



Design and Evaluation of Polyherbal Nanogel for The Treatment of Rheumatoid Arthritis

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Article History	Abstract
Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 20 Oct 2023	<p>A typical autoimmune condition known as rheumatoid arthritis is linked to progressive impairment, systemic problems, early death, and socioeconomic expenses. Rheumatoid arthritis has no known cause, and the prognosis is uncertain. However, new therapies with better results have been developed as a result of breakthroughs in our knowledge of the disease's aetiology. The current therapeutic approach, which reflects this advancement, involves starting intensive therapy shortly as a diagnosis is made and escalating the medication in the goal of clinical response while being guided by an evaluation of the disease condition. The medicinal industry is not an alternative to the increasing paradigm of nanotechnology, which is evoking advancements in practically all technological sectors. It has long been utilised for artificial medicine production. The emphasis today is on conventional therapies, though. This study has a considerable application in the developing field of nanomedicine because it focuses upon the nanogel preparations of conventional drugs. As the risks and shortcomings of contemporary medicine become more obvious, herbal therapies are experiencing a comeback because they are viewed as a fair and well-balanced method of therapy. The effectiveness of herbal medicines in the treatment and management of disease is demonstrated by developments in analytical and clinical studies. Herbal treatments' primary drawback is their failure to dissolve and stabilize. Newer technological developments may be able to solve the issues with herbal remedies. Nano-formulations show how modern technology and herbal medicines interact. Consequently, herbal medications' increased stability, homogeneity, low toxicity, and strong drug encapsulation capacities make them a promising candidate for innovative drug delivery systems.</p>
CC License CC-BY-NC-SA 4.0	Keywords: Rheumatoid arthritis, Boswellia, nanogel

1. Introduction

Millions of people throughout the world suffer from the chronic autoimmune disease rheumatoid arthritis (RA). This article seeks to give a thorough overview of RA, covering its causes, signs, symptoms, diagnosis, available treatments, and the effects it has on people's life. is a sophisticated autoimmune condition that mainly affects the joints. RA develops when the immunological system wrongly assaults the body's own tissues, as opposed to the more prevalent osteoarthritis, which is frequently linked to joint wear and tear. The synovium, the covering of the membrane that surrounding the joints, becomes chronically inflamed as a result of this inflammatory reaction. Although RA can

affect anybody, it is most commonly diagnosed in persons between the ages of 30 and 60 (12). Women typically experience it more. Rheumatoid arthritis (RA) treatment shows significant potential thanks to nanotechnology's revolutionary ways to better medication delivery, lower side effects, and increase treatment efficacy. Polyherbal nanogels for rheumatoid arthritis (RA) are a cutting-edge method of treating this debilitating inflammatory condition. These nanogels offer a focused and efficient remedy for RA by fusing the benefits of nanotechnology with the therapeutic possibilities of numerous herbal ingredients. In order to create polyherbal nanogels, numerous herbal extracts or active ingredients with well-known anti-inflammatory, analgesic, and immune-modulating effects are combined with nanogel technology. Various herbs can be used, but those with known anti-RA properties include ashwagandha, ginger, frankincense (*Boswellia serrata*), turmeric (curcumin), and others (3-5).

Traditional herbal remedies have been used by humans to relieve ailment and promote health since the dawn of humanity. As pharmaceutical preparations for the management of inflammatory illnesses, illnesses, arthritis, diabetes, anxiety, anxiety, AIDS, and other diseases, natural phyto-constituent-based preparations have won widespread recognition. The creation of polyherbal compositions has drawn more interest due to their historical roots, economic viability, and client compliance. There are many remedies possible right now that use topical, biological, and systemic medications. Some medications help to alleviate disease symptoms, but they also have some negative side impacts. In the meanwhile, it is critical to produce a drug that is highly effective and has low side effects (6). Natural remedies are both safer and more efficient at minimising symptoms than allopathic ones. A medicinal plant is one that contains substances with pharmacological benefits or substances that can be used as building blocks for semi-synthetic medicines. These phytochemicals, which are found in plants but are not nutrients, serve as the plants' defence systems towards microbial diseases. Dead skin cells restrict hair follicles, causing the skin condition acne to appear.

