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Preparation and characterization of bigel for tropical application

Shaikh Iqra, Vyas Jigar and Upadhyay Umesh

Abstract
These bigels have been the subject of academic research, but none have yet proven to be marketable or commercially viable. Despite the fact that the majority of drug-loaded bigels produced are meant for topical drug delivery, various delivery methods have been proposed in the past. Bigels are a relatively new concept, and the last 10 years have seen a lot of research in this area. the examination of the constituents of bigels (hydrogels and organogels) and the fact that certain of their combinations, such as emulsions, are already well-developed as dosage forms facilitates the construction and characterization of bigels. Research in other fields, including as cosmetics and food technology, has assisted the development of drug delivery bigels and has also offered crucial Topical formulations known as bigels are created by mixing an aqueous (hydrogels) and lipophilic (organogels) system. When applied to the skin, bigel formulations have the chilling effect, increased stratum corneum hydration, moisturising effect, are readily spreadable, include emollients, and are water washable. Bigels are stable oleogel and hydrogel combinations that lack any emulsion stabilizers or surfactants. Aqueous and lipophilic systems are combined at a high shear rate or rpm to create these homogeneous preparations. Bigels are formulated differently from creams and emulgels since they lack a surfactant or an emulsifier. The employment of two gel systems in bigels can have a synergistic effect, such as improving stratum corneum hydration and medication penetration as a result of both the phase oil and water.

Keywords: Bigel, hydrogel, organogel, skin permeation

Introduction

Topical Preparations

Topical drug administration is a localised drug delivery strategy that may be used anywhere in the body via ophthalmic, rectal, vaginal, and cutaneous channels. The skin is one of the most easily accessible organs on the human body for topical administration and serves as the primary route for topical medication delivery. Overall, scientific data suggests that topical gel is a safe and effective therapy option for the treatment of skin diseases. Topical medicines are applied to the skin to achieve effects on the surface, locally, or systemically. In certain situations, the base can be utilised on its own to provide therapeutic benefits such as emollient, calming, or protecting effect. However, many topical treatments contain therapeutically active chemicals that are disseminated or dissolved in the base. The combination of active ingredients and base allows for a wide range of topical preparations suitable for many types of drug delivery. Therapy terms used to classify the bases of topical preparations containing therapeutically active ingredients may be based on their physical properties (suspension), intended use (liniments), or composition (hydrophilic creams) [1].

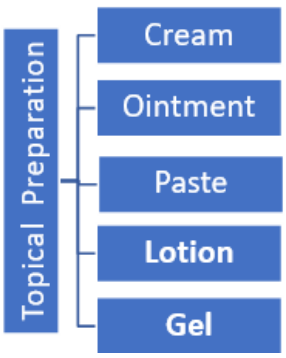


Fig 1: Topical Preparation

Creams, as opposed to transparent ointments, are semisolid emulsion systems with opaque appearances. Their consistency and rheologic character are determined by the kind of emulsion (water in oil or oil-in-water) and/or the composition of the particles in the internal phase [2]. In general, ointments are made up of fluid hydrocarbons enmeshed in a matrix of higher melting solid hydrocarbons. They often comprise a medication or medications that have been dissolved, suspended, or emulsified in an ointment base (vehicles). There are greasy things in nature [4]. Pastes are often more absorbent and less oily than ointments made from the same ingredients. They keep in place after application because to the rigidity and absorptive characteristics of the paste, with minimal inclination to soften and flow [5]. The lotions are transparent solutions containing 25-50% alcohol. They may also contain antibacterial, emollient, and hemostatic agents. They may also contain witchhazel extract, menthol, glycerin, boric acid, alum, potassium oxyquinoline sulphate, and chloroform. The majority of the lotions are used as after-shave preparation [6]. Gels are a relatively recent family of dosage forms generated by trapping of vast volumes of aqueous or hydro-alcoholic liquid in a network of colloidal solid particles, which may consist of inorganic compounds such as aluminium salts or organic polymers of natural or manufactured origin. The appearance of the gel will vary based on the colloidal components and liquid in the combination, ranging from perfectly clear to opaque. Most topical gels are manufactured with organic polymers such as carbomers, which give the product an aesthetically pleasing, clear sparkling appearance and allow it to be easily wiped off the skin with water [3]. Gels are semisolid liquid-rich two- component systems. In a typical polar gel, a natural or synthetic polymer forms a three- dimensional matrix in a hydrophilic liquid. Natural gums such as tragacanth, carrageenan, pectin, agar, and alginic acid are commonly employed, as are semi-synthetic materials such as methylcellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, and carboxymethylcellulose, as well as the synthetic polymer Carbopol. Certain clays, including bentonite, veegum, and laponite, can be used as long as the medicine does not bond to the polymer or clay. Such gels effectively release medications; the holes allow for relatively free passage of molecules that are not excessively big [5].

