Development and Characterization of Nanogels-Based Formulation for Topical Delivery of Heparinoid

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Abstract
In recent years, there has been a growing interest in the development of advanced drug delivery systems to enhance the efficacy and therapeutic outcomes of topical medications. Heparinoids, a class of glycosaminoglycans with potent anti-inflammatory and anticoagulant properties, hold immense potential for various dermatological conditions. This study aims to address this limitation by designing and characterizing a novel nanogels-based formulation for the efficient topical delivery of heparinoids.The nanogels were prepared using a biocompatible and biodegradable polymer matrix, chosen to improve the solubility and stability of the heparinoid drug. The physicochemical properties of the nanogels, including particle size, zeta potential, drug encapsulation efficiency, and in vitro drug release kinetics, were comprehensively characterized using advanced analytical techniques.The results demonstrated that the nanogels exhibited excellent colloidal stability, sustained drug release behavior, and enhanced skin permeability, surpassing the limitations associated with traditional heparinoid formulations. Further in vivo studies and clinical investigations are warranted to validate the translational potential of this nanogels-based formulation for topical delivery of heparinoid drugs.

Keywords: Nanogels, Heparinoid, Skin Permeability, Topical Drug Delivery.

1. Introduction

Topical delivery refers to the administration of drugs or active substances directly onto the skin or mucosal surfaces to achieve localized therapeutic effects. It has gained significant attention in pharmaceutical and cosmetic industries due to its numerous advantages over conventional delivery methods like oral ingestion or intravenous injections. Unlike systemic delivery routes, which can lead to potential side effects or reduced drug concentrations at the target site, topical delivery allows for targeted application, resulting in reduced systemic exposure and improved drug bioavailability at the desired location.[1,2]

The skin, being the largest organ of the human body, offers an excellent platform for drug delivery. It serves as a protective barrier against external agents, but it also presents unique challenges for effective permeation of drugs through its various layers. Traditional topical formulations often face limited penetration and absorption into the deeper skin layers, hampering their therapeutic potential.[3]

However, topical delivery offers several benefits that make it an attractive option for various medical and cosmetic applications. Firstly, it provides a non-invasive and patient-friendly approach, particularly beneficial for individuals who are averse to needles or have difficulty swallowing medications. Secondly, topical formulations are well-suited for treating localized conditions, such as skin infections, inflammation, and pain, as they can deliver drugs directly to the affected area, minimizing systemic exposure and potential side effects.[4]

Moreover, the field of cosmeceuticals has embraced topical delivery to effectively deliver active ingredients like antioxidants, vitamins, and anti-aging agents to the skin, promoting healthier and more youthful appearances. Topical formulations can also enhance wound healing processes by providing a protective barrier, preventing infections, and delivering growth factors or other regenerative substances.[5]

Despite its promise, topical delivery faces challenges related to drug stability, skin penetration, and formulation optimization. Researchers have been exploring innovative approaches, such as nanogels-based formulations, to address these challenges and improve drug delivery efficiency. These nanogels offer a promising solution due to their nanoscale size, high drug loading capacity, and ability to enhance skin penetration.[6,7]

In the field of pharmaceutical research, the development of novel drug delivery systems has been a subject of considerable interest, driven by the need to enhance therapeutic outcomes and improve patient compliance. One class of therapeutic agents that has gained attention for their potent anti-inflammatory and anticoagulant properties is heparinoids. These glycosaminoglycans have shown promise in the treatment of various dermatological conditions, such as inflammatory skin disorders and wound healing applications.

However, the successful topical delivery of heparinoids poses a significant challenge due to their limited permeability across the skin barrier. Traditional topical formulations have often failed to efficiently deliver heparinoid drugs to the desired site of action, resulting in suboptimal therapeutic effects and reduced patient satisfaction.

In this context, this study aims to develop and characterize a nanogels-based formulation tailored for the effective topical delivery of heparinoids. The primary objective is to improve the bioavailability and therapeutic efficacy of heparinoid drugs by harnessing the benefits of nanogels as a drug carrier.

Singh et al., (2016) reported that Topical administration is the favored route for local delivery of therapeutic agents due to its convenience and affordability. The specific challenge of designing a therapeutic system is to achieve an optimal concentration of a certain drug at its site of action for an appropriate duration.[8] Jeong et al., (2021) reported that Various non-invasive administrations have recently emerged as an alternative to conventional needle injections. A transdermal drug delivery system (TDDS) represents the most attractive method among these because of its low rejection rate, excellent ease of administration, and superb convenience and persistence among patients. TDDS could be applicable in not only pharmaceuticals but also in the skin care industry, including cosmetics.[9] Tiwari et al., (2012) reported that "Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. For the treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery particularly for peptide and protein therapeutics.[10] Suhail et al., (2019) reported that Nanogels have attracted considerable attention as nanoscopic drug carriers, particularly for site-specific or time-controlled delivery of bioactive mediators. A high diversity of polymer systems and the simple modification of their physicochemical features have provided multipurpose forms of nanogel preparations. Nanogels have outstandingly high stability, drug loading ability, biologic consistence, good permeation capability and can be responsive to environmental stimuli. Great potential has been shown by nanogels in many fields including delivery of genes, chemotherapy drugs, diagnosis, targeting of specific organs and several others.[11] Cuixiaet al., (2021) reported that "Nanogels have high tunability and stability while being able to sense and respond to external stimuli by showing changes in the gel volume, water content, colloidal stability, mechanical strength, and other physical/chemical properties. In this article, advances in the preparation of nanogels will be reviewed. The application potential of nanogels in drug delivery will also be highlighted. It is the objective of this article to present a snapshot of the recent knowledge of nanogel preparation and application for future research in drug delivery.[12]