Topical medicines frequently have inadequate water solubility and inadequate free drug penetration across the stratum corneum, despite the fact that they are less risky than systemic ones. However, moderate to severe instances also call for systemic therapy. By sealing or conjugating these substances with nanocarriers, it may be possible to get over the restrictions of topical therapy. Different nanocarriers can be grouped together depending to their nature. As one of the many facets of nanomedicine—the nexus of nanotechnology, medicine, and pharmaceuticals—nanogels have recently emerged as ideal vehicles for delivering and releasing drugs to patients (11). Crosslinked polymer networks with nanoscale dimensions known as nanogels are able to absorb massive amounts of water. Hydrogels that are nanometer-sized or smaller are known as nanogels. A hydrogel is a gel consisting of polymers that is created by linking polymer chains together to create a macromolecular network. The synthesis of polymeric monomers, which need to be polymerized with functional cross-linker molecules to build a 'net-like' polymer framework, is a prerequisite for all methods of producing hydrogels. The tiny pores can be used to store medicines that will subsequently be delivered via the pores. On the contrary hand, nanogels are simply hydrogels that are 20–200 nm in size. Most nanogels are produced using emulsion polymerization (7). Nanogels can be administered to patients orally, pulmonary, nasally, parenterally, or intravenously. There are several ways that the drugs are discharged from the nanogels, but each method involves activation by outside stimuli, which changes internal characteristics. The pharmaceutical payload is transported to the desired location as a result of this physical alteration, which causes the polymer network to swell or compress.

Mechanism of Action:

- The herbal elements of polyherbal nanogels have anti-inflammatory and immunomodulatory properties, which serve to lessen the immune system response that underlies RA.
- These substances can prevent the discharge of cytokines and chemokines that promote inflammation, which reduces joint injury and inflammation (8).
- Some herbal components' analgesic qualities can help reduce pain and enhance joint health.
- The antioxidant benefits of food may shield joint tissues from the oxidative harm caused by RA.

Advantages

- Targeted Therapy: Polyherbal nanogels deliver herbal treatments particularly to swollen joints, enhancing therapeutic results.
- Minimized Side Effects: The risk of systemic side effects is decreased by localized drug delivery.
- Convenience: Sustained release could lower the number of times an administration is needed, improving patient compliance.
- Combination therapy potential: Several herbal ingredients can address various RA pathogenesis-related issues (9-10).

Challenges and Considerations:

- Clinical Validation: Although encouraging, further study is required to confirm the effectiveness and safety of polyherbal nanogels for RA in clinical settings.
- Standardization is essential to assuring the reliability and calibre of herbal extracts and nanogel compositions (13).
- Clinical Use Requires Regulatory Approval: Clinical use calls for regulatory agency authorization.
- For the management of rheumatoid arthritis (RA), polyherbal nanogels can incorporate a number of herbal components recognized for their anti-inflammatory, analgesic, and immunomodulatory activities. Types of polyherbs that might be utilized into the creation of nanogels for the treatment of RA include the following:

2. Materials And Methods

Material

Boswellia were obtained from herbal distributor in Lucknow, Uttar Pradesh, and aloe vera gel was purchased from a general herbal store. All of these identified at Pranveer Singh Institute of Technology, Kanpur, and phytochemically analysed using the spectrophotometric technique. Glycerine was purchased from S D fine chem limited, Mumbai. Carbopol 940, ethanol, propylene glycol and triethanolamine was purchased from Central Drug House Pvt Ltd, Gujrat, India.

Boswellia serrata extraction

Boswellia serrata obtained from India Mart's official website. The plant's oleogum resin was combined with hot distilled water on a magnetic heater for 2 hr, after which the extract was filtered. Rotavapour was used to remove the solvent. The porous powder that resulted was kept in the refrigerator at 5-10°C until needed.

