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Formulation and Efficacy of Neem, Turmeric, and Onion Extracts for Hyperpigmentation Treatment

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ABSTRACT

Herbal ingredients have been utilized for centuries in traditional medicine across various cultures due to their healing, therapeutic, and cosmetic benefits. Turmeric is a rhizomatous perennial herb having primary and secondary rhizomes that can be present in different forms, from spherical to slightly conical, hemispherical, and cylindrical. Azadirachta indica L., (Fam. Meliaceae) also known as 'Neem', is commonly found in Indian sub-continents and most of the African countries as they can easily be grown in tropical and sub-tropical forests. A. cepa is a biennial plant with adventitious and fibrous roots and 3–8, distichous, glaucous leaves. Hyperpigmentation is a condition where certain areas of the skin develop darker patches due to an overproduction of melanin. Nanogels are nanoscale-sized, gel-based carriers that are used to deliver active ingredients more effectively to targeted areas of the skin. The present study aimed to formulate a polyherbal nanogel formulation, combining the potent properties of onion (Allium cepa), neem (Azadirachta indica), and turmeric (Curcuma longa), can provide a highly effective solution for reducing hyperpigmentation. The transverse section of A. indica showed presence of cortex and vascular bundles. Powder characteristic study showed presence of stone cells, stomatal cells, trichomes and calcium oxalate crystals. Microscopic analysis of the powder (C. longa) revealed the presence of fibres, simple starch grains mostly oval and a few rounds were abundantly found. Spiral vessels were also observed. Cells with oleo resin were also found. The optimized nanogel was shown release of more than 90 % (93.498 %) of drug in 12 hr. From skin permeation study using goat ear pinna, it was found that the optimized formulation of nanogel can pass through the skin and had a 47.178mg±0.05 of drug release showing sustained manner in 24 hrs.

Keywords: Nanogel, Hyperpigmentation, Ex-vivo permeation, Neem, Turmeric, Onion.

1. INTRODUCTION

Herbal ingredients have been utilized for centuries in traditional medicine across various cultures due to their healing, therapeutic, and cosmetic benefits. Historically, all medicines were derived from natural sources, especially plants, which provided substances with specific therapeutic effects. Medicinal plants can be defined as those plants that are used for their potential health benefits. Recently, there has been a growing interest in the use of herbal ingredients in skincare products, largely due to their natural effectiveness and reduced risk of side effects compared to synthetic chemicals. The active compounds present in these plants are known to offer significant anti-inflammatory, antioxidant, antimicrobial, and skin-regenerating properties, making them useful for treating skin conditions such as acne, hyperpigmentation, aging, and dryness. According to the World Health Organization (WHO), approximately 80% of the population in developing countries relies on traditional medicines, with medicinal plants playing a crucial role in their healthcare systems.

Turmeric commonly known as turmeric, is a flowering plant in the ginger family native to Southeast Asia, particularly India. Turmeric is a rhizomatous perennial herb having primary and secondary rhizomes that can be present in different forms, from spherical to slightly conical, hemispherical, and cylindrical. The rhizomes contain a thin, slightly brown peel (peridermis layer) having an orange-yellow flesh [1]. It is used as an herbal medicine for rheumatoid arthritis, chronic anterior uveitis, conjunctivitis, skin cancer, small pox, chicken pox, wound healing, urinary tract infections, and liver ailments. [2]

Azadirachta indica L., (Fam. Meliaceae) also known as 'Neem', is commonly found in Indian sub-continents and most of the African countries as they can easily be grown in tropical and sub-tropical forests.[3] Neem tree is known for its several therapeutic properties and known for curing diseases such as acne, stomach infection, fever, and more. Ayurveda states that

neem balances kapha and pitta out of the three doshas in the human body. [4,5]

