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HARNESSING NANOEMULGEL SYSTEMS FOR CONTROLLED DELIVERY OF DRUGS

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ABSTRACT

Timely detection of cancer rescues lives and greatly lowers cancer mortality. As a result, a lot of time and energy has gone into investigating novel technologies for the early detection of the illness. A wide variety of biochemical entities, including complete tumor cells detected in bodily fluid, proteins, carbohydrates, nucleic acids, and tiny metabolites, as well as cytogenetic and cytokinetic characteristics, are included in the category of cancer biomarkers. Risk evaluation, diagnosis, prognosis, treatment toxicity and effectiveness prediction, and recurrence may all be done using them. In this review, we provide an overview of complete detail of challenges associated with detecting early-stage tumors, discovery of biomarkers, biomarkers in cancer detection, diagnosis, and prognosis, types of cancer biomarker, role of biomarkers in cancer research & medicine as well as future perspectives of biomarkers.

KEYWORDS: Biomarkers, Cancer, Tissue-imaging, Biopsy, Cytokinetic.

INTRODUCTION

Nanotechnology is one of the growing technological applications that had been increasingly applied in various demands, especially in cosmetics, biopharmaceutical, and food industries.[1] The lipophilic nature of the drugs leads to problems like poor solubility, unpredictable absorption, and inter and intra-subject variability concerning pharmacokinetics. Various techniques have been employed to increase the solubility of active moieties. These techniques include physical and chemical modification of API along with formulation strategies, which include particle size reduction, complexation, amorphization, and nano-carrier drug delivery systems.[2] Nanotechnology is one of the developing innovative applications that had been progressively connected in different requests, particularly in beauty care products, biopharmaceutical, and nourishment businesses. Nanotechnology containing items appear a potential advertise since of the predominant characteristics' properties such as little bead measure with the tall interfacial range, upgrade the conveyance of the dynamic fixings, and amazing solubilization capacity.[3]

Nanoemulsions are emulsions that are nanoscale in size that are designed to increase the distribution of active pharmaceutical ingredients. There are thermodynamically stable isotropic structures under which an emulsifier is used to integrate two immiscible liquids into a single process.[4] Nanoemulsions are currently gaining much interest in biopharmaceutical and cosmetics industries due to their versatility in delivering both hydrophilic and lipophilic drugs. Nanoemulsions are the colloidal dispersions that consist of oil, water, and emulsifier, with the range of the droplets size between 20 nm to 500 nm.[5]It consists of two immiscible liquids like water and oil, stabilised by an interfacial film consisting of a suitable surfactant and cosurfactant to form a single phase.[6] Nanoparticles can be used to enhance site specificity. As a drug delivery system, they enhance the therapeutic efficacy of the drug and minimise adverse effect and toxic reactions.[7]

Nanoemulgels (NEGs) are oil-in-water or water-in-oil nanoemulsions that are gelled by combining them with an appropriate gelling agent. They have a high patient acceptability, exhibit greater skin penetration due to nano-sized tiny droplets, and combine the benefits of both nanoemulsion and gels.[8] Nanoemulgel is considered as one of the appropriate candidates for drug delivery for skin because of its dual characters which are nanoemulsion and gel base. The benefits from both nanoemulsion and gel have caused nanoemulgel to achieve high patient acceptability.[9] It is the insertion of the embedded nanoemulsion system into the gel core which promotes a stronger skin permeability of the skin.