Polyherbal Nanogel formulation

Formulation batches were prepared according to the formulation table. Ashwagandha, Boswellia are dissolved in ethanol and propylene glycol with continuous stirring (organic phase). Carbopol 940 is dissolved in water with stirring until a gel forms (aqueous phase). Organic phase with polyherbs is added dropwise into the aqueous phase with Carbopol. To it aloe vera gel is added with continuous stirring. Triethanolamine is added to form nanogel. Formulated nanogels are further analysed and studied (Table1).

Table 1: Formulation table for preparation of Polyherbal Nanogels

	F1	F2	F3	F4
Carbopol 940	3 gm	2.5 gm	3 gm	2.5 gm
Boswellia	2 gm	4 gm	4 gm	2 gm
Ashwagandha	2.5 gm	2 gm	2.5 gm	2 gm
Aloe Vera	2 ml	2 ml	2 ml	2 ml
Glycerine	3 ml	2 ml	3 ml	4 ml
Ethanol	15 ml	15 ml	15 ml	15 ml
Propylene glycol	15 ml	10 ml	10 ml	15 ml

Water	q. s	q. s	q. s	q. s
Triethanolamine	-	-	-	-

Evaluation Of Polyherbal Nanogel

Organoleptic Studies:

Organoleptic studies were performed by visual observations of various features of the drug like its general appearance, nature, colour, odour, etc. and were compared with standards given in pharmacopoeia for identification of the drug.

Colour: Minute amount of sample was taken and watched in an adequately lighted area.

Odour: Minute amount was sniffed to get its smell.

Determination of pH

The pH of formulations was determined using a digital pH meter. One gramme of nanogel was dissolved in 150 ml of demineralized water and stored for 3 hours. The measurement of the pH of formulations was done. The Instrument was calibrated before use with a standard buffer solution at pH 7.

Spreadability

For the determination of spreadability, an excess of sample nanogel was applied in between two glass slides and compressed to a uniform thickness by placing 25 g of weight in the pan. The time required to separate two slides, i.e., time in which the upper glass slide moves over the lower plate was taken as a measure of spreadability.

Formula $S = m \times l/t$

Where, S: Spreadability

m: Weight tied to upper slide

l: Length moved on glass slide

t: Time taken

Scanning electron microscopy (SEM)

SEM focuses on the surface and composition of the sample and provides information on the morphology of the sample. Three-dimensional picture is also produced using SEM. Jeol's scanning electron microscope model no. JSM-6490LV from Babasaheb Bhimrao Ambedkar University, Lucknow, was used to examine the surface morphology of nanogel samples.

X-ray Diffraction (XRD)

X-ray Diffraction (XRD) patterns of the Mattan tailam nanogel were analyzed on the X-ray diffractometer (Xpert-Pro). XRD technique is used to identify, characterise and investigate the crystalline structure/ nature. The structure of the nanogels was indicated by XRD analysis. At 2θ values of F-1 (26.5, 27.02, 30.40), F-2 (25.4622, 26.8926, 29.0142, 31.6524) and F-3 (24.09, 69.00, 28.02) degrees, diffraction peaks were observed.

Zeta potential

Because it is a significant indication for the particle surface charge, it is utilized to determine and control the stability of suspension particles. The nanogel all had negative zeta potential values ranging from -14.5 mV to -32.6 mV. The optimized formulation F2 had the highest negative zeta potential, which was considered favourable for formulation stability and drug transdermal permeation enhancement due to electrostatic repulsion between skin surfaces with the same charge, implying that the formulated nanogel do not aggregate rapidly. The charge of vesicles is a key factor that affects both stability and the interaction of skin vesicles.

Dynamic Light Scattering

Dynamic light scattering (DLS) is used to determine the size distribution characteristics of nanoparticles in liquids. During various studies, light scattering is captured on a microsecond time scale. An effective hydrodynamic particle radius can be used to quantify the influence of the cross-linker, and the charges of the polymer chains on the size of the nanogel that is formed. DLS may also be used to determine how much nanogels swell in various mediums. It is worth noting that the DLS data may not account for the population of smaller polymer particles. To fully comprehend the features of an object, a combination of analytical methodologies is frequently required. DLS was also used for analysing the average diameter of particles and the polydispersity index.