A. cepa is a biennial plant with adventitious and fibrous roots and 3–8, distichous, glaucous leaves. The bulb is made of concentric, enlarged fleshy leaf bases. The outer leaf base dries and becomes thin and variously coloured, forming the protective coat, while the inner leaf bases thicken when the bulb develops. The mature bulb can be globose, ovoid or elongate and its size varies depending on the cultivar. A. cepa is known to contain many vitamins and minerals and is rich in sulphur amino acids. Onion is rich in several phytonutrients that are recognized as important elements of the Mediterranean diet but it has received attention also for its biological properties and potential application in the treatment and prevention of a number of diseases. [6,7]

Neem, onion, and turmeric are three traditional herbs known for their wide-ranging benefits for skin health. The combination of these herbs in a single formulation could provide a powerful approach to treating hyperpigmentation. This research paper aims to review the existing literature on the properties of neem, onion, and turmeric and how they contribute to a polyherbal formulation for hyperpigmentation. [8]

Hyperpigmentation is a condition where certain areas of the skin develop darker patches due to an overproduction of melanin. It manifests in various forms, such as age spots, melasma, acne scars, and post-inflammatory hyperpigmentation. While many commercial treatments are available, natural products have gained popularity due to their minimal side effects and holistic benefits. Among the many natural remedies, polyherbal formulations are increasingly favoured for their synergistic effects, where the combined action of multiple herbs enhances the therapeutic outcomes. [9]

Nanogels are nanoscale-sized, gel-based carriers that are used to deliver active ingredients more effectively to targeted areas of the skin. The small size of the nanocarriers allows for better absorption, controlled release, and deeper penetration of the active ingredients into the dermal layers, enhancing their efficacy. [10] In the case of hyperpigmentation, nanogels provide

a promising platform to encapsulate and deliver the herbal extracts of onion, neem, and turmeric in a manner that ensures maximum benefits with minimal irritation. [11]

When incorporated into a polyherbal gel, utilizing turmeric, neem and onion, it works synergistically to target pigmentation, such as inflammation, melanin overproduction and oxidative stress. The gel's soothing and anti-inflammatory effects help calm irritated skin, while curcumin's ability to inhibit tyrosinase, the enzyme responsible for melanin production, helps to reduce excess pigmentation. [12] The gel form provides several advantages, including easy application, quick absorption, and non-greasy texture. The combination of these three herbs allows for a multi-targeted approach to skin lightening, acne scar reduction, and overall skin rejuvenation.

The present study aimed to formulate a polyherbal nanogel formulation, combining the potent properties of onion (*Allium cepa*), neem (*Azadirachta indica*), and turmeric (*Curcuma longa*), can provide a highly effective solution for reducing hyperpigmentation. Alongwith the formulation, pharmacognostical screening of the herbal ingredients was done. By utilizing nanotechnology, the therapeutic compounds in these herbs can be delivered more efficiently into the skin, ensuring deeper penetration and enhanced bioavailability. The anti-inflammatory and antimicrobial properties of neem help reduce inflammation and prevent acne-related pigmentation, while the melanin-reducing effects of onion and turmeric work synergistically to lighten dark spots. Furthermore, the healing properties of all three ingredients promote skin regeneration and texture improvement.

2. MATERIALS AND METHODS

2.1 Materials

Azadirachta indica, *curcuma longa* and *allium cepa* extract was obtained and authenticated from Green Vibes Biotech, New Delhi. All other reagents used were of analytical grade. Pluronic F127, Polyethyleneimine and Carbonyl Diimidazole were purchased from CDH, New Delhi.

2.2 Methods

2.2.1 Morphological Evaluation

The macroscopic examination of the *Azadirachta indica leaves, Allium cepa* and C*urcuma longa* rhizomes were conducted by analyzing their exterior characteristics, including color, shape, size, odor, and surface. The leaves of *Azadirachta indica* leaves, *allium cepa* and *curcuma longa* rhizomes plants were seen under diffused daylight condition using a magnifying lens. The plants material was examined in order of softness or hardness, brittleness and the characteristics of the shattered surface, such as whether it exhibited a fibrous, smooth, rough, or granular look. [13]

2.2.2 Microscopical Studies

Microscopical studies of the transverse section and powder of *Azadirachta indica leaves, allium cepa* and *curcuma longa* rhizomes were carried out. Transverse portions of fresh leaves of *Azadirachta indica* leaves, *allium cepa* and *curcuma longa* rhizomes were cut with a sharp blade, ensuring a thin and precise cut. Fine sections were cleared with chloral hydrate solution.