This nanoemulgel composition serves as drug repositories, controlling the release of drugs from the internal phase to the external phase, and beyond. Nanoemulgel, without affecting the skin, releases oil droplets from the gel and these oil droplets permeate the subcutaneous layer of the skin and transmit the drug to the desired site. Nanoemulsion-gel seems to have a strong adherence potential and higher solubilization of the drug in the oily phase results in higher concentration gradient towards the skin which ultimately increases the skin permeability of drug.[10]

Advantages

- The ability to resist First-pass metabolism.
- Effectiveness for a managed and long-term drug delivery system has been proven.
- It is safe for transdermal application due to its non-toxic nature.
- It shows better penetration of drug because the nanosized particles can easily enter by the rough.[11]
- Better loading capacity
- Better skin permeability of drug
- Better patient compliance.
- Provide higher Spread-ability of the formulation than creams.[12]

Disadvantages

- Bubbles formed during emulgel formulation.
- For utilisation in pharmaceutical application, surfactant used ought to be non-poisonous.
- Possibility of allergic reactions.
- Skin irritation on contact dermatitis.

NEED FOR DEVELOPING NANOEMULGEL

Nanoemulgel is considered as one of the fitting candidates for medicating conveyance for skin since of its double characters which are nanoemulsion and gel base. The benefit of nanoemulgel has been broadly applied within the field of pharmaceuticals. Various considers and examinations have been done on the formulations and advancement of nanoemulgel for the endless conveyance frameworks such as transdermal, vaginal, visual, dental, and nose to the brain for the treatment of differing local people as well as systemic afflictions from both nanoemulsion and gel have caused nanoemulgel to realise tall persistent worthiness. Right now, there has been an increment intrigued within the improvement of normal and eco-friendly products with a few useful bioactivities.

In the topical delivery system, Nanoemulgel plays an important role. The various needs of nanoemulgel for the topical delivery system are as follows: Because of its greater absorption capabilities, enhanced pharmacokinetic profile, and therefore higher therapeutic effectiveness, topical nanoemulsion gel can be regarded as a preferable alternative to traditional lipophilic drug formulations. One of the main reasons for the nanoemulgel formulation's increased patient acceptance when compared to other topical administration alternatives is its lower stickiness and superior spreading qualities.[13,14]

Topical Nano Emulgels are a more effective and convenient method of medication administration. Patient compliance is higher thanks to the gel and non-greasy qualities, and the lack of an oily foundation allows for greater medication release when compared to other formulations. With the incorporation of Nanoemulsion into the gel matrix, problems like creaming and phase separation that are linked with traditional emulsions are overcome, as is increased spare ability. In some topical conditions, a nanoemulsion-loaded gel is more beneficial. Nanoemulsion-Gel-based formulations might be a better and more dependable way to deliver hydrophobic medications in the future. Many drugs used to treat skin infections are hydrophobic in nature, and these treatments can be delivered successfully as Nanoemulgels, in which the drug is integrated into the Nano emulsion’s oil phase and subsequently merged with the gel basis. Despite a few roadblocks, nanoemulgel has a good chance of becoming the focal point for the topical delivery of lipophilic medicines in the future.[15,16]

FORMULATION REQUIREMENTS

Oil phase	Oils used in Nanoemulsion are generally mineral oils used as the vehicle for drugs E.g. castor oils and various fixed oils (cottonseed oil, maize oils, arachis oil ,Olive Oil, Coconut Oil, eucalyptus oil, rose oil, clove oil etc.[17]
Surfactant and Cosurfactant	The surfactant's amphiphilic structure allows for the dispersion of two immiscible phases, reducing interfacial tension and resulting in a sufficiently stable film capable of deforming around the droplets with the optimum curvature. Surfactants are molecules that can improve permeation across the skin, by reversibly attaching to keratin filaments.[18]The polysorbates Tween 80 and Tween 20, are the two most commonly used surfactants for the lipid based formulation.[19] Span eighty (Sorbitanmonooleate), AcrysolK a hundred and forty, Polyethylene-glycol-40-stearate, Acrysol, Labrasol, Stearic acid, PlurolOleique, Tween eight(Polyoxyethylenesorbitanmonooleate), Labrafil, metal stearate, wherever agents like Transcutol, Captex, Cammul, Migyol.[20] A co-surfactant, in particular, will decrease interfacial tension even further. Furthermore, it allows for greater oil penetration between the surfactant tails, favouring the optimum curvature of the interfacial film.PEG 400 and ethanol is

	the most commonly used cosurfactant.[21]
Aqueous phase	Commonly distilled water is used as an aqueous phase for the preparation of Nanoemulsion.
Triethanolamine	Used as a pHadjusting agent to adjust the pH in range of 5-6.
Sodium benzoate	Used as a preservative for stabilising the nanoemulsion.

