The absorbance values ranged from 0.038 to 1.447 for concentrations between 0.0001 and 1 mg/ml. This method is essential for the accurate determination of curcumin concentration in unknown samples, playing a crucial role in quality control across various applications. Specifically, the graph displays a calibration curve for CrNp, plotting concentration (mg/mL) against absorbance (nm) and showing a robust linear relationship with an R^2 value of 0.9948, described by the equation $y=1.3858x+0.0686$. This direct proportionality facilitates the determination of unknown sample concentrations based on their absorbance readings.

Antioxidant Activity

The antioxidant activity assay used ascorbic acid as the negative control and DPPH as the positive control, both in 0.02% methanol solutions. Curcumin (1 mg/mL) was diluted to 100 µg/mL and 10 µg/mL, and added to DPPH solution. Absorbance at 517 nm was measured after 1 and 2 hours, showing curcumin's antioxidant activity through decreased absorbance and color change, while controls remained stable. This suggests curcumin's potential in scavenging free radicals and reducing oxidative stress [79]. The graph titled "Antioxidant Activity" illustrates that ascorbic acid's absorbance minimally changed from 0.01 to 0.02, DPPH's absorbance slightly increased from 2.102 to 2.139, and curcumin dilutions (100 µg/mL and 10 µg/mL) significantly decreased from 2.183 to 1.808 and 2.255 to 1.784, respectively.

Curcumin Gel

The curcumin gel appeared light yellow, indicating the presence of curcumin constituent. It displayed excellent transparency and homogeneity, with no visible signs of separation or particulate matter. The surface texture was smooth and viscous, facilitating easy application and absorption.

pH of Gel

The pH of the gel was determined using a 1% aqueous solution. One gram of the gel was dissolved in 100 mL of distilled water and left to stand for 2 hours to ensure complete dissolution and equilibration. The pH measurements were conducted in triplicate, yielding consistent values of 6.94 each time. The average pH value was thus 6.94, which falls within the acceptable range of 6.9 - 7.2, close to neutral. This neutral pH range is desirable for topical formulations as it aligns well with the skin's natural pH, minimizing the risk of irritation and maintaining the skin's acid mantle.

Viscosity and Spreadability

The curcumin gel exhibited a viscosity of 2200 ± 120.12 cps, measured with a Brookfield viscometer at 25 ± 1 °C and 10 rpm [80]. The spreadability was 61.2 ± 1.7 g·cm/sec [81], determined by placing 1 gram of gel between two glass slides and adding weights until spreading ceased. These properties indicate good extrudability and spreadability, essential for effective topical application. The near-neutral pH ensures skin compatibility, while the high viscosity and excellent spreadability support easy and uniform application, confirming the gel's suitability for topical use.

Stability Studies

The stability of the curcumin nanoparticle and curcumin nanogel was evaluated by storing it at room temperature (40 °C) immediately after preparation and observing its properties over a period of 15 days. Over the 15-days observation period, the gel maintained its uniformity without any signs of separation, bubble formation, or the appearance of particulate matter. The color and pH of the gel remained consistent throughout the study. These findings indicate that the curcumin gel formulation has excellent physical stability under ambient conditions. The lack of significant changes in visual appearance or consistency suggests that the gel can be stored at room temperature without compromising its integrity.

The stability graph indicates a decline in the entrapment efficiency (E.E) of curcumin nanoparticles over time. EE decreases from 84.05 % on Day 1 to 82.34 % on Day 7, and further to 79.31 % by Day 15. This trend suggests a gradual reduction in the stability of the entrapped curcumin within the nanoparticles over the 15-day period.

Antibacterial Activity

The nanocurcumin formulation exhibited significant antibacterial activity against both *Staphylococcus aureus* and *Escherichia coli*. The inhibition zones for *S. aureus* were measured at 29.88 ± 0.53 mm, while those for *E. coli* were 24.54 ± 1.12 mm [82]. These results indicate that nanocurcumin has a stronger antibacterial effect against Gram-positive bacteria compared to Gram-negative bacteria. Further, the stability of the

antibacterial activity of Cur-Np over time was evaluated.

Nanocurcumin has been reported to be more effective against Gram-positive bacteria than Gram-negative bacteria and fungi. This higher efficacy against Gram-positive bacteria can be attributed to their lack of a protective outer membrane, making them more susceptible to antimicrobial agents despite having a thicker peptidoglycan layer. The findings suggest that nanocurcumin could be a potent antibacterial agent, particularly against Gram-positive bacteria such as *Staphylococcus aureus*.