The sections underwent staining with different staining reagents such as phloroglucinol and followed by addition of diluted hydrochloric acid to it. The sample was permitted to remain undisturbed for approximately five minutes and finally affixed with glycerin. Several characteristics transverse section of the leaves of *Azadirachta indica* leaves, *allium cepa* and *curcuma longa* rhizomes were observed. The photographs were captured. [13,14,15]

2.2.3 Determination of Physicochemical Parameters

Physicochemical standards like extractive value, total ash, loss on drying were determined as per the standard procedures stated in IP-2022 (Indian Pharmacopoeia 2018, Volume 2). The procedures of the tests performed are explained below.

Determination of Ash Value

The objective of ash value is to remove all traces of organic matter which may interfere in an analytical determination.

1. **Total Ash**

About 2g of air-dried drugs was accurately weighed in a previously ignited and tarred silica crucible (empty crucible weight was taken). The sample was ignited by gradually increasing the heat from 500 to 600±25°C until it formed white ash in a muffle furnace for 4 hr. The furnace and crucibles were allowed to cool and carefully removed from the furnace using tongs and placed in the desiccator until it cools of to room temperature. [16] The % w/w total ash concerning the air-dried material was calculated by the given formula:

Total ash %= [Total ash formed in the crucible/ weight of sample] X 100

2. **Acid Insoluble Ash**

Using 25ml of dil. HCl washed the ash obtained from the dish used for determination of total ash value into 100ml beaker. Boiled for 5 minutes over a Bunsen burner and filtered the above solutions through an ashless filter paper, washed the residue twice with hot water, ignite a crucible in a flame, cool and weighed. Cooled the silica crucible in desiccator weighed the residue and calculated the acid insoluble ash value.

Acid soluble ash (%) = [Total ash formed in the crucible with ashless filter paper/weight of sample] X 100

3. **Water soluble ash**

Total ash obtained was boiled for five minutes with 25mL of distilled water. Cooled and collected the insoluble matter on an ashless filter paper, washed with hot water and again ignited for 15 minutes at temperature not exceeding 450˚C and percentage of water-soluble ash was calculated.

Determination of Foreign Matter

Taken 100g of selected plant material and spread in a thin layer. Check the foreign matter either by visual inspection or by using a 10X magnifying lens. Weight each selected plant material of foreign matter separately, and calculated the percentage of foreign matter.

Determination of Moisture Content

Individually weighed air-dried leaves of *A.indica*, bulb of *allium cepa* and rhizomes of *curcuma longa* were placed in tarred crucibles. The plants material was dried at a temperature of 105°C until a constant weight. The disparity in weight prior to and after the drying process was measured, and the percentage was calculated. The experimental protocol was performed in triplicate [17].

% Loss on Drying = (Difference in the weight of air-dried sample and oven dried sample/ weight of air-dried sample) X 100

Determination of Extractive value

1. **Water soluble extract**

Accurately weighed 5 gm of crude drug sample of *Azardirachta indica*, *Allium cepa* and *Curcuma longa* leaves taken in a weighing bottle and then transfer it to different dry 250 ml. conical flask. Each flask was filled to the delivery mark with the chloroform water for water soluble extractives. Tightly packed the flask and keep aside for 24 hours. Then it was filtered, when sufficient filtrate has collected, takes 25 ml. of the filtrate and transferred to a, thin porcelain dish. Evaporated to dryness on a water bath and subjected for drying in an oven at 1000c. Cool in desiccators and of Percentage water soluble extractive was calculated.

