



FORMULATION AND EVALUATION OF HERBAL NANO GEL

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ABSTRACT:

Objective: To prepare Nanogel using bio-active compound (Gingerol). To develop Nanoformulation using biodegradable polymer. To evaluate the black cumin oil as penetration enhancer. To formulate the Nanogel, using Carbopol 940 as gelling agent which one is more commonly used and easily available. To evaluate physical properties of Nanogel. To conduct in vitro diffusion study of Nanogel. To optimize selected formulation batches of Nanogel. To conduct stability testing of selected formulation batches of Nanogel. **Material:** Formulations were developed with varying concentrations of polymers and Black cumin oil using Reverse Micellar Method. The nanogel were tested for clarity, viscosity, spreadability, surface pH, drug content uniformity, and skin irritation study. **Result:** formulations are characterized for the particle size and found to be below 150 nm. The drug The content in the formulations was found satisfactory. The formulation showed optimum stability and possessed a sustained drug release during the study period. The nanogel formulation showed the favorable alternative to oral administration. **Conclusion:** From the overall study, it was concluded that the nanogel of Ginger(Gingerol) with Black Cumin Oil as prnrtration enhancer with Carbopol as Polymer was successfully formulated and evaluated.

Keyword: Anti-inflammatory effect, Topical, Nanogel, Gingerol, blackcumin oil, Herbal Anti- inflammatory nanogel.

Introduction:

Nanotechnology, a novel technique which having the broad scope for the drug delivery. Development of novel drug delivery system has a impact as a disease prevention diagnosis, and treatments. This novel way have is overcome therapeutic value as they have fewer adverse effect as compared with modern medicines the issues by improving absorption of drugs sustained release of drugs, controlled release of drugs by reducing toxicity of drugs etc the application of nanotechnology in medicines has the development of nanoparticles which act as carriers can be loaded with drugs or genetic material which release in controlled onsustainable manner to specific target site Many nanotechnological techniques) available nowadays for drug delivery like mulsion, nancnpensins, sanotubes, and nanogel but despite other techniques nanogels are mostly available in market due to its advantages over the other formulations. A nanoparticle which contains hydrogel with crosslinked polymer network called as "Name". A nanogel which is nanosized hydrogels which is cross-linked, small swollen particles which is made up from amphiphilic or hydrophilic polymer networks, these networks might be anionic or nonic They act as carrier for drug molecules and design in the way that can absorb active compounds by the formation of biomolecular interactions like bystrogen honding salt bonds etc. The main biological compound can be loaded into nanogels by allowing the interaction between matrix and active agent and these results more dispersed hydrophilic particles And for that manogels become the more flexible structure for controlled and sustained drug release to the targets site.

Nanogels are innovative drug delivery system that can play an integral part in pointing out many issues related to old and modern courses of treatment such as nonspecific effects and poor stability. Nanogels may be defined as highly crosslinked nanosized hydrogels range from 20 to 200 nm. They can be administered through various routes, including oral, pulmonary, nasal, parenteral, and intraocular. They have a high degree of drug loading capacity and it shows better permeation capabilities due to smaller size. They release the drug by pH responsive, thermos sensitive, volume transition, photochemical internalization, and photo isomerization mechanism. Nanogels have found an application dermatology and cosmetology as topical delivery systems of non-steroidal anti-inflammatory drugs (NSAIDs) and for the treatment of allergic contact dermatitis and psoriatic plaque. Nanogels are ideal for this application since they can overcome the major limitation of topical delivery systems, which is the relatively short contact time between active drugs and the application site. This is done by retaining water into the gel matrix and forming a uniform a dispersion of the nanogel. Oleic acid was used for surface modification. A variety of inflammatory disorders can be treated using this nanogel system as it can effectively permeate to deep layers of the skin.

Herbal medicines that are those with working ingredients made from plant parts, like leaves, roots or flowers Herbal medicine in a special and remarkable form of traditional medicine in which the traditional healer, in this case known as the herbalist, specializes in the use of herbs to treat various ailments. Herbal medicine is often defined as "the therapeutic practices that are alive for many years before the event and spread of recent medicines" This branch of other medicines that utilize medical plants for therapy is applied as berbal medicine whic exploits medicinal plants for therapy is applied as herbal medicine which is mostly researched by many researchers. Herbal medicines from traditional herbs or natural herbs are logically considered as alternative medicines during this period to treat and care est communicable diseases also as non-communicable diseases like cancer and diabetes Herbal medicines have played an crucial role in fixing the inspiration for current phanmugocia which is within the pharmaceutical market Herbal medicines get favour over modern medicines due to minimum side effects and also healthier option for the patients. Mostly 85% of Worlds population used herbal drugs to treat skin related diseases like viral, fungal, diabetic related issues, hypersensitive reactions etc. But in reality, despite their appropriate pharmacological