Ex Vivo Permeation and Kinetic Release Study of Polyherbal nanogel

Following anesthetization, rats were sacrificed, the abdominal fur was removed with a razor and the skin was carefully excised and washed with normal saline. A circular piece of skin in contact with the receiver medium and the epidermis side in contact with the donor chamber was securely sandwiched between the receptor and donor compartments with the dermal side (contact area= 0.75 cm²). Nanogel in vitro permeation experiments were conducted using the Franz diffusion cell through an excised rat abdominal skin. 1.5 gm nanogel has been placed in intimate contact with the skin excised. The donor compartment was charged with an adequate sample amount to keep the drug quantity constant and the receptor compartment was filled with 20 ml of pH 6.8 phosphate buffer saline and stirred at room temperature with a magnetic stirrer at 300 rpm. The samples were withdrawn at different intervals of time, filtered, adequately diluted and then analysed at 248 nm using a UV spectrophotometer and replaced with the same fresh buffer volume.

3. Results and Discussion

Organoleptic Studies:

Table 2: Organoleptic analysis of polyherbal nanogel

DRUG	COLOUR	ODOUR
Polyherbal nanogel	Golden brown colour	Citrus like odour

pH and Spreadability

It was also observed to have easy washability, good spreadability, pH was found to be 6.62±0.02, which is ideal for topical use. It shows spreadability range from 5–6.9 cm. All these ranges are considered to be good properties for nanogel

UV - Vis spectroscopic analysis

The development of polyherbal nanogels was first analysed using UV spectroscopy in the 200–900 nm range. The absorption spectra of nanogel displayed a characteristic peak of 418. Calibration curve was determined (Fig.1)

Table 3: Standard curve of Boswellia

S. No	Conc. (µg/ml)	Absorbance (nm)
1	0	0.0
2	0.5	0.049
3	1.0	0.078
4	1.5	0.139
5	2.0	0.195
6	2.5	0.225

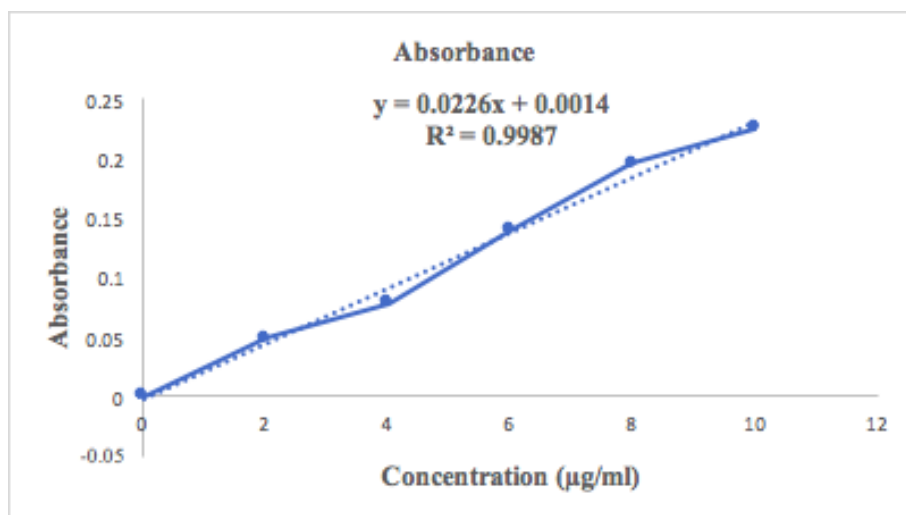


Fig. 1: Calibration curve of Boswellia

Fourier-transform infrared spectroscopy (FTIR)

Infrared spectroscopy examinations reveal the presence of any functional groups in an unknown chemical. We used a Perkin Elmer FTIR spectrometer to identify the functional group for this work. All formulations were examined in the 400-6000 cm^{-1} wavelength range (Fig.2).