Invitro Release Profile

The in vitro release profile of curcumin nanoparticles from the curcumin nanoparticle loaded gel in PBS at pH 5.5 demonstrated sustained release characteristics over 48 hours, with the percentage release increasing steadily to 24.8 %. This indicated controlled and prolonged release, suitable for sustained drug delivery application [71]. The graph titled "In vitro release of CrNp in PBS (pH 5.5 and 25 °C)" shows a steady increase in curcumin release from 10.12 % at 1 hour to 24.8 % at 48 hours, with a trend line equation of $y=3.519x+6.351$ and an R^2 value of 0.9832, indicating a strong linear relationship.

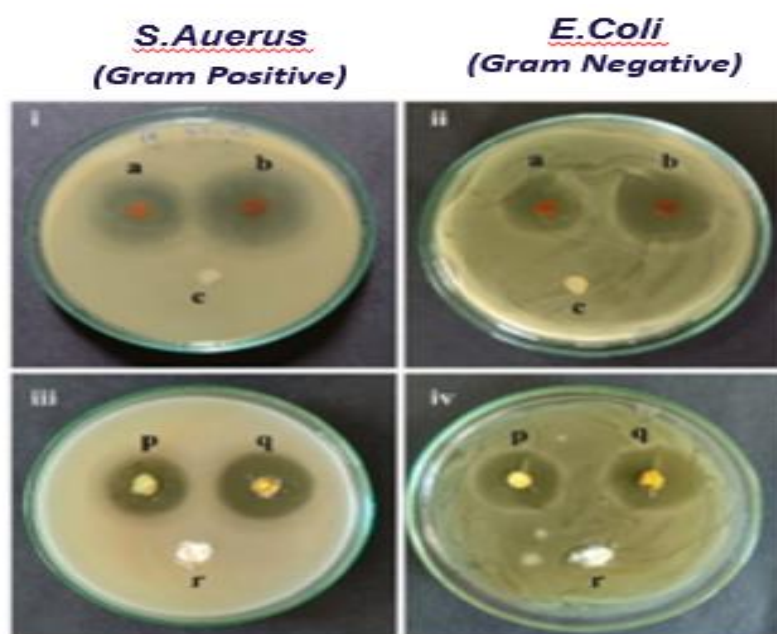


Figure 9: Antibacterial activity of nanocurcumin and their respective gel formulation.

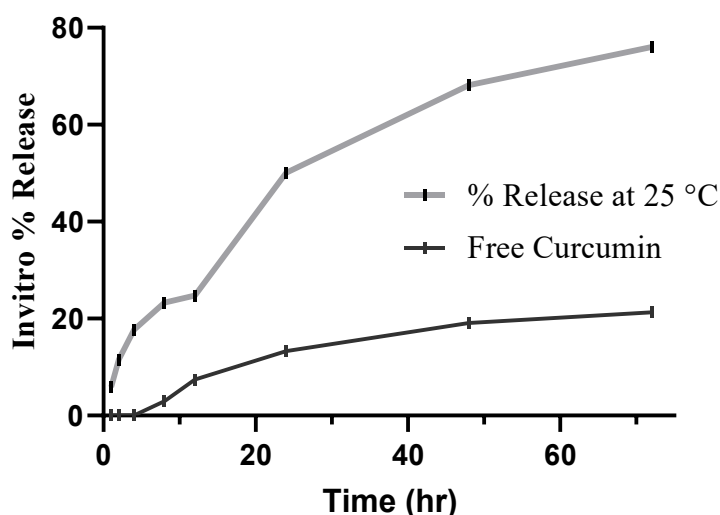


Figure 10: In vitro release of curcumin from the curcumin nanoparticle loaded gel in PBS at pH 5.5 and 25 °C.

CONCLUSION

In conclusion, the formulated curcumin nanoparticle gel demonstrated significant potential as a therapeutic agent, showcasing robust antioxidant and antibacterial properties achieved through the antisolvent evaporation method. This study provided a comprehensive evaluation of the preformulation characteristics, biological activity, and in vitro release profile of curcumin nanoparticles at pH 5.5. The findings revealed favorable flow properties, excellent solubility in organic solvents, and efficient encapsulation of curcumin into nanoparticles. The gel formulation exhibited desirable attributes such as stability, neutral pH, optimal viscosity, and good spreadability, confirming its suitability for topical applications. Notably, the in vitro release profile showed an improved release of up to 80% over 72

hours, highlighting its potential for controlled and sustained drug delivery. These results, combined with the demonstrated antimicrobial efficacy, position the curcumin nanoparticle gel as a promising candidate for innovative pharmaceutical and therapeutic applications, particularly in the realm of topical treatments.

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