activity. they are less used in medicinal practices due to many reasons like solubility is, bioavailability problems, high dose requirement etc. They can be used in day-to-day medicinal practices by using them in a new way. And it results to reduce the dose of the herbs as a drug which is used for pharmacological activity, however many accessibility and also cost-effectiveness of these traditional medicines by making them more desirable as an alternative option for modern medicines. Curcumin is the most widely used herbal compound which has been studied extensively in cancer research. Herbal medicine has been widely used all over the world since age-old times and has been known by physicians and patients for their better.

The objective of the research study was to formulate the herbal nanogel of ginger (Gingerol) which is widely used as anti-inflammatory, and analgesic effect in herbal medicine. In this study, an attempt was made to formulate novel (nanogel) formulation of ginger (Gingerol) along with the skin permeation enhancer (Blackcumin oil) for the treatment of pain associated with inflammation.

Formulation design :

Topical route is not useful for delivery of all kinds of drugs. Drug selection is based on pharmacokinetic parameters and physicochemical properties of the drug. Any type of topical formulations consist of three important constituents Drug, Permeation enhancer and Polymer.

1. Gingerol has powerful anti-inflammatory and antioxidant effects, according to research. Ginger appears to speed up emptying of the stomach, which can be beneficial for people with indigestion and related stomach discomfort. It is also helpful in pregnancy-related nausea. Antioxidant helps to prevent all kind of disease and it also slows down the aging process.
2. The word "polymer" means "many parts" (from the Greek poly, meaning "many," and meros, meaning "parts"). Polymers are giant molecules with molar masses ranging from thousands to millions. Carbopol940 polymer is a white powder, crosslinked polyacrylic acid polymer. It is an extremely efficient rheology modifier capable of providing high viscosity and forms sparkling clear gels or hydro-alcoholic gels and creams.
3. Permeation enhancers are defined as substances that are capable of promoting penetration of drugs into skin and transdermal therapeutic systems offers a more reliable mean of administering drug through the skin. Black Cumin Oil is said to be great for hayfever and allergies as it is a natural immune booster. It aids with skin ailments from dry skin to eczema. As penetration enhancer. Rich sources of antioxidant & unsaturated essential fatty acids.

Advantages of nanogel:

1. Less amount of drug is required.
2. Provide protection from biodegradation of drug molecule inside the body system.
3. Size of nanogel can be adjustable according to delivery molecule.
4. Reduce the toxicity of drugs.
5. Nanogels are able to cross physiological barrier of skin also the blood brain barrier.
6. Nanogels with loaded drug can be delivered inside the body without any side effects and also can be applied topically.
7. Easy for set up and friendly formulation route.
8. Appropriate for many of bioactive compounds like proteins, antibodies, peptides etc.
9. Enhance permeation capability.
10. Improved ability to access areas that is not accessible by hydrogel, upon intravenous administration.

Limitation of Herbal Nanogel:

1. It is expensive to remove the surfactant and the solvent at the end of the preparation process.
2. Adverse effects might occur if any scraps of polymers or surfactants remain in the body.
3. Limited drug-loading capacity and suboptimal regulation of drug release.
4. The drug-polymer interaction may lead to a collapse in the structure, hence irreversibly trapping the drug molecules and improving the hydrophilicity of the nanogel matrix.

Challenges and Opportunities for Herbal Nanogel in Future:

Nanogels are a valuable, novel, and successful medication delivery approach that addresses both traditional as well as modern healing concerns, including specific side effects and limited stability. Each new study claims that it has discovered unique polymeric mechanisms and mechanistic views with potential therapeutic applications and nanogel design studies. Nanogels have a key role to play in the management of ophthalmic disorders, nasal medicine transport, and vaginal drug administration, according to a new study in nanogels and nanotechnology. The booming pharmaceutical business now has a multibillion-dollar market for nanogels produced with natural medications. However, there are still considerable obstacles in the way of using natural medicines in clinical studies. Nanogels appear to have a bright future in biomedical applications, according to recent research. For example, to control diabetes, a poly(4-vinyl phenyl boronic acid-co-2-(dimethylamino) ethyl acrylate) nanogel with insulin-loaded silver nanoparticles has already been developed. According to a report published by the World Health Organization, herbal-based pharmaceuticals will be used by 80% of the world's population to address their health needs. Despite allopathic pharmaceuticals' market potential, people seek alternative medicine as a complementary medical practice. Due to considerable changes in people's attitudes, be it social, political, or economic, the therapeutic application of herbal drugs has dramatically decreased. A viable platform for improving herbal characteristics is nanogel formulations. Natural products are transformed into the most effective pharmaceuticals for treating a variety of ailments, which includes cancer, skin diseases, diabetes, and others, using herbal nanogels. Cross-linked