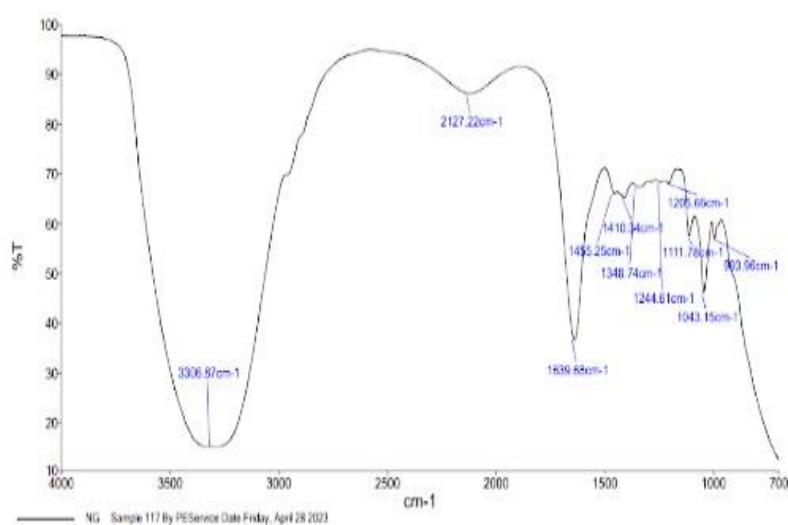


Fig.2: FTIR Analysis of Polyherbal Nanogel

Table 3: Functional Groups and corresponding IR Peaks of Polyherbal Nanogel

S. No.	Functional group	Peak
1.	C-H	2397.05
2.	C=O	3779.17
3.	O-H	4135.09
4.	C-F	1254.01
5.	C=C	2703
6.	C-N	1801.98

Scanning electron microscopy (SEM)

The morphological properties of the elemental compositions of the Mattan tailam nanogel, including the size and shape, the uniformity of the nanogels, and the dispersibility, were identified at nanoscale 600 nm by Field Emission Scanning Electron Microscopy (FE-SEM) (TESCAN MIRA3) (Fig 3 and Fig 4).