Wijnhovenet al.,(2008) reported that "Heparinoids are used in the clinic as anticoagulants. A specific pentasaccharide in heparinoids activates antithrombin III, resulting in inactivation of factor Xa and-when additional saccharides are present-inactivation of factor IIa.In addition, the immunoprofile could be indicative for heparinoid-induced side-effects, such as heparin-induced thrombocytopenia, as illustrated by reactivity with antibody NS4F5, which defines a very high sulfated domain. In conclusion, immunoprofiling provides a novel, fast, and simple methodology for the characterization of heparinoids, and allows high-throughput screening of (new) heparinoids for defined structural and biological characteristics.[13]

The aim of this study is to develop and characterize a nanogel-based formulation for the topical delivery of heparinoid, with the goal of improving the therapeutic efficacy and bioavailability of the drug.

2. Materials used

The drug as well as different excipients and reagents utilised in this investigation are HeparinoidMethanol, Ethanol, Sodium chloride, Phosphate buffer saline (PBS 7.4), Distilled water, Ferric, Chloride SolutionAll Chemicals, drug and reagents were of analytical grade.

3. Determination of flow properties of pure drug [14]

3.1 Bulk density

In this procedure, a graduated cylinder was prepared by ensuring it was thoroughly cleaned and dried to guarantee precise measurements. The initial mass (M1) of the empty graduated cylinder was recorded in grams (g) using a weighing scale after taring the balance. A known mass (W) of heparinoid powder was then carefully added to the graduated cylinder, and its mass was also recorded. To determine the total volume of the powder, the graduated cylinder was gently tapped on a non-absorbent surface to allow the powder to settle and reach its maximum density. If necessary, a funnel was used to prevent spillage during the process. The final volume (V) of the heparinoid powder in the graduated cylinder was then read and recorded in milliliters (ml) or cubic centimeters (cm^3). These precise measurements are crucial for accurate dosing and the development of formulations, ensuring the reliable and effective delivery of the heparinoid for various pharmaceutical applications.

Calculate the Bulk Density:

Bulk density= Mass of powder/volume of powder

Where:

- **W = Mass of the powder (grams)**

- **V = Volume of the powder (milliliters or cubic centimeters)**

3.3 Tapped density[14]

In this procedure, the steps for preparing the graduated cylinder and measuring the mass and volume of heparinoid powder are outlined. Firstly, the graduated cylinder is thoroughly cleaned and dried to ensure accurate measurements. The mass (M1) of the empty graduated cylinder is then measured and recorded in grams (g) using a weighing scale after taring the balance. Next, a known mass (W) of heparinoid powder is carefully added to the graduated cylinder, and its mass is recorded. To achieve an initial bulk volume, the cylinder is gently tapped on a non-absorbent surface to settle the powder and remove any voids. The graduated cylinder is then placed into a tapping apparatus, and a specified number of taps are applied at a specified tapping height. After completing the tapping process, the final volume (V) of the heparinoid powder in the graduated cylinder is measured and recorded in milliliters (ml) or cubic centimeters (cm^3). This tapping procedure ensures proper packing of the powder, enabling accurate measurements for the formulation and dosing of heparinoid-based pharmaceutical products**.**

Calculate the Tapped Density

Tapped density= Mass of powder/Tapped volume

Where:

- W = Mass of the powder (grams)
- V = Volume of the tapped powder (milliliters or cubic centimeters)

3.4 Compressibility index and Hausner ratio[14]

The Compressibility Index (CI) is a measure of the powder's ability to reduce in volume under pressure. It is calculated using the bulk density (ρ_bulk) and tapped density (ρ_tapped) of the powder and is expressed as a percentage.

The formula to calculate the Compressibility Index is as follows:

Compressibility Index (CI) = [(ρ_tapped - ρ_bulk) / ρ_tapped] × 100

The Hausner Ratio (HR) is another parameter used to evaluate the flow properties of powders. It is the ratio of tapped density (ρ_tapped) to bulk density (ρ_bulk) and is a dimensionless value.