herbal nanogels are commonly made with chitin, chitosan, PLGA, PEG, and other polymers. These cross-linked nanogels show a lot of promise for delivering medications through the skin. This has less adverse effects on patients' compliance with herbal treatments than oral pharmaceuticals. Despite the fact that numerous natural therapeutic remedies have been created, not all of them are safe. Some are extremely hazardous and can interact with other medications. The Formulation of Nanogel along with Herbal substance are The best combination of medication.

Material And Method:

Material:

Gingerol purchased from Zenobia laboratories, Delhi. Black cumin Oil Purchased from Mohammedia Product, Karimnagar. Triethanolamine Purchased from Prithvi Chemical, Nashik. Carbopol 940 Obtained from Colorcon Laboratories, Ltd. Goa. Ethanol obtained from Jitendra Scientific, Jalgaon. Methyl paraben obtained from S.D. Fine chemicals Ltd. India. Guar Gum obtained from Gunine Chemical co, Mumbai.

Method:

Reverse Micellar Method:

The polymer (Carbopol 940) and drug (Gingerol) added to the surfactant dissolved in an organic solvent. The crosslinking agent was added and stirred overnight.

- The evaporation of solvent takes place which results in dry mass after purification of nanoparticles present in the buffer was obtained.
- The gelling agent (Guar Gum) dissolved in water was prepared. The nanoparticles obtained were mixed with an aqueous phase comprising a gelling agent, resulting in the formation of nanogel.
- pH adjuster was added to neutralize the pH.

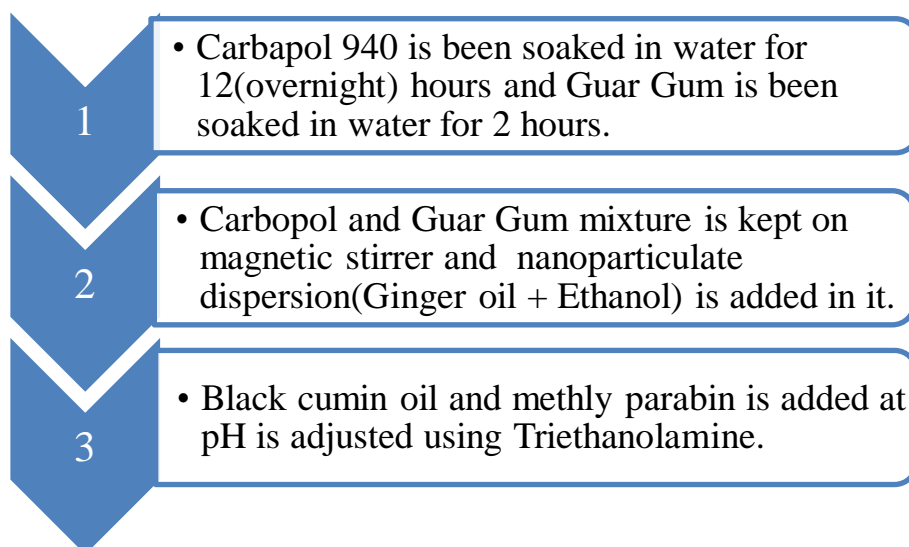


Fig. Flowchart for Preparation of Nanogel.

Formulation batches Nanogel :

Ingredients	Formulation batches with different concentration of ingredients. (% w/w)			
	F1	F2	F3	F4
Ginger Oil (Gingerol)	1	1	1	1

Carbapol 940	0.5	1	0.5	1.5
Guar Gum	1	0.7	0.5	0.7
Black cumin Oil	0.5	0.5	1	1
Ethanol	10	10	10	10
Methly Paraben	0.2	0.2	0.2	0.2
Triethanolamine	1.0	1.0	1.0	1.0
Distilled Water	q. s.	q. s.	q. s.	q. s.