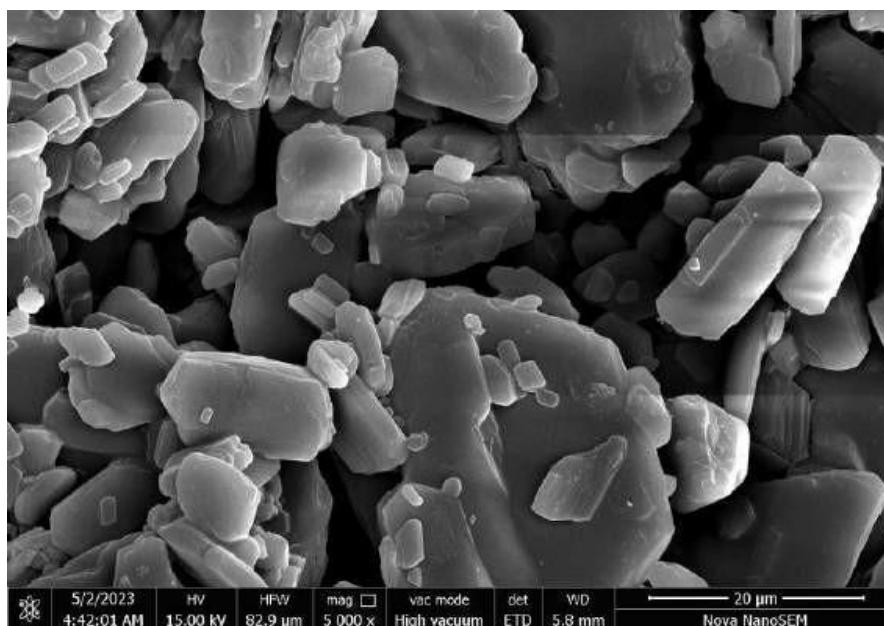


Fig 3. FESEM representation of F1 at magnification 2.0kx

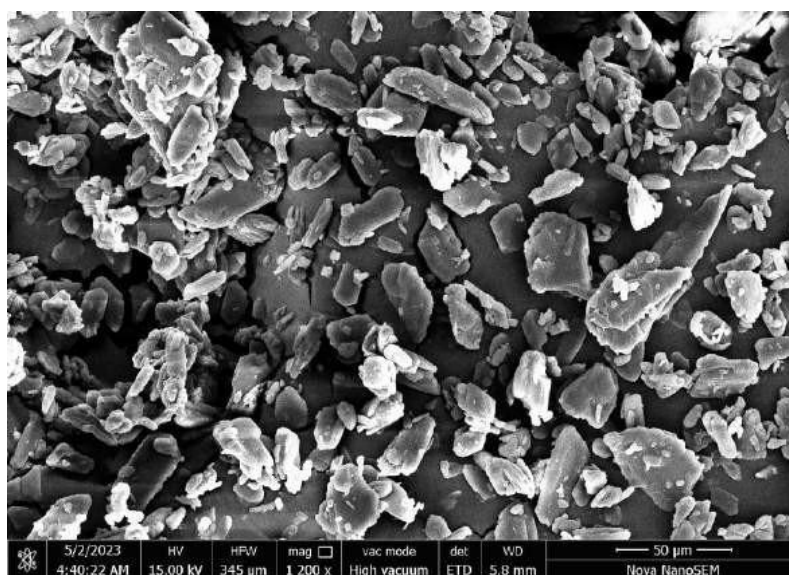


Fig 4. FESEM representation of F1 at magnification 10.0kx

XRD analysis

The structure of the nanogels was indicated by XRD analysis. At 2θ values of F-1 (26.5, 27.02, 30.40), F-2 (25.4622, 26.8926, 29.0142, 31.6524) and F-3 (24.09, 69.00, 28.02) degrees, diffraction peaks were observed (Fig.5). Amorphous nature was observed from this analysis.

