REVIEW ARTICLE

Oleogel: A promising base for transdermal formulations

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Since last two decades the work on oleogels is being exploited in pharmaceutical, cosmetics, and nutraceutical industries for their desired rheological, physical, and chemical stabilities in semisolid formulations. Recently, we had developed a stable and efficacious oleogel containing diclofenac diethylamine for topical application. The present review article deals with the literature of oleogels including its application in various fields from last few decades till date. The literature reveals that the oleogels have simplicity in manufacturing, high physical, chemical, and mechanical stability and better invivo efficacy, which make them appropriate to employ as bases for topical formulations.

Key words: *Applications, oleogel, organogelators, transdermal formulation*

INTRODUCTION

In the recent years, semisolid products have acquired much importance in the pharmaceutical, cosmetics, nutraceuticals, and food industries. They have been used either as gels, lotions, creams, ointments, and jellies. The method of preparation of these products is very tedious and complicated. In addition to this, there is a great concern associated with the long-term stability of most of these products due to which there is a reduced shelf-life of these products. The semisolid preparations having both solid and liquid components in its structures have been regarded as gels.[1] Gel-based semisolid products have been found to be more stable than other types.[2]

In general, gel-based products may be categorized as hydrogels, emulgels, and organogels or oleogels, depending on the polarity of the liquid component. Hydrogels have water as the dispersion medium gelled with suitable hydrophilic gelling agent, whereas organogels or oleogels have non-polar dispersion medium like fixed oil, mineral oil, organic solvents, etc gelled with a agent referred as organogelator. Among gel-based products, the use of oleogels based products is increasing, which may be attributed to the easy method of preparation and inherent long-term stability of these products.[3] Initially, organogelators were frequently discovered serendipitously, while now new strategies of chemical syntheses are being explored with increasing success in the design of new gelators[4,5] reviewed the different classes of organogelators. Some pharmaceutical excipients were also identified as organogelators, namely sorbitan esters[6] and gelators with the cholesterol moiety.[7] Depending on the mechanism of the formation of the three dimensional skeleton, which help in immobilizing the non-polar phase, the oleogels are further categorized as fluid-filled structure and solid fiber-based oleogels.[5] With the advancement in the pharmaceutical, food, nutraceutical, and cosmetics industries, various oleogels based on non-biocompatible components are replaced by biocompatible one and have in use for human use.[8,9]

TYPES OF ORGANOGELATORS

Organogelators may be differentiated as one component and two component organogelators. Two component organogelators are dependent on one or more other compounds to gel the organic liquid. One component organogelator possess an ability to gel the organic solvent alone, without help or addition of any other component.[2] Organogelators are broadly classified

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into two categories depending upon molecular weight of gelator.[8]

Low Molecular Weight (LMW) organogelators (LMWOG) andPolymeric organogelators.

Low molecular weight organogelators

Many classes of LMW compounds form stable and efficient gels with various organic solvents at low concentrations. They are characterized by their good solubility in organic solvents upon heating and smooth gelation at low concentration.[10] Gels formed using LMW organogelators are also termed as supra-molecular gels. In recent years, they have got more attention due to great structural variety and diversity range they offer for a selector.[2] Depending upon the major driving force involved in molecular aggregation LMW organogelators can be sub classified as below.[11] Hydrogen bonding based, non hydrogen bonding based some of the LMWOG are discussed below:

Amygdalins

Amygdaline has worked as good gelator for broad range of solvents such as non-polar hexanes to polar aqueous solutions. These supermolecular hydrogels were demonstrated as an enzyme triggered drug-delivery model for hydrophobic drugs.[12]

Carbohydrates

Trehalose, a-D-glucopyranosyl-(1-1)-ß-D-glucopyranoside is an alpha-linked disaccharide. It is obtained by fungi, plants, and invertebrate animals and it has been extensively used in the food, pharmaceutical, and cosmetic industries. It is used to gel many organic solvent at very low concentrations (0.04% w/v).[12]

Amino acids

Simple cyclos (dipeptides) are consisting of many amino acids and possesses remarkable gelation ability for many organic liquids such as, edible oils, glyceryl esters, alcohols, and aromatic molecules.[10]