2. **Alcohol soluble Extract**

Accurately weighed 5 gm of each *Azardirachta indica*, *Allium cepa* and *Curcuma longa* leaves powder drug taken in a weighing bottle and transfer it to separate dry 250 ml conical flasks. Each flask was filled to the delivery mark with the solvent (90% alcohol). Tightly packed all flasks and kept aside for 24 hours, then it was filtered rapidly in order to prevent the loss of alcohol. When sufficient filtrate has collected, take 25 ml. of the filtrate and transferred to thin porcelain dish.

Evaporated to dryness on a water bath and subjected for drying in an oven at 100ºC. Cool in desiccators and Percentage ethanol soluble extractive was calculated. [18]

2.3 Preparation of Extracts

The extraction was carried out using the Soxhlet method. Leaves of *Azadirachta indica*, *Allium cepa*, and *Curcuma longa* were collected, shade-dried until completely dry, and then powdered. Three different extracts were prepared for *A. indica* leaves, namely aqueous, methanol, and hexane. For each extract, 10 g of coarsely powdered leaves was refluxed with 100 ml of hexane and methanol separately for 2 hours in a round-bottom flask using a Soxhlet apparatus. The resulting filtrates were concentrated using a rotary evaporator under vacuum. Similarly, extracts of *A. indica* were prepared using aqueous, methanol, and chloroform solvents in separate Soxhlet extractions. For *C. longa*, 10 g of dried powder was continuously extracted using hot Soxhlet extraction with various solvents (aqueous and methanol) in the desired ratios. The solvents were then removed under reduced pressure and controlled temperature using a rotary evaporator. The dried extracts were placed in desiccators and stored in airtight containers for further research. The percentage yield and observed color of the extracts were also recorded. [19,20]

2.4 Preparation of Drug loaded Nanogel.

The CDI-activated Pluronic F127 was obtained by dissolving the polymer in anhydrous THF. A white powder was obtained which was further used for preparation of F127/PEI nanogel by solvent evaporation method. The powder was dissolved in chloroform and then further dissolved in aqueous solution of PEI with constant stirring. The mixture was sonicated for 3min and the organic solvent in the emulsion was removed by rotary vacuum evaporation at 50°C for 45 min. The remaining solution was centrifuged at 3000 rpm for 30 min to remove adhesive fragments. The drug (Extract powder of *curcuma longa*, *allium cepa* and *azadirachta indica*) and lyophilized empty nanogels were dissolved separately in mixture of methanol and water (1:1), and then both were mixed, and the solvent was subsequently removed by rotary vacuum evaporation. The resulting film formed was further hydrated with a suitable amount of phosphate buffered saline pH 7.4. [21]

2.5 Evaluation of Optimized Polyherbal Nanogel

pH

The pH of nanogel formulation was determined using digital pH meter as per the method. Before measuring the pH of optimized formulation, the pH meter was calibrated with the phosphate buffer pH 7.4. Then nanogel was taken in a small glass beaker and the electrode of pH meter was dipped into it for a minute and the pH was noted. The measurement of pH of each formulation was done in triplicate and mean values were calculated.

Rheological Studies

The viscosity of the prepared formulations was determined using Brookfield viscometer. The selected formulations were poured into the sample adaptor of the viscometer. The viscosity was measured at 10 min after the rotation of the spindle. The viscosity measurements were made in triplicate.

For the measurement of spreadability, 1gm of developed hydrogels were kept at the centre of inverted petri-plate. Then, another pre-weighed petri-plate was kept over the gel in such a way that the base of both petri-plate faces each other and forms a sandwich in which gel is kept. Later, increasing weight was kept over the upper petri-plate, until the spreading of the gel becomes constant. Simultaneously, the time was noted down till the formulations achieve constant spreading. The cumulative weight kept, and the maximum diameter obtained were also noted down and spreadability was calculated with the formula given below:

Spreadability = M x L/t

Where: M is the cumulative weight kept over the upper petri-plate

L is the maximum diameter that gel achieves after spreading

T is the total time, gel took to spread

Appearance

About 1 week after preparation, the dispersions were visually assessed for optical appearance (e.g., colour, turbidity, homogeneity, presence of macroscopic particles).