The formula to calculate the Hausner Ratio is as follows:

Hausner Ratio (HR) = ρ_tapped / ρ_bulk

3.5 Angle of repose

In this procedure, the steps for measuring the angle of repose of heparinoid powder are outlined. First, a rigid flat surface, such as a clean sheet of paper, is placed on a level horizontal plane. Next, a funnel is set up at a fixed height (H) above the surface, typically between 2-5 cm. The heparinoid powder is then poured gently into the funnel, allowing it to flow freely onto the flat surface below without interruptions. As the powder accumulates, a cone-shaped pile naturally forms with its own angle of repose. Once the pile stabilizes, the height (h) and radius (r) of the cone-shaped pile are measured using a ruler or calipers. This angle of repose measurement is essential in understanding the flow properties and cohesiveness of the heparinoid powder, which can impact its behavior during manufacturing, processing, and formulation development.

The angle of repose (θ) can be calculated using the following formula:

Angle of Repose (θ) = tan^(-1) (h / r)

3.6 Method of preparation of Nanoparticles

3.6.1 Emulsification

Emulsification is a commonly employed method for the preparation of nanoparticles, widely used in the pharmaceutical and biomedical fields. The process involves a series of well-defined steps. Initially, the desired polymer or lipid material is dissolved in an organic solvent, forming the organic phase. Simultaneously, the drug or active ingredient is dissolved in another compatible solvent, establishing the aqueous phase. Under mechanical agitation, the organic phase is mixed with the aqueous phase, leading to the formation of an emulsion, where tiny droplets of the organic phase become dispersed in the aqueous phase. Subsequently, the organic solvent is removed through evaporation or other suitable methods, resulting in the presence of nanoparticles suspended in the aqueous phase. To prevent aggregation and ensure long-term stability, surfactants or other stabilizers can be optionally added to the nanoparticle formulation. This straightforward and versatile technique allows for the efficient production of nanoparticles with controlled drug release properties, making it a valuable approach for drug delivery systems and various biomedical applications**. [15,16]**

Table 1. Optimization Of Components Of Albumin Loaded Nanoparticle Formulation

S.NO	Formulation Code (Nanoparticle Formulation- NP)	Tween 80	Phosphatidyl choline	Ethanol:Distilled Water	Heparinoid (mg)
1.	NP-1	2.5%	2.5	30:70	10
2.	NP-2	3%	3	35:65	10
3.	NP-3	3.5%	2.5	25:75	10
4.	NP-4	4%	1.5	10:90	10
5.	NP-5	2.5%	2.5	15:85	10

3.7 Physicochemical characterization of nanoparticles

3.7.1 Drug loading and loading efficiency

The amount of medication that is encapsulated or integrated into a drug delivery system, such as nanoparticles, micelles, liposomes, or other carriers, is referred to as drug loading. Typically, a percentage or weight ratio is used to indicate it:[17]

$$\text{Percentage of loading} = \frac{Amount\ of\ in\ present\ drug\ nanoparticles}{Weight\ of\ nanopartic\ le\ analyzed} \times 100$$

$$\text{Percentage of efficiency} = \frac{Actual\ loading\ drug}{Theoretical\ \ drug\ loading} \times 100$$

3.7.2 Yield Percentage

Yield %, commonly referred to as product yield, is a metric used to assess the effectiveness of a manufacturing process or chemical reaction. It shows the proportion of the intended end product that was produced compared to the theoretical maximum yield that was possible given the amount of starting material utilised.[18]

The formula to calculate the yield percentage is as follows:

$$\text{Percentage of loading} = \frac{Amount\ of\ nanopartic\ obtained}{Total\ of\ polymer\ and\ drug\ used} \times 100$$

3.7.3 Preparation of nanoparticle Gel

Gels were prepared using a dispersion method with a polymer as the gelling agent. Propylene Glycol was accurately weighed and dispersed in distilled water, followed by 30 minutes of swelling and mechanical stirring at 1200 rpm. The gelling agent was dispersed in distilled water, allowed to swell overnight, and neutralized with Triethanolamine while adjusting the viscosity with glycerol. The Nanoparticle concentrate, containing the drug at 1% w/w, was added to the pre-formed gel base using Triethanolamine to maintain pH and facilitate gel formation. Thorough mixing resulted in a transparent gel. To preserve the gels, Paraben was added as a preservative, and the final gels were stored in glass vials at temperatures ranging from 4-80°C. This process yielded a stable and transparent gel formulation, potentially suitable for drug delivery applications.[19-27]

Table 2. Preparation of Nanoparticle Gel

S.NO	Formulation Code (Nanoparticle Gel -NGH)	Propylene Glycol	Purified Water	Coconut oil	Triethanolamine	Nanoparticle Suspension
1.	NGH-1	15	20	As much as suffices	2.5	Nanoparticle Formulation1
2.	NGH-2	10	25	As much as suffices	3.5	Nanoparticle Formulation 2
3.	NGH-3	20	25	As much as suffices	2.5	Nanoparticle Formulation 3
4.	NGH-4	20	25	As much as suffices	3.5	Nanoparticle Formulation 4
5.	NGH-5	15	25	As much as suffices	4	Nanoparticle Formulation 5

3.8 Characterization & Evaluation of Formulation [28-34]

3.8.1 Evaluation of Gel Formulation

All prepared formulations of gel were characterized for:

3.8.1.1 Physical Evaluation

Physical parameters such as color and appearance of the herbal gel were observed manually.