Cinnamic acids

Organic salts prepared from dicyclohexylamine and substituted of non-substituted Cinnamic acid act as good gelators for organic liquid. They are capable of selective gelation of oil from oil/water mixture. Dicyclohexylammonium 4-chlorocinnamate, 3-chlorocinnamate, 4-bromocinnamate, 3-bromocinnamate, 4-methylcinnamate are some of the examples.[11]

Soyabean lecithin

Soyabean lecithin was gelled by addition of water and extensively employed for drug delivery.[13]

Silicon dioxide

Non-polar liquids such as vegetable oils, liquid paraffin, or isopropyl myristate can be converted to spreadable gels with colloidal silicon dioxide. If the refractive index of the oil is near to that of the colloidal silicon dioxide (1.48) then the gel will be transparent. These gels are distinguished by a high viscosity that has little dependence on temperature, and by a pronounced thixotropic behavior. They are therefore suitable for preparations that must meet strict requirements for storage and thermal stability.[14] Lipophilic ointment bases and non- aqueous suspensions may be thickened with materials such as Aerosil®, a Coagulated silica sol. Incorporation of the silica into oil leads to an increase in viscosity, which is brought about by hydrogen bonding between the silica particles: 5-10 percent silica imparts a paste–like consistency on a range of oils such as isopropyl myristate, peanut oil, and silicon. As shown in Figure 1, the degree to which viscosity is increased is a function of the polarity of the oil, the silica being more effective in polar media.[15] Suspensions of silica in oil are thixotropic: on storage for several days the viscosity increases due to the slow aggregation of the silica particles.

Aluminum and zinc soaps

These agents are also capable to gel various non polar solvents like liquid paraffin and fixed oils.[16]

Polymeric organogelators

Polymeric organogelator acts in similar way as that in case of LMW organogelators. Polymeric organogelators also immobilizes the organic solvent by formation of network structure formed by physical interactions between polymer molecules. Polymers may be either linear, hyperbranched or star shaped polymer.[8] Organogelators based on photochromic dihydroindolizine (DHI) system were developed by chemical synthesis. Controlled delivery of drug from these polymeric organogels can be achieved by using temperature, acidity, or light, as an external stimuli. These novel materials can be also used as photoreponsive materials and in nanotechnology.[17] Polymeric micelles made up of self assembly of amphiphillic molecules have been used in oral drug delivery. These micelles increases solubility of hydrophilic compounds in oil and hence

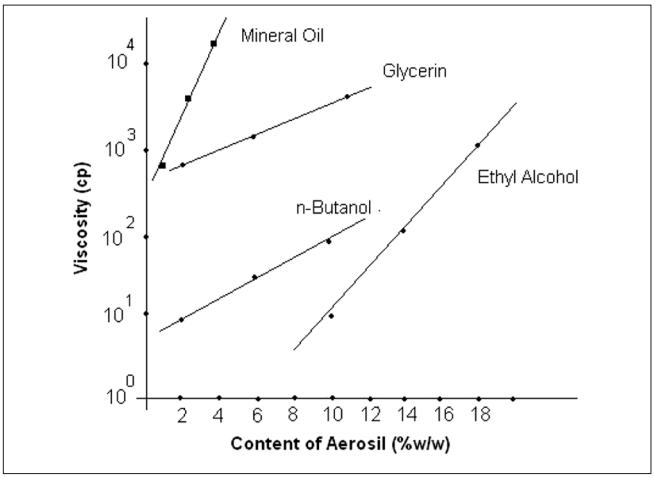

Figure 1: Influence of the polarity of the medium on the increase in the viscosity attainable with Aerosil 200, a coagulated silica solution

can be used in preparation of anhydrous peptide products.[18] Smart polymeric gels have been extensively used as a stimuli sensitive drug delivery in various biomedical applications like sensors and actuators.[19] They involve polymers that respond to change in common physiological triggers including change in pH, electrolyte concentration. Recent work has demonstrated an ability of the specific polymers to respond to antigen-antibody interaction, glucose, and enzymes.[20] Hence, organogels made up of smart polymers is area with wide scope in biomedical applications. Novel pH sensitive copolymer gelators have been prepared for controlled drug delivery. Dipyridamole was used as model drug and its controlled release rate was obtained by optimizing, polymer concentration, polymer molecular weight, temperature, and pH of the solution [Table 1].[21]