Drug Content Uniformity

To confirm the content uniformity of the drug, a pre-weighed (0.5g) amount of developed cubosomal hydrogel was dissolved in 10ml PBS (pH 6.8). The solution was then sonicated and filtered. The filtrate was then subjected to measurement of absorbance via UV spectrophotometer using PBS (pH 6.8) as a blank. The obtained absorbance was noted down and concentration was calculated by putting absorbance in regressed equation. The percent drug content was determined using the following formula:

Theoretical Value/ Practical Value* 100

In-vitro drug release study

In vitro drug release study of prepared nanogels was performed according to the method using Franz diffusion cell and dialysis membrane 50. The receptor compartment was filled with 25 ml of phosphate buffered saline pH 7.4 diffusion media. The donor compartment was placed in such a way that it just touches the diffusion medium in receptor compartment. The 5 ml nanogel was placed in the donor compartment. The whole assembly was fixed on magnetic stirrer and the solution in the receptor compartment was continuously stirred using magnetic beads to ensure uniform distribution of permeating solutes for later sampling and the vessels were double-jacketed with water circulating between the jacket walls throughout the study to maintain the temperature 37 ± 0.5°C. 2 ml sample of the receptor fluid were withdrawn at predetermined time intervals and replaced immediately with same volume of fresh diffusion media.

Ex-vivo skin permeation study

An F-D cell with a 1.25 cm^2 diffusing cell area and a fifteen mL receiver volume was used with goat ear membrane was used for ex vivo tests. The goat ear pinna was collected from the local butcher an hour after it was sacrificed. Goat ear skin hair was properly removed using blade razor. The skin of the F-D cell was positioned between the donor and receiver chambers. The dermis was in close touch with PBS (pH 7.4), and the developed formulation was evenly applied to the dermis's uppermost layer. To resemble the skin conditions, the F-D cell was placed atop a magnetic stirrer set at a speed of 50 rpm and a temperature of 37 ± 1ºC. The aliquots were taken out at specified times and replaced with a fresh medium at the same time. The withdrawn samples were analysed via UV spectrophotometer and the mean ± SD was obtained by taking three readings of the data.

Stability Study

In the present study, the stability studies of optimized nanoparticle formulation were carried out after storing the formulation at freeze temperature (4°C±1°C), room temperature (25°C±2°C/ 60%±5% RH) and (45°C±2°C/75%±5% RH) as per ICH (Q1C) guidelines. The optimized formulations were evaluated for various parameters such as particle size and % cumulative drug release after 1st, 2nd, 3rd and 6th month.

3. RESULTS AND DISCUSSIONS

3.1 Morphological Studies

Curcuma longa

It is a group of rhizomes, the central primary rhizome being conical to ovoid in shape with a number of longer secondary rhizomes or fingers attached to it laterally. Both are covered with scale leaves whose remnants are seen as transverse scars and differentiated into nodes and internodes. Fresh rhizomes are light yellow/brown in colour externally and deep orange internally, has characteristic aromatic smell and bittery hot taste.

Azadirachta indica

Neem fruits are 1-2 cm long drupes, smooth and green with white milky juice when unripe, turning to yellow to brown when mature. They have a thin epicarp, a mucilagenous fleshy meshocarp and a hard endocarp. They contain a variable number of ovoid (1-2 cm) oil seeds.

Allium cepa Linn.

A short shoot-root axis and a long cotyledon make up the embryo, which is crescent-shaped or wrapped in a spiral and has a little distinctive aroma. The seeds are irregularly wrinkled, triangular, about 3mm long and 1mm wide, convex on one side and flattened on the other, and covered in a black seed coat.