3.8.1.2 Measurement of pH

The pH of the skin is a crucial determinant of the durability of topical preparations, particularly for gels. Human skin has a pH that typically varies from 5.5 to 6. Therefore, the pH of topical medicines must match the pH of the skin.With the use of a digital pH metre, the pH of several gel compositions was measured. In 100 ml of distilled water, one gramme of gel was dissolved before being let to stand for two hours. Each formulation's pH was measured three times, with the average value being computed.

3.9.1.3 Spreadibility

The instrument, which consists of a wooden block with a pulley at one end, was used to measure spreadability. By using this technique, spreadability was assessed based on the gels' properties of slip and drag. On the bottom slide, more gel (approximately 2g) was added for the experiment. The gel was then placed in a sandwich between this glass slide and another glass slide with a hook and a set ground slide dimension. For five minutes, a one kilogramme weight was put on top of the two slides to force air out and create a homogenous gel coating between them. The excess gel was scraped off the edges.The time (in seconds) needed for the top slide to move 7.5 cm was then recorded when the top plate was pulled by an 80 g weight with the aid of a string tied to the hook. Better spreadibility is indicated by a shorter gap. Spreadibility was determined using the following formula:

$S = M \times L / T$

Where,

S = Spreadibility,

M = Weight in the pan (tied to the upper slide),

L = Length moved by the glass slide

T = Time (in sec.) taken to separate the slide completely each other.

3.9.1.4 Consistency

By dropping a cone linked to a holding rod from a fixed distance of 10 cm in such a manner that it should land on the centre of the glass cup filled with the gel, the consistency of the created gels was measured. From the gel's surface to the cone's tip inside the gel, the cone's penetration was measured. After 10 seconds, the cone's distance was measured.

3.9.1.5 Homogeneity

After placing the generated gels in the container, ocular examination was used to check all of the gels for homogeneity. They were watched to see how they looked and whether there were any aggregates.

3.9.1.6 Viscosity

At room temperature, spindle No. 7 at 50 revolutions per minute on a Brookfield viscometer was used to measure the gel's viscosity. At 0.3, 0.6, and 1.5 revolutions per minute, the gels were spun. The relevant dial reading was recorded for each speed. By multiplying the dial value with a factor specified in the Brookefield Viscometer handbook, the viscosity of the gel was determined.

3. Results

4.1 Organoleptic properties

Organoleptic features, such as those of pharmacological compounds, refer to the sensory perceptions of different characteristics or traits of a substance. These characteristics include the look, colour, and smell of the drug substance. Studying the morphological and sensory properties of medications is part of this qualitative assessment strategy. We use our unaided eyes to evaluate a drug's outward look when studying its macroscopy. Table 3 provides an overview of the pertinent features.

Table 3. The organoleptic properties of Heparinoid

S.NO	Properties	Heparinoid
1.	Colour	white or off-white color
2.	Odour	Generally odorless or may have a very faint, characteristic odor
3.	Texture	Smooth and creamy to slightly greasy
4.	Taste	Not expected to have any specific taste

4.2 Determination of flow properties of pure drug

4.2.1 Bulk density and tapped density

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder. Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken until little further volume change is observed. The values are shown in table below.

The provided data represents the determination of flow properties of a pure drug. The flow properties are evaluated based on two parameters: bulk density and tapped density. Here's a summary of the data:

Table 4. Determination of flow properties of pure drug

Parameters	Values
Bulk density	0.65
Tapped density	0.54

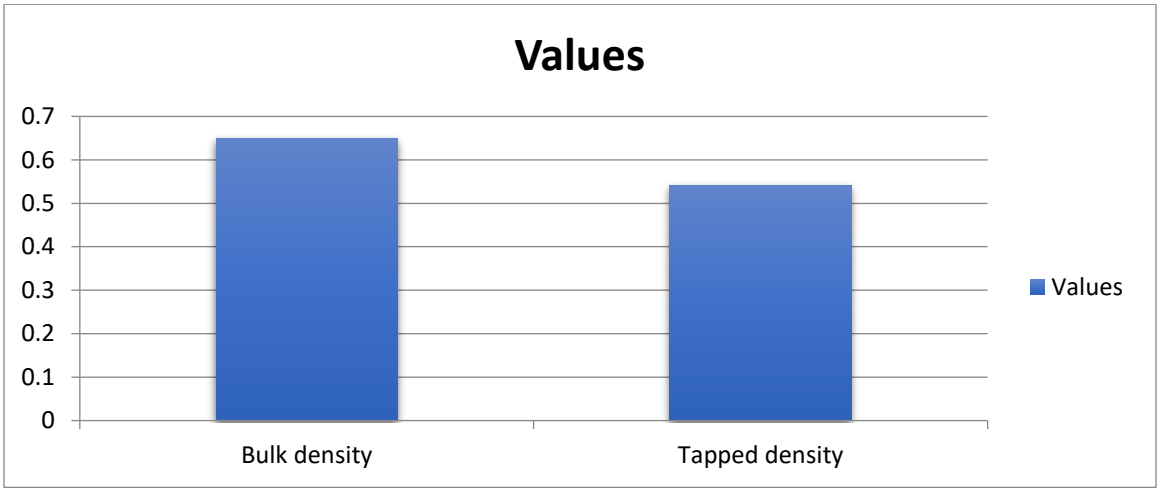

Figure 1. Graph of flow properties of Heparinoid

4.2.2 Compressibility index, hausner ration and angle of repose

The characterization of the drug powder reveals important properties for its formulation and processing. The compressibility index, measured at 20.4%, indicates moderate compressibility, implying that the powder may require some force during tablet formation. The Hausner ratio, recorded as 0.84, demonstrates good flowability, signifying that the powder can flow easily. Lastly, the angle of repose, measured at 25.380 degrees, suggests favorable flow properties and cohesiveness. Overall, these results indicate that the drug powder possesses suitable compressibility and excellent flow characteristics, which are essential factors.

Table 5. Determination of flow properties of pure drug

Parameters	Values
Compressibility index	20.4%
Hausner ratio	0.84
Angle of repose	25.38^0

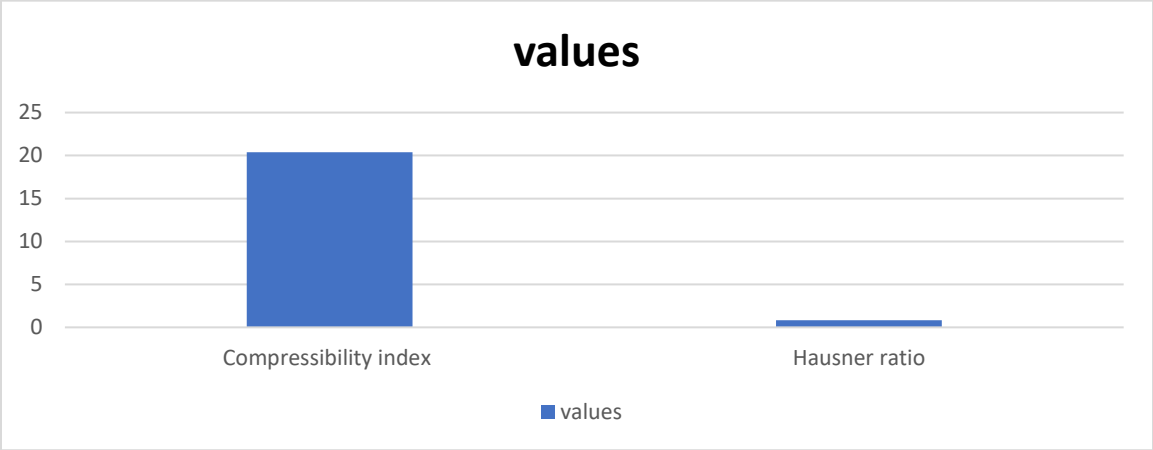

Figure 2. Graph of flow properties of Heparinoid

4.3 Physicochemical characterization of nanoparticles

The provided data represents the physicochemical characterization of five different nanoparticle formulations (NF-1 to NF-5). These formulations are evaluated based on their drug loading percentage, loading efficiency, and yield percentage.

Table 6. Physicochemical characterization of nanoparticles

Formulation (Nanoparticl Formulation-Nf)	Drug loading (%)	Loading efficiency(%)	Yield Percentage(%)
NF-1	**45.21**	62.06	65.16
NF-2	**46.20**	64.05	75.20
NF-3	**48.72**	59.30	71.20
NF-4	**46.20**	58.10	51.12
NF-5	**43.60**	61.28	56.41