1.1.2

Advantages of topical preparation [6]

- Useful for local delivery of agents, particularly those which have toxic effects if administered systemically.
- Used for most dermatologic and ophthalmologic preparations.
- Avoidance of first pass metabolism.
- Convenient to use and easy to apply.
- The gastro-intestinal incompatibility will be avoided.
- Avoidance of the risks and inconveniences of administration and the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time, etc. in enteral or parenteral routes.
- Easy termination of medications when needed.
- Drug delivered selectively to a specific site.
- Provides drug utilization with short biological half-life and narrow therapeutic window.

1.1.3

Disadvantages of topical preparation

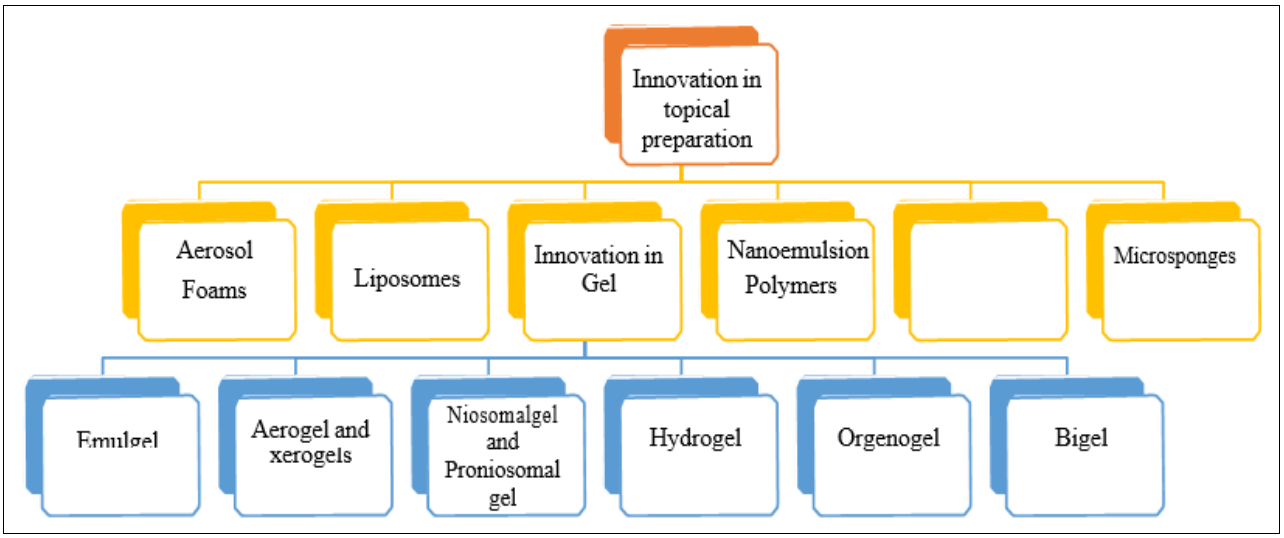
- Most drugs have a high molecular weight and are poorly lipid-soluble, so are not absorbed via skin or mucous membranes.
- Possibility of local skin irritation at the site of application.
- Contact dermatitis due to some drug and/or excipients may occur.
- Can be used only for those drugs which require low plasma concentration for action.

1.1.4

Application of topical preparation

- The purpose of using topical medicine is to deliver medication directly onto areas of the skin that are irritated, inflamed, itching or infected.
- Topical medicines are often applied directly onto a rash or an irritated area on the skin or rapid relief of symptoms.