3.2 Microscopical Studies

Curcuma longa

T.S of the rhizome is more or less circular in outline. (Figure 1) The outermost layer is the periderm which consists of 5-6 layers of tangentially elongated cells. This is followed by a broad cortex made of thin-walled parenchymatous cells with intercellular spaces. Some cells contain deposition of orange red substance oleoresin. Some others contain yellowish oil globules which almost fill the cells. There is a single layered endodermis composed of thin-walled rectangular cells. Close to the endodermis many compactly arranged conjoint collateral vascular bundles are present. A number of small bundles are also present scattered inside. Abundant starch grains are found, more in cells lying towards the centre. The starch grains are oblong with hilum towards the narrower end. The powder is yellow in colour. Microscopic analysis of the powder revealed the presence of fibres, simple starch grains mostly oval and a few round were abundantly found. Spiral vessels were also observed. Cells with oleo resin were also found.

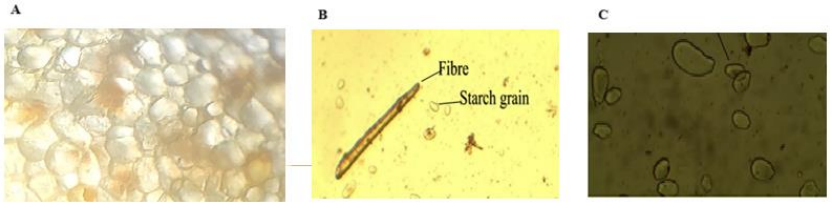

Figure 1: (A) T.S of curcuma longa rhizome (B) Fibre and Starch grain (C) Starch

Figure 2: Powder microscopy of Turmeric

Azadirachta indica

Transverse section of leaf showed presence of calcium oxalate crystals, arc shaped vascular bundles, Anomocytic stomata, unicellular covering trichomes, etc. The transverse section of bark showed presence of cortex and vascular bundles. Powder characteristic study showed presence of stone cells, stomatal cells, trichomes and calcium oxalate crystals.

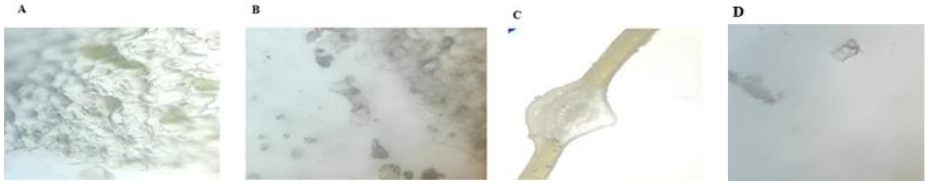

Figure 3: T.S. of (A) Lamina (B) Mature Bark (C) Midrib (D) Trichomes

Allium cepa

Fresh bulb fruit from *Allium cepa* was examined under a microscope and revealed to have stomata, upper and lower epidermis, vascular tissue including xylem and phloem, palisade tissue, cork cells, starch grains, and calcium co-oxalate crystal. The powder microscopy shows epidermal cells with strong walls and polygonal shapes filled with a dark reddish black brown substance.

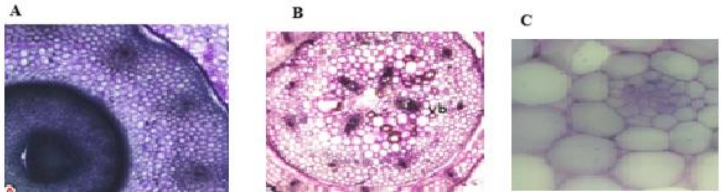

Figure 4: T.S. of *Allium cepa*

Determination of Physicochemical Parameters

Table 1: Table 7.1: Ash value of Azadirachta indica, Curcuma longa and Allium cepa