MECHANISM OF GEL FORMATION

A gel can be divided into primary, secondary, and tertiary structure like a protein to understand the mechanism of gel formation. Primary structure (A° to nm scale) is composed of unidirectional aggregation of gelator molecules. The secondary structure (nm to μm scale) is nothing but the morphology of the aggregates like micelles, vesicles, fibers, ribbons[29,30] or sheets. Whereas tertiary structure of a gel (μm to mm scale) involves the interaction of individual aggregates to form gel network.[2]

As stated earlier, oleoogels are formed by 3-dimensional network of intertwined fibers.[11] Fibers may be either fluid filled hollow fibers or solid fibers. The mechanism of formation of both is illustrated in Figures 2 and 3, respectively.

Gels prepared by using LMW organogelator are stabilized by solid fibers. They are generally prepared by dissolving gelator in organic solvent at higher temperature and subsequent cooling at room temperature [Figure 3]. During cooling process three situations are possible, i.e., a highly ordered aggregation giving rise to crystals, or a random aggregation resulting in an amorphous precipitate or an aggregation process intermediate between these two, which gives rise to a gel [Figure 4].

Table 1: Some commonly used oleogels

Organogelator used	Organic solvent gelled
L-alanine derivatives	Various pharmaceutical grade vegetable and synthetic oils[22]
Cholesterol	Liquid paraffin[23]
Sorbitan tristearate + Lecithin	Sunflower oil[24]
Phytosterol + Oryzaznol	Various edible oils[25]
TAG, DAG, MAG, FA, Waxes	Various edible oils[25]
12-Hydroxystearic acid (12-HAS)	Soyabean oil or capric/ caprylic triglyceride[26]
ß-Cyclodextrin (ß-CD) Para substituted anilines (ps-An)	Lithium chloride in N, N- dimethyl formamide[27]
Triazine functionalized with a-amino acidic appendages	Haloalkanes, and aromatic solvents[28]

The physical gels formed by LMW organogelators are stabilized by relatively weak inter-chain interactions such as hydrogen bonding,[10] van-der Waals forces, metal coordination,[32] and π-π-stacking.[11] These organogelators form fibers, strands, tapes or helix via unidimensional growth of the molecules.[2,8,11]

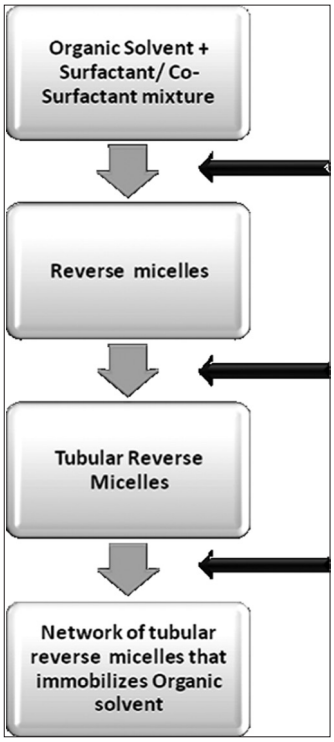

Figure 2: Method of formation of organogels by fluid-filled fiber mechanism[8,31]

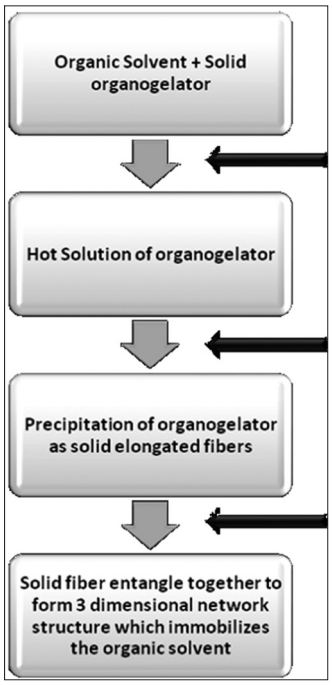

Figure 3: Method of formation of organogels by solid fiber mechanism[8,31]