Authentication of Drug:

Authentication of Ginger Oil (Gingerol) was carried out by evaluating its organoleptic Properties and spectral analysis.

Organoleptic Properties

Gingerol sample was studied for its physical properties such as colour, odour and Appearance results were reported in table.

Melting Point:

The melting point of gingerol was determined by capillary method.

UV Spectroscopy:

Methanol was selected for preparation of calibration curve. 100mg of crude extract was dissolved in methanol and diluted upto 100ml to get concentration of 1000ppm which is treated as stock solution. This stock solution was diluted further to get different concentrations. Resultant solutions were scanned for λ_{max} in the range of 200-400 nm using UVspectrophotometer.

Calibration curve of Gingerol:

In Methanol Stock solution of ginger extract were pipette out in to series of 10ml volumetric flasks and diluted with methanol to get final concentration of 20-100mcg/ml. The absorbance of resultant solution was measured at 281.40nm.

Characterization of Nanogel:

Appearance:

The Nanogel bases were inspected visually for clarity, color and appearance of any particles.

Homogeneity:

All formulated gels were tested for homogeneity by visual inspection after the gels has been set in container. They were tested for their appearance and presence of any aggregates.

pH of Nanogel:

Two gram of gel was dissolved in 100 ml of phosphate buffer solution and pH of the solution was measured by using digital pH meter.

Determination of Spreadability:

An excess of gel sample 1.5g was placed between two glass slides and 1000g weight was placed on slides for 5 minutes to compress the sample to uniform thickness. The weight (50g) was added to pan. The time in seconds required to separate the two slide was taken as measure of spreadability. (Pandey et al 2011)

It was calculated using following formula,

$$S = m \cdot l/t$$

Where,

S Spreadability in g.cm/sec.

m= weight tied to upper slide in gram.

l= length of glass slide in cm (11.3 cm²)

t= time in seconds

Stability studies:

The aim of stability study is to predict the shelf life of a product by accelerating the rate of decomposition, ideally by increasing temperature and relative humidity (RH) condition. Stability studies were carried out as per ICH Q1A guidelines. The stability study was performed at $37 \pm 20^{\circ}\text{C}$. and $60 \pm 5\%$ RH in an environmental stability chamber over three months to assess the stability of topical nanogel. The nanogel of optimized batch were packed with aluminum strips and stored for 3 months. Samples were analyzed after 3 months for physical appearance and drug entrapment efficiency. The formulations were evaluated mainly for their physical characteristics at the predetermined intervals of 1 month such as appearance/ clarity, pH, viscosity, and drug content.

Drug content:

1 g of nanogel which was quantity equivalent to dose, that is, 1% of drug was dissolved in 100 ml of phosphate buffer pH 7.4, a sample (5 ml) was taken from this solution and diluted to 25 ml, then gingerol concentration was determine by measuring the absorbance at 272 nm using UV-visible spectrophotometer (Shimadzu, UV-2600) and calculate the drug content on the basis of slope and intercept obtained from linearity equation, that is, $Y = mx + C$ of pure drug.

e) Viscosity:

Viscosity of prepared gel was measured using Brookfield at different RPM viscosity that was measured and noted. The measurement was made over whole range of speed settings from 50–200 rpm with 10 s between two successive speeds.

Measurement of Particle Size of Formulation:

The mean size of selected nanogels were determined by using Malvern Mastersizer 2000 MS. The mean particle size was recorded.

Result:**Authentication of Nanogel:**

The Authentication of nanogel was carried out by various methods such as organoleptic properties, melting point, appearance of solution, and observed experimental values are shown in following Table. 7.1

Table: Organoleptic properties of gel.