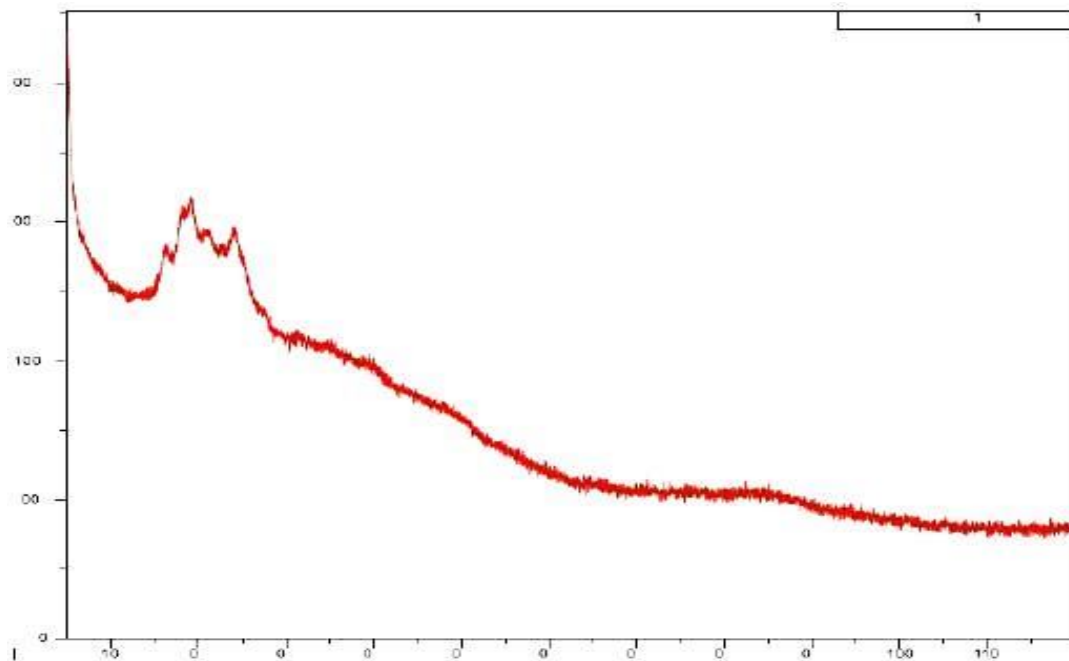


Fig.5: XRD analysis of Polyherbal nanogel

Dynamic Light Scattering

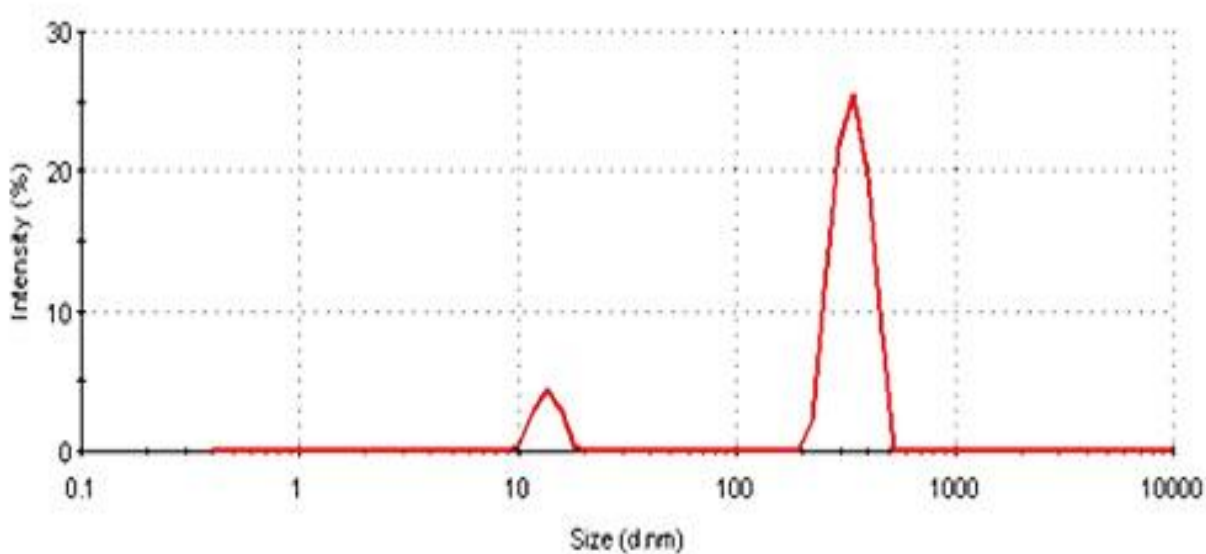


Fig.6: DLS of Polyherbal nanogel

In vitro drug release of polyherbal nanogel

The cumulative amount of drug permeated per unit area was plotted as a function of time. The steady-state permeation rate (J_{ss}) and lag time (LT, hrs) were calculated from the slope and X-intercept of the linear portion, respectively. The permeability coefficient (K_p) was calculated by dividing transdermal flux values (J_{ss}) by the initial concentration of drug in the donor cell (C_0) (Fig.7).