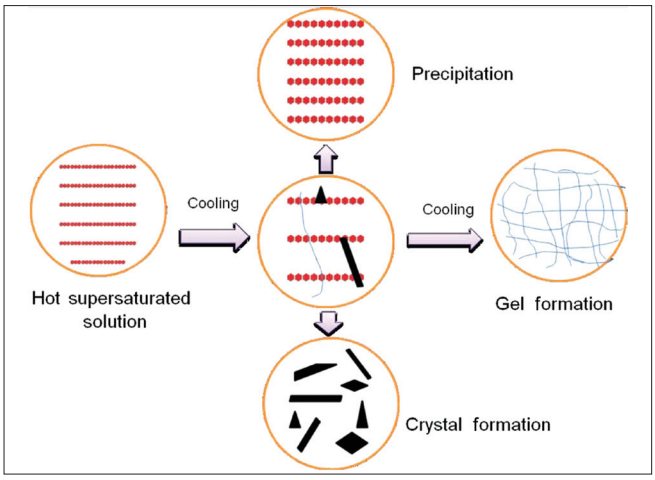

Figure 4: Various possible aggregation modes of gelator molecules[2]

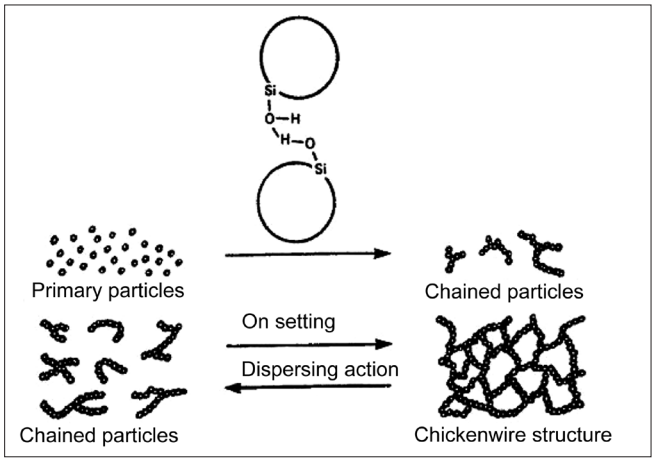

Figure 5: Schematic representation of the interaction between two colloidal silica particles (top), the formation of chain structure (Center) and the development of 'Chickenwire' structure as well as the thixotropy (bottom): Mean diameter of colloidal silica particle is 10 nm

In case of cinnamic acid salt gelators it has been investigated that, prerequisite for the one-dimensional (1D) growth of the gel fibrils is mainly governed by the 1D hydrogen-bonded networks involving the ion pair. Whereas all the non-gelators show either two- (2D) or zero-dimensional (0D) hydrogen bonded assemblies involving the ion pair.[11] Specialized type of heat set gel has also been developed using ß-CD and para substituted aniline with lithium chloride in N, N-Dimethylformamide. These gels are thermo-reversible in nature. They give clear solution at room temperature but solidify and turn into gel on heating to higher temperature.[27]

The phenomenon of interaction between two colloidal silica particles and viscosity is represented in Figure 5. When dispersed in a liquid, the silanol groups on the surface of colloidal silicon dioxide form hydrogen bonds with each other, either directly or indirectly through the liquid. The result is a temporary, three-dimensional network that is macroscopically visible as "thickening". The more non-polar the medium, the more pronounced the effect. When shear forces are applied (stirring, shaking) the hydrogen-bond lattice is broken down and the viscosity decreases. This is the typical thixotropic/ pseudoplastic flow behavior of gels that contain colloidal silicon dioxide.[33]

CHARACTERIZATION OF OLEOGELS

Following are the various methods that have been used for the characterization of oleogels.