METHODS OF PREPARATION

Preparation of nanoemulsion

Nanoemulsions may be made spontaneously by blending the compositions and lowering the interfacial tension between the oil/water interfaces, or by introducing high energy into the heterogeneous mixture. Thus, high-energy and low-energy emulsification processes may be used to develop a thermodynamically stable nanoemulsion.[22]

High pressure homogenization

Nanoemulsion preparation requires high shear force, therefore in this strategy high-pressure homogenizer or piston homogenizer is utilised for production of nanoemulsions with very small particle size (up to 1 nm). In this technique, a mixture is forced to pass through an orifice at a very high pressure ranging from 500 to 5000 psi. The resultant product is further subjected to intense turbulence and hydraulic shear resulting in emulsion with extremely fine particles. This has been proved to be the most efficient method for nanoemulsion preparation but the only drawback associated with this technique is high energy consumption and rise in temperature of emulsion during processing. For obtaining a smaller particle size, it also requires larger runs of homogenization cycles. Yilmaz et al. formulated phytosphingosine O/W nanoemulsions by employing high pressure homogenization method.[23]

Extremely small droplet sized nanoemulsions are achieved because during the process several forces like hydraulic shear, intense turbulence and cavitation act together. However, obtaining of small droplets that are in submicron levels requires large amount of energy (Lovelyn&Attama, 2010). This amount of energy and increasing temperatures during the high pressure homogenization process might cause deterioration of the components. Thermolabile compounds such as proteins, enzymes and nucleic acids may be damaged.[6]

Ultrasonication

The rough emulsion is converted into desirable nano-sized emulsion droplets using a sonicator probe. High-intensity sound waves having a frequency of even more than 20 kHz are generated by the sonicator probe. which has the ability to shatter the rough emulsion into nano-sized droplets (5- 500 nm). Different types of probes with varying dimensions are available for reduction in size up to recommended values. The sonication input intensity, time, and the probe type affect the droplet scale.[24]

Low-energy method

The production of nanoemulsions using a low-energy emulsification process uses less energy than high-energy methods. They produce nanoemulsions by utilising the system's inherent chemical energy and just requiring mild stirring. Low-energy approaches include phase inversion methods and spontaneous emulsification.[25]

Spontaneous emulsification

One of the most practical methods of nanoemulsion preparation is spontaneous emulsification. It has two liquid components, one of which is aqueous and the other is organic. Solvents, surfactants, and co-surfactants that are water miscible are shifted from the organic phase to the aqueous phase. The process starts with an organic phase, such as oil and surfactant, being introduced into an aqueous phase, which is made up of water and cosurfactant. Massive turbulence at the phase interface is caused by the rapid migration of water-miscible components into the aqueous phase, which increases the oil–water interfacial area. As a result, small oil droplets form spontaneously.[26]

Phase Inversion Methods

These methods utilise the chemical energy that is released because of the phase transitions during the emulsification process. Required amount of phase transitions are achieved by changing the composition at constant temperature or by changing the temperature at constant composition.