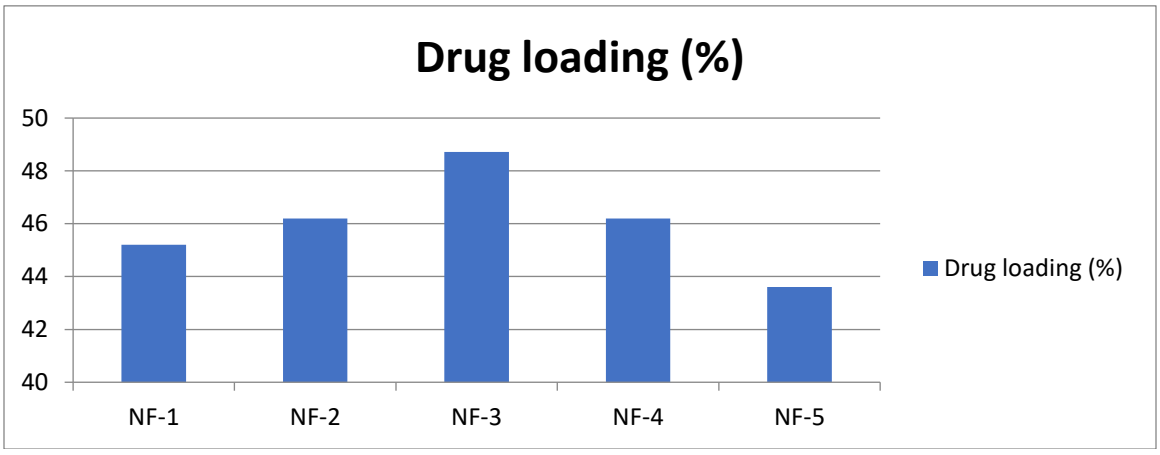

Figure 3. Graph of Drug loading

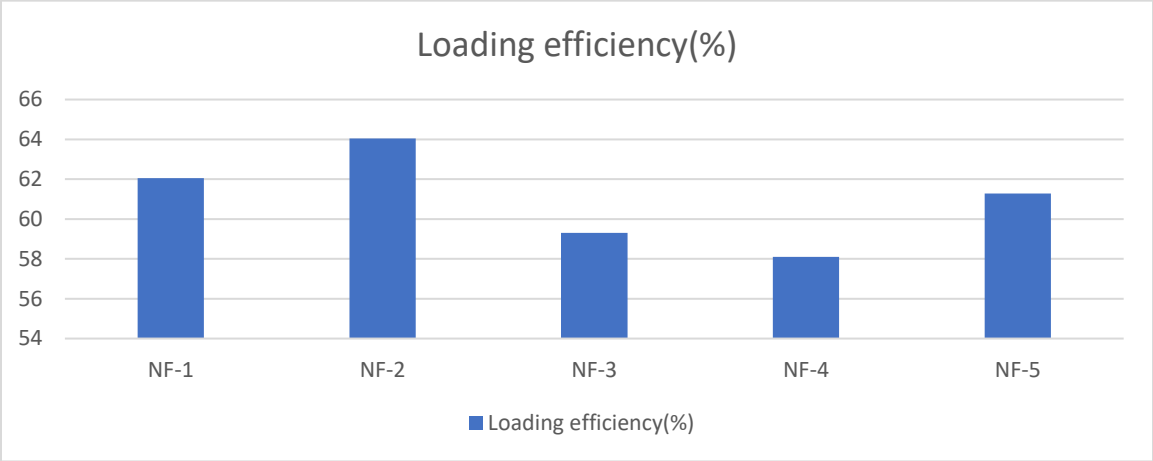

Figure 4. Graph of Loading efficiency

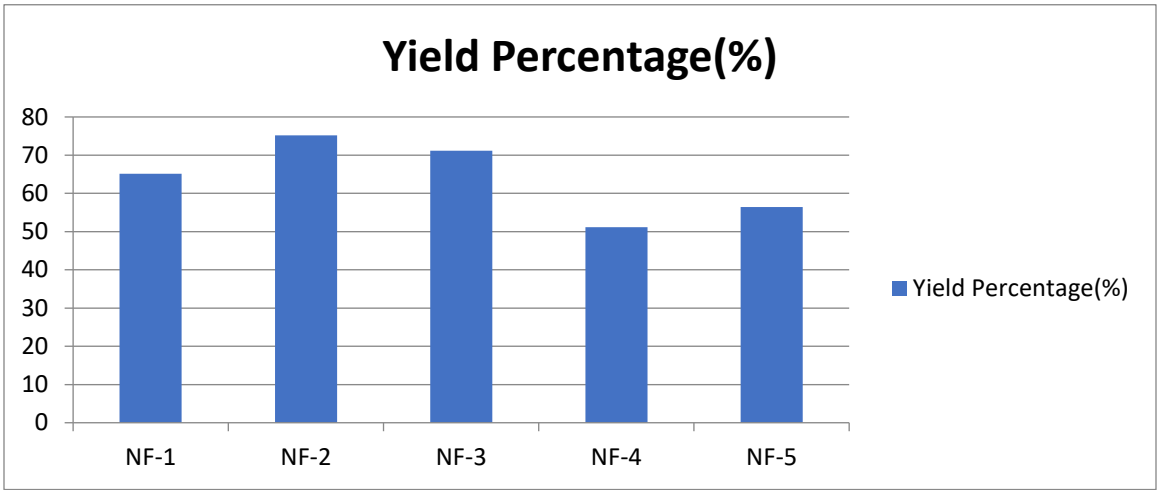

Figure 5. Graph of Yield Percentage (%)

4.4 Evaluation of Gel Formulation

Gel formulations are used to deliver the drug topically because of easy application, increase contact time and minimum side effects as compare to other topical preparation and oral administration. The evaluation parameters of gel formulation are shown in table 7 and table 8.