Test for gelation/determination of critical gelation concentration

Inverted tube or inverted vial method is the most common method to confirm the gelation. In this method, the weighed amount of organogelator is taken into a vial with weighed amount of organic solvent. The vial is then closed properly to create a pressure inside and so as to increase the boiling point of the liquid. The vial is carefully heated to an optimum temperature so as to melt its content completely. Then the vial is allowed to cool for sufficient time before inverting. After inversion absence of flow indicates the formation of gel.[2,34]

Gel-Sol transition temperature

Gel-sol transition temperature (Tg) is the temperature below which gel does not shows any distinct flow property. Gel loses its structural integrity at the temperatures above Tg. It is one of the important characteristic of organogel. It can be determined with either glass ball drop method,[35] bubble motion,[36] or by simple tube inversion method.[34,37] Tg depends on physical and chemical properties of organogelator and solvent, as well as their interaction (either physical or chemical). It increases with the rise in the gelator concentration.[11] Thermal stability of organogels can be accessed by plotting Tg against gelator concentration. Permanent gels formed by the chemical interaction between the large polymeric molecules do not show gel-sol transition.

Analytical methods

Analytical techniques like FT-IR, NMR Spectroscopy, X-Ray diffraction[29] analysis have been employed for the characterization of organogels. These methods provide valuable information regarding molecular interaction during aggregation of organogelator molecules. FT-IR gives profitable information regarding hydrogen bonding. The presence of intermolecular hydrogen bonding can be confirmed by NMR spectroscopy.[10,27] Shape of fibrillar network of organogelators can be studied by small-angle neutron scattering (SANS) technique.[30]

Information about morphology, specific interactions, internal mobility of the constituents, and molecular organization of organogels can be obtained by NMR measurement, which involves magic angle spinning (MAS) in the solid-state NMR, spin relaxation times, nuclear overhauser enhancements

(NOE), or multiple-quantum (MQ) spectroscopy, the pulse field gradient (PFG) technique, and magnetic resonance imaging (MRI).[38]

APPLICATIONS OF OLEOGELS

Pharmaceutical

Skin acts as an effective barrier for most of the drugs except nitroglycerine scopolamine, nicotine, clonidine, fentanyl, estradiol, testosterone, lidocaine, and oxybutinin. Hence, topical formulation, which will enhance permeability of drug and reduce the side effects is always a need of formulation.[39] Many organic substances like lipids act as a penetration enhancer and hence give an additional edge to the organogel formulations prepared from them. Organogels have been investigated successfully as dermal pharmaceuticals.[40] Severe gastric irritation caused due to oral administration of aceclofenac can be avoided by topical transdermal drug delivery.[41] It is a choice of drug for osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Ethyl oleate-based lecithin organogels (EO/Lecithin) were used for topical delivery of aceclofenac. They have found to be more effective than conventional hydrogels. The histopathological studies also proved the safety of the system.[34] Aceclofenac was also formulated in the form of microemulsion for topical application.[42] Microemulsion has disadvantages that it needs a large amount of surfactant and cosurfactants for stabilization of nanodroplets, poor viscosity, and spreadabillity. On the other hand, lecithin organogels do not require addition of any additional surfactant or penetration enhancer, as lecithin serves both the purposes. Organogels are having better viscosity and spreadability than microemulsion.

Soyabean lecithin organogels shows a faster rate of transdermal drug delivery of scopolamine and broxaterol as compared to conventional patches.[43] It has found to improve skin penetration of Diclofenac and Indomethacin when used with isopropyl palmitate.[44] Piroxicam an effective NSAID has been successfully incorporated into lecithin gels.[45] Ketorolac Tromethamine could also be incorporated into lecithin organogels in high amounts.[46]

Organogels have been extensively used as controlled drug delivery systems as summarized in Table 2.

Oleogels in cosmetics

Today's skin care products mainly are emulsion-based which means that they contain water and an oil respectively lipid phase. In addition, there are still products with only an oil phase. Oils but also oleogels belong to this group. They are primarily recommended for problem skins and therefore used in the dermatological cosmetics. As particularly individuals with skin barrier disorders depend on physiological lipids in high dosage problem solutions for this specific group gain more and more importance. In this case, oleogels are recommended which are also known as lipogels. In contrast to the liquid oils oleogels have a gel-like and semi-solid consistency just like cream emulsions. This consistency will be achieved with additives, which build-up a sponge-like structure thus enabling them to assimilate large amounts of lipids.