Innovation in topical preparation



Aerosol foams are a common type of topical preparation for a range of skin diseases, including acne vulgaris. The aerosol base is administered via a gas-pressurized container that releases foam. Liposomes are extensively utilised in medications and cosmetics as carriers for regulated and optimised distribution to specific skin layers. Liposomes are spherical vesicles with amphiphilic lipid membranes (lipids that are hydrophilic on one side and lipophilic on the other) that contain an aqueous core, comparable to live cell bilayer membranes [7]. Nanoemulsions are a kind of emulsion (water-in-oil or oil-in-water formulations) distinguished by the dispersion of very minute droplets when combined [8]. Polymers are huge molecules made up of recurring structural units or monomers linked by covalent chemical connections. These molecules are the building blocks of natural (such as paper and amber), biological (such as proteins and nucleic acid), and manufactured (such as plastics and polyethylene) materials. Microsponges are physiologically inert particles constructed of synthetic polymers that can hold an active substance volume up to their own weight. An emulgel is a cross between an emulsion and a gel. While gels offer numerous advantages, the delivery of hydrophobic medicines has always been a source of worry. To address this restriction, emulgels were developed and are now employed for hydrophobic drug delivery [9, 10]. Aerogels and xerogels are both classified as inorganic gels since they are made of silica. Aerogels and xerogels have both been explored as possible drug delivery vehicles. Niosomes are liposomes that contain a nonionic surfactant. They can be unilamellar or multilamellar vesicles that can transport both hydrophilic and hydrophobic medicines [11].

Materials

Hydrogel

Carbopol 934 is used as hydrogelator in formulation of hydrogel. Carbomers are acid-based polymers that exhibit good mucoadhesion, especially at low pH levels when they are protonated. They are cross-linked acrylic polymers with a high molecular weight. Different grades of carbomers are available, based on the degree of cross-linking and production circumstances. Each grade is significant and useful in medicinal dose forms in its own right [12]. Carbopol 934 is polymerized in benzene after being cross-linked with allyl sucrose. Jangam *et al.* (2016) produced the levodopa-loaded in situ nasal gel to increase its bioavailability and commencement of action by using Carbopol 934 as a gelling agent. Carbopol 934 and HPMC K4M ultimately improved drug retention duration, inhibited drug drainage, and hence extended drug release. As a result it enhances bioavailability while avoiding the influence of the first pass, bypasses the BBB, and functions as a directed drug delivery mechanism to target the medicine to the brain area via direct nose-to-brain routes. (13) Distilled water is used as aqueous base in the formulation of hydrogel.

Organogel

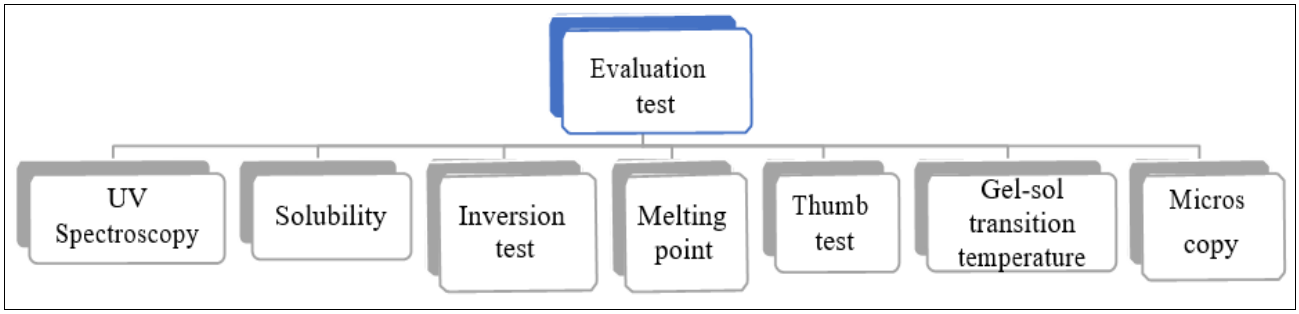
Span 80 is used as organogelator in the formulation of organogel. Polysorbate 80 is a polyethoxylated sorbitan and oleic acid derivative. This compound's hydrophilic groups are polyethers, commonly known as polyoxyethylene groups, which are ethylene oxide polymers. The numeral indication after polysorbate refers to the lipophilic group, in this example, oleic acid, in polysorbate nomenclature [14]. Polysorbate 80's complete chemical names are: 80 polyoxyethylene Poly (oxy-1, 2-ethanediyl) sorbitan monooleate (x)-sorbitan mono-9-octadecenoate.