The data provided represents the evaluation of five different gel formulations (NGH-1 to NGH-5) based on three parameters: pH, consistency (measured in mm), and homogeneity.

Table 7. Evaluation of Gel Formulation

Formulation	Ph	Consistency(mm)	Homogenecity
NGH-1	6.4	6.1	Homogenous
NGH-2	5.5	5.4	Homogenous
NGH-3	5.4	6.3	Homogenous
NGH-4	6.3	5.9	Homogenous
NGH-5	5.1	5.1	Homogenous

Table 8. Evaluation of Gel Formulation

Formulation	Spreadability(g.cm./sec.)	Viscosity
NGH-1	6.3	8270
NGH-2	5.9	8430
NGH-3	6.0	7825
NGH-4	6.0	7714
NGH-5	5.9	8045

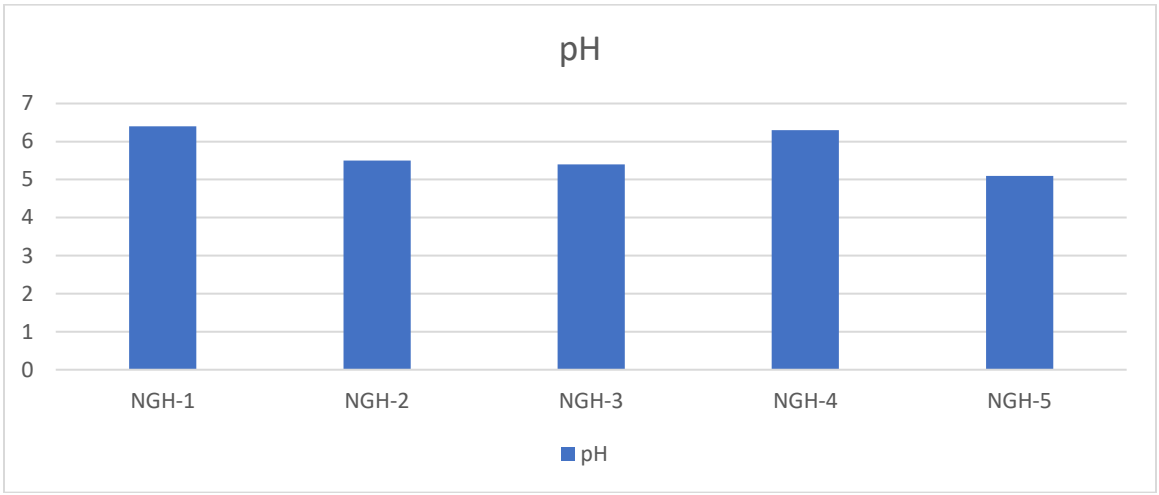

Figure 6. Graph of pH

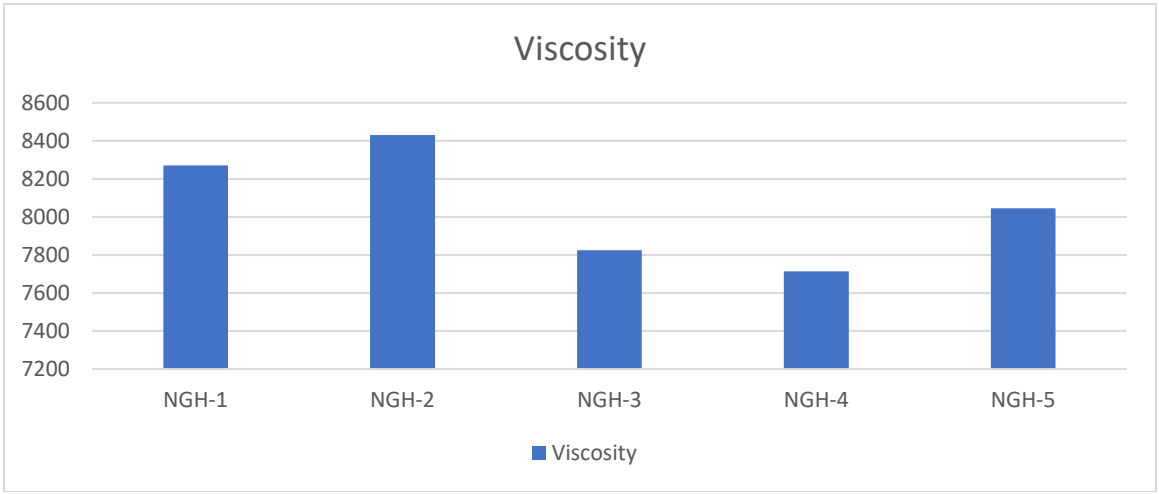

Figure 7. Graph of VISCOSITY

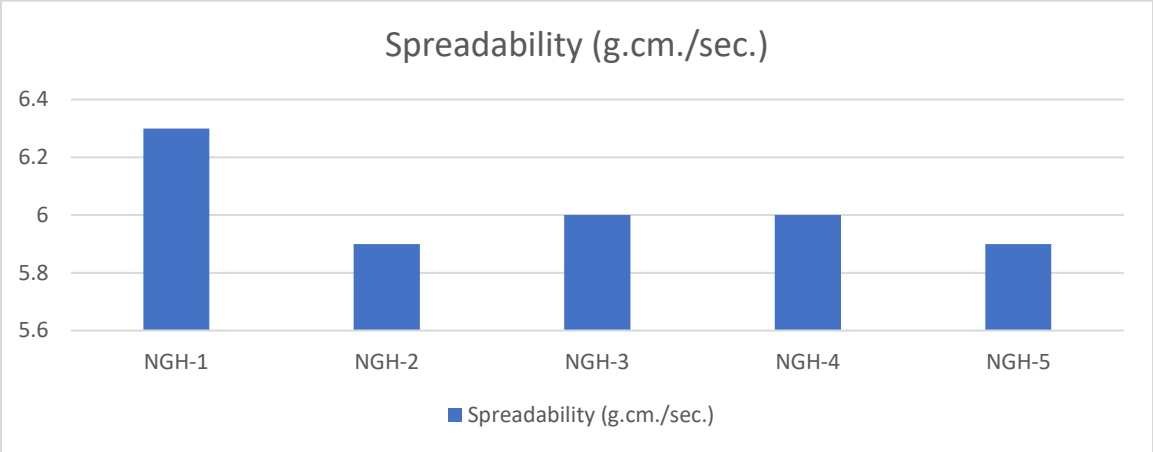

Figure 8. Graph of Spreadability

5. Conclusion

Heparinoid is a substance with a white or off-white color, generally odorless, and possessing a smooth and creamy texture, sometimes slightly greasy. It is not expected to have a specific taste. The pure drug exhibits differences in density between its loose and tapped states, with a bulk density of 0.65 and a tapped density of 0.54. Its compressibility index is 20.4%, and it shows good flowability with a Hausner ratio of 0.84 and an angle of repose of 25.380 degrees, indicating favorable flow properties. Different nanoparticle formulations (NF-1 to NF-5) display varying drug loading percentages, loading efficiencies, and yield percentages, suggesting differences in their physicochemical properties. NF-3 has the highest drug loading, NF-2 has the highest loading efficiency and yield percentage, while NF-5 has the lowest drug loading, and NF-4 has the lowest loading efficiency and yield percentage among the nanoparticle formulations. The data also provides pH values, consistency measurements, and homogeneity assessments for each gel formulation (NGH-1 to NGH-5). The pH values indicate the acidity or alkalinity of the gel, consistency measures the thickness or viscosity, and homogeneity assesses the uniformity of the gel. The gel formulations display varying spreadability and viscosity values, reflecting differences in their consistency and ease of spread. NGH-1 has the highest