Plant Name	***Azadirachta indica***	***Curcuma longa***	***Allium cepa***
Total Ash (%)	9.25	10.03	4.23
Acid Insoluble Ash (%)	1.56	1.48	1.06
Water soluble (%)	6.35	5.87	14.12

Extractive value

Table 2: Extractive value of Azadirachta indica, Curcuma longa and Allium cepa

Plant Name	*Azadirachta indica*	*Curcuma longa*	*Allium cepa*
Alcohol-soluble extractive value	8.41	20.65	10.14
Water-soluble extractive value	12.61	23.46	21.02

Table 3: Different parameters of Azadirachta indica, Curcuma longa and Allium cepa

	Azadirachta indica	*Curcuma longa*	*Allium cepa*
LOD	5.12	4.57	6.18
Foreign Matter	0.16	0.24	
Swelling index	4.02	3.67	

3.3 Preparation of Nanogel

By utilizing solvent evaporation method, drug loaded polyherbal nanogel was prepared. The results of all parameters are compiled in Table 4. The colour and homogeneity of the optimized formulation was found to be white to light pale yellow translucent. No grittiness was reported. The consistency of the nanogel was found to be viscous.

Table 4: Compiled Evaluated Parameters for Polyherbal Nanogel

Evaluated Parameter	PHN-1
Colour and Texture	White to light pale yellow in colour
pH	6.06
Viscosity (cps)	23591
Drug Content Uniformity	92.06±0.06
Spreadability (g/cm^2)	44.9

Further, the developed polyherbal nanogel was evaluated for in-vitro and ex-vivo studies using goat ear pinna.

In-vitro Drug Release Studies

The *in-vitro* drug release results are shown in table below. *In-vitro* drug release study of optimized nanogel was performed using Franz diffusion cell. From the release study, it was found that optimized nanogel shows initial burst release of drug in first 30 minutes and afterward provides sustained release of drug. The optimized nanogel was shown release of more than 90 % (93.498 %) of drug in 12 hr.

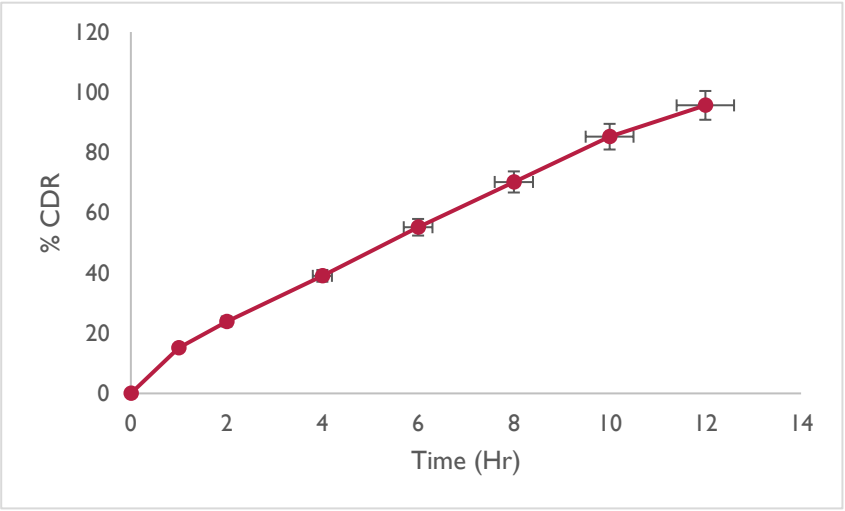

Figure 4: In-vitro Drug Release Study of the Polyherbal Nanogel

Ex-vivo Permeation Study

The skin permeation study was performed by using goat ear pinna. From skin permeation study using goat ear pinna, it was found that the optimized formulation of nanogel can pass through the skin and had a 47.178mg±0.05 of drug release showing sustained manner in 24 hrs. The graph was plotted between cumulative amount of drug permeated (mg) and time (h) as shown in Figure 1.