Sweet almond oil, sesame oil etc. are used as oil base in the preparation of the organogel. The primary components are present in sweet almond oil. 5.26-7% palmitic acid, 0.33-0.6% palmitoleic acid, 1.61-4.40% stearic acid, 65.33-76.73% oleic acid, 17.36-25.17% linoleic acid, 0.44-0.64% myristic acid, 21.25-17.89% linoleic acid, 90.50-92.1% unsaturated fatty acids, 7.61-11.48% saturated fatty acids ratio [15, 16]. There is a lot of scientific evidence that sweet almond oil contains anti-inflammatory, immune-boosting, and anti-hepatotoxicity properties, as well as the ability to prevent the development of primary and metastatic colon cancer cells [17]. The ripe seeds of Sesamum indicum L are used to make sesame oil.

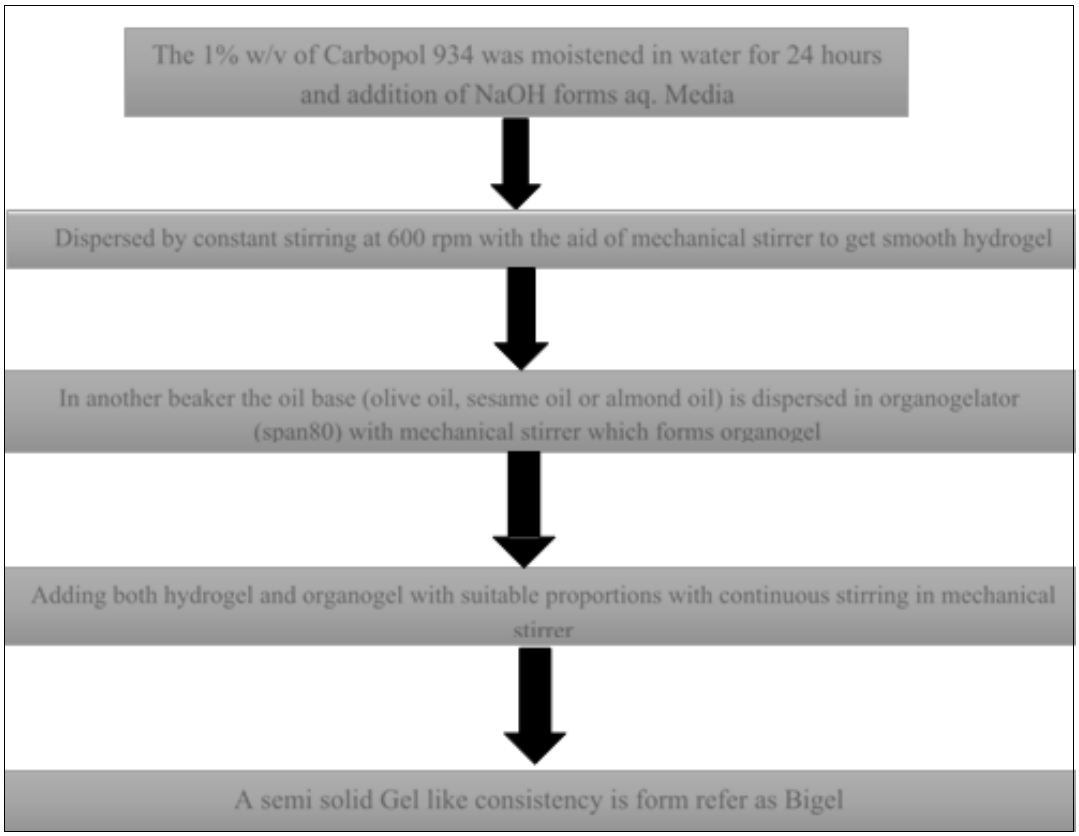
Among the principal edible oils, sesame seeds have the most oil (44-58%), followed by proteins (18-25%) and carbs (13.5%) [18]. Because of its antiseptic, disinfecting, anti-inflammatory, ant tubercular, antiviral, antibacterial, and antioxidant characteristics, sesame oil has been widely employed in medicinal and cosmetic applications [19]. The main components of sesame oil (sesamin, sesamolin, and sesamol) give formulation stability against oxidative degradation [20, 21]. Sesame oil has the greatest antioxidant level of any main edible oil [22]. It also has a high concentration of fatty acids such as oleic acid (43%), linoleic acid (35%), palmitic acid (11%), and stearic acid (7%).It has a unique flavour, making it a viable contender for usage in the culinary sector [19]. Many scientists have shown an interest in using sesame oil in medications, cosmetics, and food items because of these properties [23].