Unlike emulsions the skin hydration increases only gradually when using oleogels. Also, in contrast to emulsions there will be no external supply of water, which means that hydration can only be provided from internal processes of the skin. The lipids of the oleogels support this process by reducing the transepidermal water loss (TEWL). In addition to that, natural water-retaining substances like e.g. urea, which also has antipruritic effects, can be integrated in oleogels. Unlike water-containing emulsions there will be no problem here with the long-term stability of urea.

The high lipid content of the products causes an optimal reduction of any skin roughness. Hence, oleogels are recommended for hand care products and for general skin protection purposes. Oleogels are above all recommended for the care of the lips, for cold protection products as well as for the care around the eye where spreading formulations as well as such containing emulsifiers should be avoided. Dry and cracked foot skin will become soft and smooth. They are also recommended for the supportive care of diabetic skin, perianal skin disorders, and decubitus oleogels can also be applied as sun protection product provided that appropriate sun protection filters are included. A major advantage here is the fact that they are resistant against water and perspiration. Oleogels can also be applied for massages whereas their applicability is considerably increased because of their semisolid consistency. By including pigments it is also possible to prepare products for decorative cosmetics like makeup, mascara, and eye shadows. Oleogels meet the major preconditions for corneotherapy which was coined by Albert M. Kligman in the late nineties. The "outside-in-therapy" requires that the composition of a product is physiologically adapted to the skin and that counterproductive effects by non-physiological additives will be avoided. Both the requirements apply for oleogels.[69]

Nutraceutical applications

In an effort to provide alternatives to trans and saturated fats, scientists have modified the physical properties of oils to resemble those of fats. In this fashion, many food products requiring a specific texture and rheology can be made with these novel oil-based materials without causing significant changes to final product quality. The major approach to form these materials is to incorporate specific molecules (polymers, amphiphiles, waxes) into oils to form oleogels. Ethylcellulose is showing great potential to bind oil at levels of 10% and under, forming oleogels of wide varying properties. These ethylcellulose oleogels have been used as

Table 2: Oleogels used in controlled or sustained delivery of drugs

Organogelator used	Organic solvent gelled	Model drug used	Pharmaceutical application
12-HAS (Hydroxystearic acid)	Soybean oil	Ibuprofen	Topical NSAID[47]
Isostearyl alcohol	Isostearyl alcohol, Propylene glycol	Haloperidol	Transdermal drug delivery[48,49]
Stearyl acrylate	Oleyl alcohol	Indomethacin	Topical NSAID[50]
N-stearoyl L-alanine (m) ethyl esters	Vegetable oils and biocompatible hydrophilic solvent	Leuprolide	LH-hormone releasing hormone agonist in prostate cancer, endometriosis and precocious puberty[51]
PG (Propylene glycol) or GP1 (dibutyllauroylglutamide)	Terpene (Limonene)	Haloperidol	Anti-Psychotic and as a transdermal patch[48]
Pluronic lecithin organogels	Water	Morphine	topical analgesic for cancer pains[52]
Modified tyrosine organogelator	Safflower oil	Rivastigmine	Acetylcholinesterase Inhibitor in Alzheimer's disease[53]
Gelatin containing microemulsion based gel	Isopropyl myristate and Tween 85	Sodium salicylate	Topical drug delivery through iontophoresis[54]
Poly (N-isopropylacrylamide)	Oleyl alcohol and water	Indomethacin	Temperature dependent pulsatile drug release system[55]
Egg lecithin span 40 cholesterol	Alcohol water	Propranolol derivatives	Non selective ß–blocker for hypertension[56]
Sorbitan monostearate	Sweet almond oil, alkanes like hexane, decane, vegetable oils, etc.	Propranolol, cyclosporin	antihypertensive and immunosuppressant[23]
Lecithin	Various organic	Diclofenac	Analgesic[57]
Glyceryl fatty acid esters	MygliolÒ	Ethinyl estradiol, Piroxicam	Orally bioactive estrogen,[50] NSAID[58]
Soya lecithin	Isopropyl mysristate	Ketorolac Tromethamine, cyclo benzaprine+ketoprof en+diazepam	NSAID[46] anti-psychotic[59]
Soybean lecithin	Isopropyl palmitate	Diclofenac, indomethacin.	Analgesic[44]
bis-(4-stearoylaminophenyl) methane (BSAPM)	Propylene carbonate	Ferrocene, ferricenium	Anti-cancer[60]
N-stearine-N0-stearyl-L-phenylalanine	i-propyl myristate, tween 80, propylene glycol and water	Sodium salicylate	Anti-bacterial[61]
1,3:2,4-di-O-benzylidene-D-sorbitol (DBS)	Propylene glycol	5-Flurouracil (5-FU)	Antifungal[62]
Span 60	Hexadecane	-	-[63]
Silicon dioxide	Sesame oil liquid paraffin	Herbal extract Diclofenac diethylamine	Topical anti-inflammatory oleogel[64,65]
Betullin	Fixed oils	Triterpene extrct from birch bark	Oleogel for actinic keratoses[66]
N-stearoyl l-alanine methyl ester (SAM)	Safflower oil	rivastigmine	treatment of alzheimer's disease[67]
Cholesterol	Liquid paraffin		Topical application[68]
Sorbitan monostearate	Almond oil		Topical application[68]