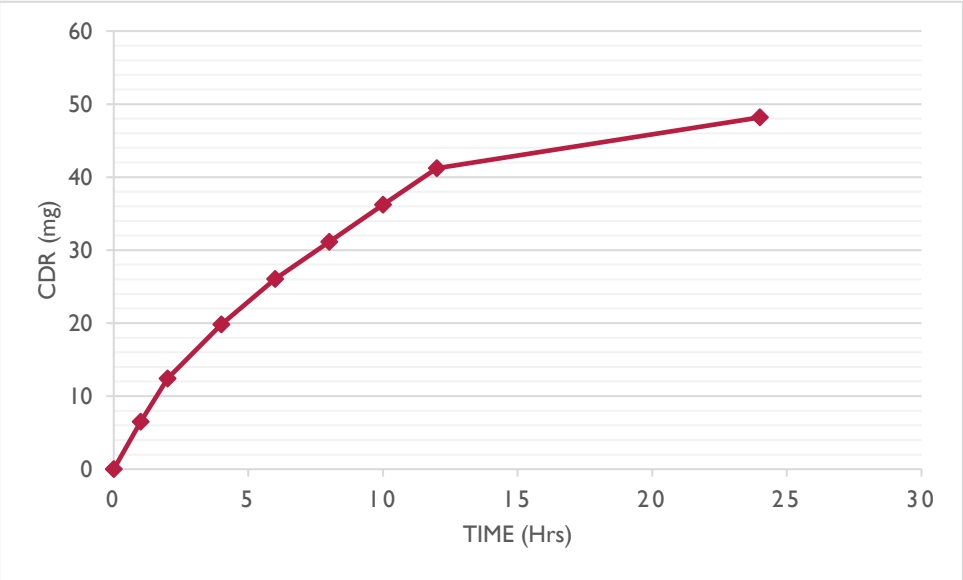

Figure 5: *Ex-vivo* Permeation Study

Stability Studies

Stability study of the optimized nanogel was performed as per ICH guidelines Q1. After 3 months of stability study formulation was evaluated for its particle size and % entrapment efficiency. From the results it was found that formulation was shown increase in particle size and decrease in % Entrapment efficiency at refrigeration condition (4±0.05°C). While formulation stored at 40 ± 2°C/75% ± 5% RH (relative humidity) was being precipitated and degraded. So, it was concluded that optimized nanogel formulation was stable at refrigeration condition and unstable at room temperature.

Table 7.22: Stability Result of Formulation

Evaluation Parameter	**Temperature**	**Time (Months)**		
		1st	**2nd**	**3rd**
Particle Size (nm)	4°C	114.7	115.4	116.2
	Room Temperature	114.7	116.1	116.9
	45°C	114.7	116.1	116.4
Entrapment Efficiency	4°C	82.91	80.14	78.12
	Room Temperature	82.91	80.67	78.64
	45°C	82.06	80.99	78.45

4. CONCLUSION

In conclusion, the formulation of a polyherbal nanogel incorporating neem, onion, and turmeric extracts presents a promising approach for the management of hyperpigmentation. These natural ingredients are rich in bioactive compounds known for their antioxidant, anti-inflammatory, and skin-lightening properties. The nanogel formulation enhances the bioavailability and stability of these active compounds, ensuring efficient delivery to the skin layers and improving their therapeutic effects. The combination of neem's antibacterial and anti-inflammatory benefits, onion's skin-regenerating properties, and turmeric's ability to inhibit melanin synthesis creates a synergistic effect in reducing hyperpigmentation. The nanogel matrix offers

advantages over conventional formulations, including sustained release and enhanced penetration, potentially leading to more effective treatment outcomes.

5. FUTURE PROSPECTS

Despite the promising results, further research, including clinical trials, is required to validate the efficacy and safety of the polyherbal nanogel in diverse populations and over extended periods. Moreover, optimization of the formulation to address factors such as texture, stability, and patient acceptability would be essential for translating this novel approach into a practical skincare solution.

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