Phase Inversion Temperature (PIT)

In this method, temperature is changed at constant composition. Non-ionic surfactants which have temperature dependent solubility like polyethoxylated surfactants play an important role. Emulsification is achieved by modifying affinities of surfactants for water and oil as a function of temperature.[27] During heating of polyethoxylated surfactants they become lipophilic due to dehydration of polyoxyethylene groups. Therefore, this circumstance establishes the principle of producing nanoemulsions by the PIT method. In order to prepare nanoemulsions by using PIT method, it is necessary to bring sample temperature to its PIT level or hydrophile–lipophile balance (HLB) level.[28] In the PIT method, the droplet sizes and the interfacial tensions reach their minimum value. This method promotes emulsification by benefiting from the extremely low interfacial tensions at the HLB temperature. Nevertheless, it has been observed that although emulsification is spontaneous at the HLB temperature, coalescence rate is greatly fast and emulsions are highly unstable. It has been reported that stable and fine emulsion droplets can be produced by

rapid cooling of the emulsion near the temperature of PIT.

Phase Inversion Composition (PIC)

In this method, composition is changed at constant temperature. Nanoemulsions are obtained by consistently adding water or oil to the mixture of oil surfactant or water-surfactant. The PIC method is more suitable for a large scale production than the PIT method since adding one component to an emulsion is easier than to generate abrupt change in temperature.[29] By adding water to the system, volume of water increases and this results in a transition composition. In other words, the level of hydration of the polyoxyethylene chains of the surfactant increases and thus spontaneous curvature of the surfactant goes to a change from negative to zero. As in the HLB temperature, in the transition composition a balance is obtained for the surfactant hydrophilic–lipophilic properties. When this transition composition is exceeded, small sized metastable oil in water droplet are composed due to the separation of the structures that have zero curvature.[6]

CHARACTERIZATION

pH measurement

The most widely used method for measuring pH is the electrochemical method, which involves a pH sensor or electrode that generates a voltage proportional to the hydrogen ion concentration in the solution. The pH sensor consists of a reference electrode, a measuring electrode, and a temperature sensor. The reference electrode provides a stable reference point for the measuring electrode, which is usually made of glass or other material that is sensitive to hydrogen ions. The temperature sensor compensates for the effect of temperature on the pH measurement. The pH sensor is connected to a pH meter or transmitter that displays or transmits the pH value.

The pH of nanoemulgel depends on the applications whether for skin or for other mucous membrane, for example The pH of human skin is known to be between 4.5 and 6.[30]

Determination of Viscosity

- Set up the base level of instruments using level indicator on the top of instrument and plug in for constant electric supply.
- Clean the spindle and all over to the instrument.
- Rotate the spindle in the gel till to get a constant dial reading on the display of the viscometer.
- Repeat the determination at least three time for reproductable results.

The gel's viscosity is crucial for effective application to the skin. It is important for gel to know the rheological behaviour. Viscosity can be defined as the resistance of fluid to flow and higher viscosity means higher resistance to flow. Fluids generally are classified into Newtonian and non-Newtonian systems. In Newtonian flow, the fluid with higher viscosity, requires greater force per unit area (shear stress) to generate a certain shear rate. In Newtonian flow, the viscosity is constant with different shear rate. In contrast to the Newtonian fluid, non-Newtonian flow does not comply with newton low and the viscosity is changed with the differences in shear rate.[31]

Spreadability measurement

Place a sample evenly in a container with a 90^o tip and cone-shaped hole for he compression test with a 90^o cone-shaped jig from the upper part. The sample is extruded and spread between the upper jig and the lower jig, and the spreadability is evaluated from the test power at that time.

The therapeutic efficacy of the developed formulation will be determined by the spreadability of the topical preparation. The ease with which a gel spreads over the application site on the skin and the affected area is referred to as spreadability. The 'Slip' and 'Drag' properties of nano emulgels are used to determine their spreadability.[32]