$$K_p = J_{ss} / C_0 \quad (7)$$

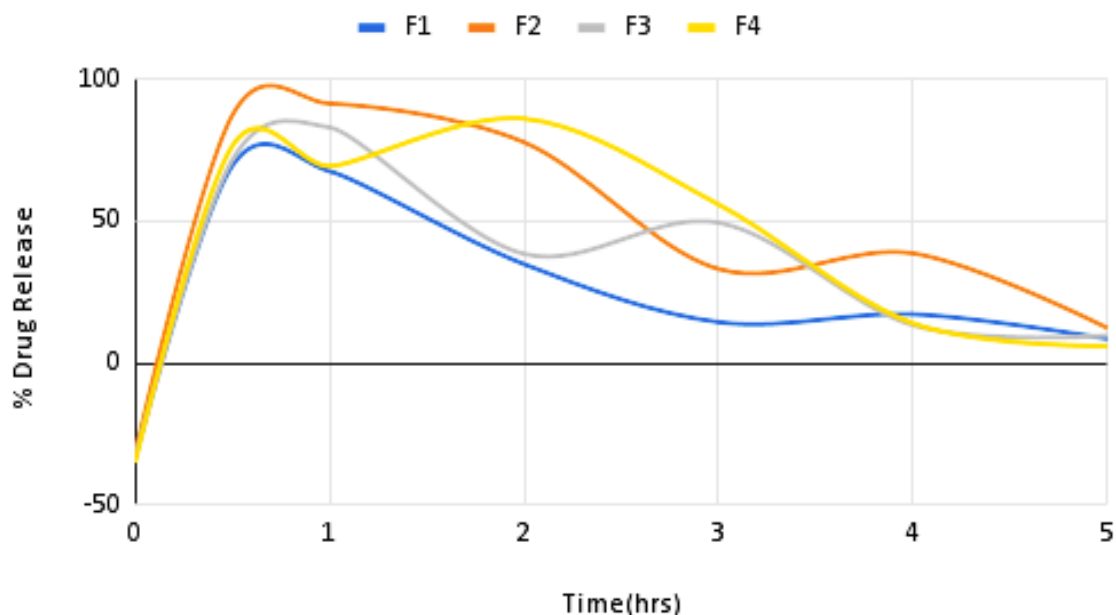


Fig.7: In vitro drug release of polyherbal nanogel

Table 3. Percentage drug concentration of all preparation

Formulation	% Drug content
F.1	91.3%
F.2	95.4%
F.3	90.8%
F.4	93.5%

Table 4. Cumulative % Drug Release

Time(hrs)	F1	F2	F3	F4
0	-33.7	-31.6	-32.6	-35.1
0.5	69.4	87.2	71.5	76.4
1	67.5	91.3	82.9	69.3
2	34.8	77.7	38.4	86
3	14.4	33.1	49.4	55.8
4	17.2	38.6	13.3	14
5	8.5	12.3	9.7	6

4. Conclusion

As a focused and possibly successful therapeutic strategy, the creation of polyherbal nanogels for the management of rheumatoid arthritis (RA) shows tremendous promise. The advantages of several herbal ingredients, each recognised for its antioxidant, anti-inflammatory, and immune-modulating characteristics, are combined in these nanogels. In recent decades, nanotechnology has advanced, and as a result, nanocarriers have changed and become more significant in biomedicine. In the fight against new coronaviruses, nanomedicine is an essential weapon, but it still faces significant challenges in clinical practise, such as in vivo behaviour, nanocarrier toxicities, and commercial production. Due to their capability for drug entrapment, nanocarriers have been utilised as systems for combination therapy, multipurpose diagnostics, and theragnostic as well as carriers of conventional chemotherapeutic drugs. Nanocarriers have been employed for site-specific and time-controlled delivery of drugs techniques utilising stimuli-responsive nanocarriers, active targeting by ligand alteration of nanoplatform surfaces, and passively targeting utilising the effect of EPR. Nanogels have shown to be preferable in that they can simplify this delivery system whilst also doing away with the drawbacks of earlier approaches. Innovations in the areas of drug and delivery of genes, smart

modalities of imaging, responsive materials, and multivalency as a therapy approach highlight the enormous promise of functioning nanogels as distinct polymeric platforms for biomedicine. Although polyherbal nanogels are an interesting region of study and development for the management of rheumatoid arthritis, they are currently in the exploratory state.

Polyherbal Nanogel was prepared successfully by using different concentrations of constituents as well as the incorporation into Carbopol 940 base to obtain gel formulations. The prepared formulations were characterized for various properties. The compositions of gels were manipulated to investigate their effects on the characteristics of final formulations. It can serve as a useful vehicle for the delivery of herbal extracts through the affected part of the skin for extended period of time. This study also revealed that herbal nanogel resides at targeted site for a relatively longer period of time with a zero-order release profile. It signifies the improved patient compliance.

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