NSAID: Non-steroidal anti-infl ammatory drug

a replacement for highly saturated beef fat in comminuted meat products with great success in minimizing the risk of cardiovascular diseases.[70]

Engineering and oleogels

Oleogels has much higher decomposition temperatures than standard lubricating greases and other conventional

bases for topical application. Also they are much more chemically stable than lubricating greases.[71] In that the Chitin and chitosan-based oleogels show higher thermal stabilities than formulations containing acylated chitosan.[72] Oleogels of castor oil and ethyl cellulose/a-cellulose or ethyl cellulose/methyl cellulose blends are potentially applicable as environmentally friendly lubricating greases with high thermal and mechanical stabilities.[73] Oleogels based on sorbitan and glyceryl monostearates and different types of vegetable oils, potentially applicable as biodegradable alternatives to traditional lubricating greases, the use of low-viscosity oils, such as rapeseed and soybean oils, yields gels with significantly higher values of the linear viscoelastic functions.[74]

Miscellaneous applications

Smart gels which show novel response to photochemical, thermal, or metallic response have been developed.[75,76] Development of biomaterials based soft materials will be a need of time.[12] Polymeric gels have found many industrial applications such as food, cosmetics,[77] athletic shoes, preservation of arts,[78] and chromatography. LMWOGs have also been found to be promising structure-directing agents (templates) to make helical transition- metal oxides[79] and silica,[80] to make microcellular materials, and in a CO_2 based coating process[81] to make dye-sensitized solar cells.[82] Selective water gelation property of some organogelators has been used in containment of oil spills. Organogelators can be useful in easy disposal of used edible oil in family kitchens.[83] Extended unidirectional packing and long range intermolecular interactions make organogels a potential candidate in the research of molecular-based ferromagnetism, linear-anisotropic energy transfer, charge carrier transporting, and light harvesting.[84] Organogels has been used in the lubricant industry from 1970's.[5] They are applied for the gelation of flammable solvents.[85] Organogels have been successfully used as a substitute for edible saturated trans fats.[9] Extractant impregnated organogels have been successfully employed for the separation of metal ions from their aqueous solutions.[86] The Triton-X100 based quaternary w/o microemulsion organogels consisting of Triton-X100, water, 1-hexanol and n-hexane, were utilized in immobilization of lipase enzyme obtained from Candida rugosa.[87] Immobilization of Mucor Javanicus lipase enzyme in gelatin-based microemulsion gel formed with tween-85 and sodium bis (2-ethylhexyl) sulfosuccinate (AOT) was also carried out successfully.[88]

CONCLUSION

Numbers of formulations are available in the market as solid, liquid, and semisolid dosage forms. Ointments, creams, and gels are well known dosage forms for topical use. These bases are associated with various problems related to physical and microbial stability. Nowadays customer prefers gels due to their elegance in addition to efficacy. Current literature reviews that oleogel is a promising base for various drugs to design topical formulations. As this base do not contain water, its physical, microbiological, and chemical stability is much more as compared to conventional topical bases with added simplicity in manufacturing process. Thus, oleogels are systems with interest as promising topical bases for semisolid formulations.

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