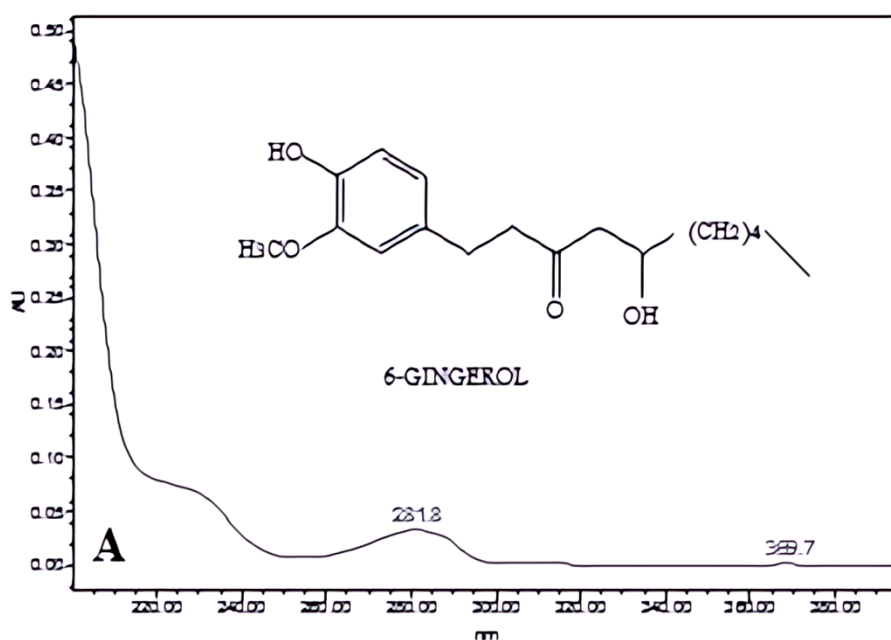
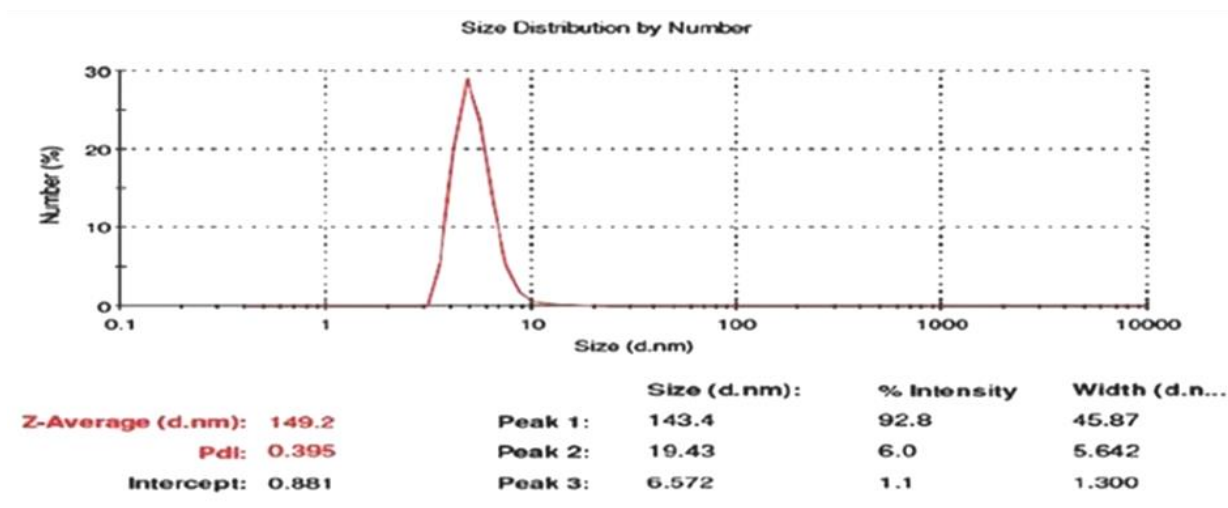
Sr.No	Method / Property	Result
1	Organoleptic Properties	
	Colour	Whitish
	Odour	Characteristics
	Appearance	Gel
2	Melting Point	-5 ^o c
3	Appearance of solution in 95% ethanol	Solution was found to be clear.



Fig. Nanogel

UV Method :

After studying the UV- spectra of ginger rhizome extract, it was found that it shows maximum absorbance at 281.8 nm. So absorbance at 281.8 nm was considered as λ_{max} for Ginger extract. The identity of drug was confirmed by comparing IR spectrum of drug with reported spectrum of Gingerol. Extract was found to obey Beer-Lambert's law in the concentration range of 20-100 $\mu\text{g/ml}$ with regression coefficient (r^2) values 0.9995. The regression equations were calculated as $y = 0.0097x + 0.0132$ for methanol.



UV Spectra of Ginger Extract

Particle Size:

Particle size was done by zeta sizer of optimized batch F3. The particle size was found to be 149.2 nm. Graph was observed, in which the particle size ranges from 100 to 250 nm which is in increasing order due to increase in concentration of excipients but after certain concentration, the ratio of drug to excipients was increased the particle size decrease. This was because of high drug to excipients ratio; amount of the excipients available was less. Hence, it was concluded that particle size varies with the concentration of drug excipients ratio. The average particle size of optimized batch F3 was observed 149.2 nm.