spreadability, NGH-2 has the highest viscosity, and both NGH-2 and NGH-5 have the lowest spreadability. NGH-4 has the lowest viscosity among the gel formulations. This comprehensive characterization data is crucial for understanding the properties of heparinoid, nanoparticle formulations, and gel formulations, facilitating their formulation optimization and potential pharmaceutical applications.

6. Future Prospective

The data provided on heparinoid, nanoparticle formulations, and gel formulations opens up exciting future prospects for pharmaceutical research and development. The utilization of nanoparticle formulations can pave the way for advanced drug delivery systems with enhanced stability, controlled release, and targeted delivery, revolutionizing therapeutic outcomes. Researchers can delve into novel gel formulations, leveraging the varying spreadability and viscosity values to design customized gel-based delivery systems with optimized consistency and efficient topical drug delivery. Additionally, exploring the biomedical applications of heparinoid nanoparticles beyond drug delivery, such as tissue engineering and medical imaging, holds promise for innovative therapeutic approaches. Combination therapies combining heparinoid nanoparticles with other therapeutic agents offer potential synergistic effects and improved treatment outcomes. Long-term stability studies are essential to ensure the reliability and safety of the formulations over time. Moving towards preclinical and clinical studies will validate the formulations' efficacy and safety, facilitating their translation into real-world medical practice. Continuous optimization and biocompatibility studies will further refine heparinoid-based formulations, creating superior products with minimal side effects and maximum therapeutic benefits. Overall, the comprehensive data presented in this study signifies a promising path for advancing pharmaceutical science and positively impacting patient care in the future.

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Conflict of interest

The author has declared no conflicts of interest

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