Methods

Evaluation test



Preparation of bigel



UV Spectroscopy: UV Spectroscopy is used to determine the absorbance of the drug. The drug here used to determine the absorbance is diclofenac. With the increase in the concentration of the drug the absorbance value increases. The calibration curve is obtained using UV Spectrometer which provide a graphic data of Absorbance with respect to the Concentration (mcg/ml).

Concentration in mcg/ml	Absorbance
10	0.148
20	0.258
30	0.384
40	0.517
50	0.647
60	0.795

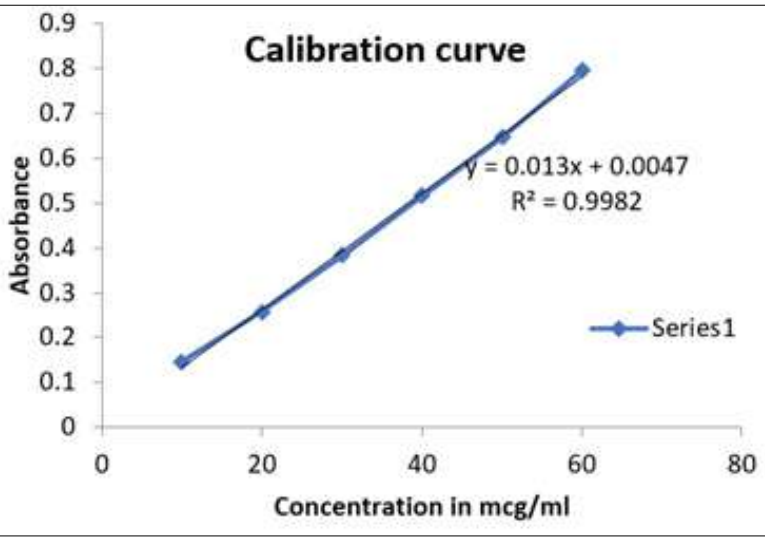


Fig 2: Calibration curve of discofenac sodium

Solubility: Solubility is a chemical attribute that refers to a substance`s ability to dissolve in a solvent. It is defined as the maximum quantity of solute that may be dissolved in a solvent at equilibrium.

Inversion test: The most common diagnostic test of gelation is to turn a beaker containing the sample upside down and then note whether the sample flows under its own weight. It was performed for bigels.

Gel-sol transition temperature

A constant temperature bath ranging from 25 ℃ - to 60 ℃. Within a 5 min interval, the temperature of the water bath was increased with an increment of 5 ℃. The temperature was noted at which the gel started to flow when the beaker was inverted.

Melting point, Viscosity and pH of the formulations were determined using digital melting point device, Brookfield viscometer and digital pH meter respectively.

Thumb test
The thumb test was carried out by placing a little of mucoadhesive gel between the thumb and the middle finger and kept for some time. The quality of adhesiveness was measured by how difficult it would be to separate fingers

Spreadability
The spreadability of the bigels was determined by placing 0.5 g of bigel inside a 1 cm diameter circle pre-marked on a glass plate. A comparable glass plate was placed on top of this glass plate. For 300 s, 1 kg mass was held on the upper glass plate. The augmented diameter formed by the bigel spreading was measured. Spreadability was measured using the formula;

$$S = \frac{MxD}{T}$$

Where,
S-Spreadability, g.cm/s.
M-Weight put on the upper glass slide D-diameter of spreading (cm).
T-Time for spreading gel in section (Approximately 300 s).