Zeta Potential

The particles in a solution usually possess a layer of ions on their surface, referred to as the stern layer. Adjacent to the stern layer, there exists a diffuse layer of loosely bounded ions, which along with the stern layer collectively called an electrical double layer. There is a boundary between the ions in the diffuse layer that move with the particle and the ions that remain with the bulk dispersant. The zeta potential is the electrostatic potential at this “slipping plane” boundary.[33] Zeta potential measurement provides an indirect measure of the net charge and is a tool to compare batch-to-batch consistency. The higher the zeta potential, the greater the repulsion resulting in increased stability of the formulation. For example, the high zeta potential of emulsion globules prevents them from coalescing. A surface charge modifier may also be used to adjust the surface charge. For instance, if a negatively charged surface modifier is used, the zeta-potential value becomes negative, and vice-versa.[34,35]

Droplet Size Measurement and Polydispersity Index (PDI)

The size of globule in nanoemulgel is referred as its hydrodynamic diameter, which is a diameter of equivalent hard sphere that diffuses at the same rate as the active moiety. The PDI determines the distribution of droplet size and is defined as the standard deviation of droplet size divided by mean droplet size. The droplet size and the polydispersity index are closely connected to the stability and drug release, as well as the ex-vivo and in-vivo performance of the dosage form. In addition, it is important to measure consistency between different batches. The globule size and PDI of the formulation can be measured using a zetasizer or master sizer. The globule size of the emulsion can be determined using the

principle of dynamic light scattering, in which the transitional diffusion coefficient is measured by monitoring the interaction between the laser beam and dispersion, as well as the Polydispersity index.[36,37]

APPLICATIONS

Controlled release

Nanoemulgel acts as a drug reservoir and has shown prolonged residence time leading to sustained release of drug. Thus, it is beneficial for the drugs having shorter half life.

Used as an anti-inflammatory agent.

Better loading capacity

It has been observed by nanoemulgel as compared to other novel drug delivery systems. Due to its nano scale size ,it has a larger surface area and better entrapment efficiency which enable it to load more amount of drug in its network like system.[38]

Better stability

Nanoemulgel system is more stable than other transdermal drug delivery systems, because it decreases the interfacial as well as the surface tension of the formulation, which make it superior from a conventional transdermal delivery system.[39]

Better pharmacokinetic profile

Nanoemulgel formulation gives higher Tmax and peak plasma concentration of lipophilic drugs than the conventional gel as well as oral formulation. There by, nanoemulgel preparations improves the bioavailability of lipophilic drug many folds than the other lipophilic drug formulations.[40]

Enhanced drug permeability through skin

Nanoemulgel has shown significant enhancement in the permeability of the drug through skin than other formulation since from nanoemulgel preparation, the drug can permeate the skin layer through both paracellular and transcellular, whereas, in nanoemulsion, only transcellular permeation is seen.[41]

Antifungal agent

High skin permeability of nanoemulgel has made it a better alternative for the faster treatment of fungal infection.

Alopecia

Minoxidil is a commonly used drug for the treatment of hair loss also known as alopecia. Nanoemulgel is capable of increasing solubility and permeability of drug through the skin which is more effective and safer than conventional preparation.

Table 1: Previous research works on nanoemulgels.

S.no	TITLE	METHOD	OILS	REFERENCE
1	Formulation development of pharmaceutical nanoemulgel for transdermal delivery of febuxostat	High speed stirrer and high speed homogenisation technique	Olive oil	[42]
2	Development of Coriandrum sativum oil nanoemulgel and evaluation of its antimicrobial and anticancer activity	Self emulsification technique	Coriandrum sativum oil	[43]
3	Development of a novel nanoemulgel formulation containing cumin essential oil as skin permeation enhancer	High speed homogenisation technique	cuminum cyminum seed essential oil	[44]
4	Development of a nanoemulgel for the topical application of mupirocin	Ultrasonic probe homogeniser	Eucalyptus oil	[45]
5	Preparation of clotrimazole nanoemulgel and its antifungal studies	Self emulsification technique	Almond oil, olive oil	[46]
6	Formulation and evaluation of topical nanoemulgel of methotrexate for rheumatoid arthritis	Spontaneous emulsification method	Peanut oil	[47]
7	Formulation and evaluation of nanoemulgel for the topical drug delivery of posaconazole	Self emulsification technique	Almond oil, oleic acid	[48]
8	Design and characterisation of nanoemulgel for topical fungal infection: Box behnken design approach	Self emulsification technique	Argan oil,ginger oil	[49].
9	Development of miconazole nitrate nanoparticles loaded in nanoemulgel to improve its antifungal activity.	Self emulsification technique	Almond oil, olive oil	[50]
10	Formulation and evaluation of voriconazole loaded nanoemulgel for the treatment of onychomycosis	Aqueous titration technique	Olive oil	[51]