9.2 Drug content, pH, Spreadability, Viscosity for formulation batches:

Formulation	Drug Content	pH	Spreadability g.cm/sec	Viscosity
F1	76.12±0.012	6.91	15.85±1.56	1228
F2	82.30±0.023	7.20	12.65±2.42	1831
F3	91.21±0.034	7.10	14.25±1.68	2258
F4	83.96±0.049	7.5	11.25±1.56	1069

- ✓ All formulated nanogel exhibited the drug content in the range of 76.12 to 91.21. Maximum drug content was found to be in F3 batch i.e 91.21. Drug content was found in the order as F3>F4>F2>F1
- ✓ The pH of all formulations was found in the range of 6.91 to 7.20. Black cumin oil consist benzoquinone ring which is alkaline in nature, hence pH values was in acceptable range and close to that of skin pH.
- ✓ The spreadability was very low for F4 i.e. 11.25 g.cm/sec. and high for that of F1 i.e. 15.85 g.cm/sec, the spreadability of all formulations was between this range. Generally spreadability was increased with increase in concentration of carbopol 940, it might be due to viscous nature of carbopol 940. The good spreadability results were obtained for formulation F2, F3, F4 among these three batches the spreadability value for F3 can be considered as nice one, slight higher than that of F2 and lower than that of F1. Formulation F3 required less time to separate the glass slides and better spreadability value, hence both are well balanced.
- ✓ The viscosity of nanogel is taken in different RPM, such as 60,100,150, and 200, respectively, for all formulations. The torque is set up at 95% for constant viscosity. F3 formulation batch shows good viscosity as compare to other batches. The concentration of Carbapol 940 was a major factor affecting viscosity of formulation. The viscosity of F3 formulation is 2258 rpm.

9.3 Stability Study:

The optimized formulation is subjected to stability study for the period of 45 days. The sample is stored in described condition as per ICH guidelines. After the stability study sample is subjected to evaluation test and compared to test values just before to that of stability study.

Table: pH, drug content, viscosity of optimized formulation after stability study.

Formulation	Before Stability Study	After Stability Study
F3		
Drug Content	91.21±0.034	91.5±0.015
Ph	7.10	7.8
Viscosity	2258	2213
Spreadability g.cm/sec	12.25±1.56	12.72±1.57

Conclusion:

The Origin of research work starts from literature review. It is often difficult to start the work in particular direction if bypassed literature review. By considering the same thing, prove literature review was carried out. The selection of nano drug delivery system was carried out because of having large no. of advantage over the drug delivery system. Improved efficacy by controlled delivery of the therapeutic agent. Targeted and controlled release of the drug, decreased systemic toxicity. Enhanced solubility; Improved drug loading and bioavailability; Slow release of drug. There are many types of natural penetration enhancer among of that black cumin oil were found to be more effective than other natural penetration enhancer. Black cumin oil was found to be more effective than volatile oil. Black cumin oil was natural origin, safe, effective, non-irritant. After selection of penetration enhancer, Ginger (Gingerol) selected as drug for developing the NDDS. Nano Drug Delivery System is one of the safe, effective, advantageous, and non invasive drug delivery system as compared to other drug delivery system. Nanogel are having no. of advantageous properties over other topical formulations, non oily in nature, easily applied and removed, elegance of appearance. Formulation of Nanogel was carried out using carbopol 940 as polymer which is safe and more commonly used. It is also easily available. Formulation of Nanogel was carried using Guar Gum as gelling agent, methyl paraben as preservatives, triethanolamine as neutralizing agent, and ethanol as co solvent.

Next to the formulation evaluation of formulation is carried out to find out best formulation. Formulation batches were subjected to no. of evaluation test, pH, drug content, spreadability, viscosity. Optimization of formulation batches was carried out by considering all of the evaluating parameters. The formulation batch which followed best results for majority of evaluation test, is considered to be optimized formulation.

When compared to F4 the formulation F3 showed better pH value, drug content and spreadability; hence F3 was one of the best formulation among the all formulations ranging from F1 to F4. The optimized formulation is further subjected to stability testing. The optimized formulation found to be stable over long period of time under the described condition and no significant interaction was reported. After stability test period, when sample is subjected to evaluation test no significant deviation was reported for test values as compared to test values of sample just before to stability study.

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