Microscopy: Microscopy was performed for optimized bigel formulation using Sudan red as an indicator. Which highlight the fibre of Gel and introduce to the Bigel Structural.

Stability studies: The bigel's stability is assessed using a long-term stability study and accelerated stability study. Because the bigels are a mixture of 2 semisolid phases, their thermodynamic stability improves many times. The formulations are tested for pH, colour, homogeneity, uniformity, phase separation and physical appearance.

Result and Discussion
Formulation of Bigel
The preparation of bigel involves three steps as they consist of two individual gels in making, the steps are; Formulation of organogel, hydrogel and mixing of two forms bigel.

Formulation of organogel
The organogel was prepared with the sweet almond oil/olive oil/sesame oil as a polar solvent, and span 80 as organogelator as shown in table 1. The complex was prepared at 60 ºC by continuous stirring and then cooled over night at 4 ºC.

Table 1: Formulation and of organogels

Ingredients	F1 (10g)	F2 (10g)	F3 (10g)
Sweet Almond oil	8g	-	-
Olive oil	-	8g	-
Sesame oil	-	-	8g
Span 80	2g	2g	2g

Table 2: Physiological parameter of organogel

Physiological parameter	F1	F2	F3
PH	4.5	8.5	4.33
Viscosity	24.42 cSt	84 cSt	34.98cSt

Formulation of hydrogel
Carbopol 934 is hydrogelator used for the preparation of hydrogel. Required quantity of Carbopol 934 was added to distilled water with continuous stirring. Add dilute NaOH if required to adjust the pH to nearly 7 (neutral to slightly alkaline).

Table 3: Formulation and characterization of hydrogel

Ingredients	F(10g)
Carbopol	0.3(1%)
Water	9.7
Physiological parameter	Value
PH	7.4
Viscosity	16-2700cSt

Formulation of bigel
Bigel was prepared by mixing hydrogel and organogel with continuous stirring. Add drug and mix it properly and stored at 25 ± 0 ºC.

Table 4: Formulation of bigel

Ingredients	Amount of drug in gm								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
Drug	1	1	1	1	1	1	1	1	1
Organogel [F1]	25	50	75	-	-	-	-	-	-
Organogel [F2]	-	-	-	25	50	75	-	-	-
Organogel [F3]	-	-	-	-	-	-	25	50	75
Hydrogel	75	50	25	75	50	25	75	50	25

The preparation of nine batches from B1-B9 consist of three different proportion with three different oil in each in individual batches in three different ratios with each oil and hydrogel combine and forming three Varing formulation possessing of individual characteristics of sweet almond oil, Olive oil and Sesame Oil with Hydrogel consisting of 1% of Carbopol and distilled water providing a water based gel. At a proper viscous mixing and proper temperature a clear adherent gel is form which is further processed for evaluation study as shown in table 5 and table 6 below.

Table 5: Physico-chemical evaluation of bigel

Parameter	B1	B2	B3	B4	B5	B6	B7	B8	B9
Viscosity	4484	5096	4135	4238	4882	4137	3926	4331	4655
PH	5.43	5.21	5.64	5.34	5.16	5.55	5.26	5.48	5.63
Melting Point	288 ℃	289 ℃	285 ℃	283 ℃	285 ℃	290 ℃	288 ℃	283 ℃	285 ℃
Inversion Test	Fail	Fail	Pass	Fail	Fail	Pass	Fail	Fail	Pass

									
Microscopy	No fibre structure found	No fibre structure found structure	Gel fibre Net like	No fibre structure found	No fibre structure found structure	Gel fibre Net like	No fibre structure found	No fibre structure found	Gel fibre Net like structure
Spreadability	13.23	12.11	11.15	16.17	13.13	12.11	11.04	16.14	11.15
Gel Sol transition	Phase separated at 65 ℃	Phase separated at 55 ℃	Phase not separated at 60 ℃	Phase separated at 50 ℃	Phase separated at 45 ℃	Phase not separated at 58 ℃	Phase separated at 50 ℃	Phase separated at 52 ℃	Phase not separated at 62 ℃

The prepared bigel batches were exposed to stability study for a period of one month and the data is reported in table 6.