Table 2: Patents on nanoemulgels.

Patent Number	Title	Reference
US11185504B2	Transdermal non-aqueous nanoemulgels for systemic delivery of aromatase inhibitor	[52]
CA3050535C	Methods of treating inflammatory disorders and global inflammation with compositions comprising phospholipid nanoparticle encapsulations of anti-inflammatory nutraceuticals	[53]
CN107303263B	Tripterygium glycosides nanoemulsion gel and preparation method thereof	[54]
EP3099301B1	Besifloxacin for the treatment of resistant acne	[55]
WO2020240451A1	In-situ gelling nanoemulsion of brinzolamide	[56]
WO2020121329A1	Minoxidil and castor oil nanoemulgel for alopecia	[57]
BR102019014044A2	Nanoemulgel based on ucúuba fat (Virola surinamensis) for transungual administration of antimicotics	[58]

Future perspectives

Delivering hydrophobic drugs to the biological systems has been a major challenge in formulation development owing to their low solubility, leading to poor bioavailability. Some of the topical formulations include creams, ointments, and lotions. They possess good emollient characteristics, however, have slow drug release kinetics due to the presence of hydrophobic oleaginous bases such as petrolatum, beeswax, and vegetable oils, which inhibit the incorporation of water or aqueous phase. On the contrary, topical aqueous-based formulations like gels enhance the drug release from the medication since it provides an aqueous environment for medicament. Therefore, hydrophobic APIs are blended with oily bases to form an emulgel, which further undergoes nanonization to form a nanoemulgel with enhanced properties. The superior properties of a nanoemulgel like thermodynamic stability, permeation enhancement, and sustained release make it an excellent dosage form. There are several marketed emulgels and patents being filed for the same, demonstrating its tremendous progress in this field. By making advancements in the ongoing research, nanoemulgel, as a delivery system, would outshine, in formulating the drugs that are being eliminated from the development pipeline owing to their poor bioavailability, therapeutic non-efficacy, etc. Despite these advantages, the manufacturing of nano-emulsion limits its commercialization. However, with the progressing technology, commercially feasible and profitable manufacturing techniques could be possible in the future. With the advantages of nano-emulgel over other formulations, a tremendous increase in the production of nano-emulgel can be foreseen.

CONCLUSION

The selection of ingredients and their appropriate ratios play a vital role in deciding the properties of a nano-emulgel. Deviation from this could affect the conversion of a nano-emulsion to a nano-emulgel and its thermodynamic stability. The nano-emulgel is more stable compared to that of a nano-emulsion mainly due to its less mobile dispersed phase and the decreased interfacial tension. Thus, the former is a better alternative in delivering lipophilic moieties mainly due to improved permeation, and better pharmacokinetics, which subsequently improves the pharmacological effect. Patient compliance is also elevated due to its non-greasy and improved spreading properties on topical administration. Despite its advantages, nano-emulgel is still at its infancy in the prospect of the pharmaceutical industry. However, various emulgels are being marketed e.g., Voltron emulgel, which holds out hope for the commercialization of nano-emulgel in near future. Hence it has the potential to become a centre of attention due to its safety, efficacy, and user-friendly nature for topical drug delivery. Despite some disadvantages, nano-emulgel is a tool for the future which may be an alternative to traditional formulations.

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