Table 6: Stability studies

Duration (in days)		Parameters	B3	B6	B9
	PH Vis	Cosity	5.66 4135	5.64 4655	5.66 4137
0 days	Phase Separation		Phase not Separated	Phase not Separated	Phase not Separated
	PH Vis	Cosity	5.63 4122	5.62 4557	5.67 4102
15 days	Phase Separation		Phase not Separated	Phase not Separated	Phase not Separated
	PH Vis	Cosity	5.58 4023	5.54 4258	5.78 4017
30 days	Phase Sepration		Phase not Separated	Phase not Separated	Phase not Separated

Discussion

First, a discussion of the nine batches that have been assessed using various formulas is considered with an evaluated value. Each batch has different ratios of hydrogel and organogel, creating a bigel by combining. There are nine batches constructed using the various oil bases mentioned, such as sweet almond oil, olive oil, and sesame oil, which are made with span 80 acting as an organogelator when combined with hydrogel (Carbopol: Water). The hydrogel is combined with the three different oil base organogel formulations in proportions of 50:50, 75:25, and 25:75. Consequently, nine batches were formed, with each batch being assessed using a standard evaluation criteria. While batches with higher hydrogen content tend to have a more gel-like consistency and are rated as better gels, batches with larger amounts of organogel oil bases frequently get greasy and have their gel formation disrupted. The assessment parameters were established using UV spectroscopy, gel sol transition, inversion testing, viscosity, PH, and solubility testing. The batch containing a large quantity of oil base organogel is found to have low viscosity as a result of the evaluation test indicated above, which causes the gel to invert. It is also determined to have a low absorption in value and a poor solubility of diclofenac. In contrast, the batches with a higher proportion of hydrogen give the water base a gel consistency, determining the evaluation test to have the right viscosity and giving diclofenac the right solubility. Additionally, the jail does not change into a phase separation during the gel's sol transition at a higher temperature of 65 degrees Celsius. The batches with the organogelator and hydrogel in a 50:50 ratio was found to have a low viscosity and were consequently inverted in an inversion test on the side where the solubility of diclofenac in the gel was found to be close to zero. The solubility transition temperature for gels was also found to be between 50 and 60 degrees the phase is being split and the gel is converting at degree Celsius. The use of diclofenac in the treatment of rashes, sexually transmitted diseases, and other conditions has been determined to have a particular benefit over the effective biphasic content composition, according to research on the creation and assessment of bigel. There is still much work to be done in this field, despite the fact that some Bible characteristics, like their microstructures and mechanical properties, have recently been the focus of extensive research by Gill for drug delivery. One of their most promising features is the capacity to incorporate medication into both the Aquarius and oily face of the same formulation.

As a result, bigel are a relatively new concept, and the last ten years have seen a lot of research in this area. Different criteria have been used to analyse the components of bigel, particularly the hydrogen and organogel.

Conclusion

Academic study has looked into these bigels, but there aren't any yet that are commercially viable or marketable. Different delivery strategies have been suggested in the past, even though the bulk of drug-loaded bigels that are created are intended for topical drug delivery. Bigels are a relatively recent idea, and much of the study in this field has taken place in the last ten years. The investigation of bigels' components (hydrogels and organogels) and the creation and characterisation of bigels are made easier by the fact that some of their combinations, including emulsions, are already well- developed as dosage forms. The development of drug delivery bigels has benefited from research in other disciplines, such as cosmetics and food technology, which has also provided important tools and insights. These biphasic systems are appealing for use in pharmaceutical applications because to the outcome of mixing two forms of gel and their arrangement in bigels. There is still much work to be done in this area even if some bigel characteristics,

such as their microstructure and mechanical properties, are the subject of much research. Recently, bigels for drug delivery have started to take use of some of their most promising characteristics, such as the ability to incorporate medicines into both the aqueous and oily phases of the same formulation. Thus notably it's found to be useful in the anti-inflammatory as an anti rashes and sexually transmitted disease and many such which provide a specialize result over the effected result due to biphasic content constitution. There is various drawback too which is found throughout this report compare to other tropical drug delivery system but it can be overcome with the various progressive development and evolution in further research studies

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