Review Article

Gelling agents: Can they formulate a perfect emulgel?

Kajal D. Chaudhari[1], Sagar N. Ande[2], Ravindra L. Bakal[2], Gunjan P Malode[2]

[1]Department of Pharmaceutics, Dr. Rajendra Gode College of Pharmacy, Amravati, Maharashtra, India, [2]Department of Pharmacology and Toxicology, Dr. Rajendra Gode Institute of Pharmacy, Amravati, Maharashtra, India

Correspondence:
Kajal D. Chaudhari, Dr. Rajendra Gode Institute of Pharmacy, Amravati - 444 602, Maharashtra, India.
E-mail: kajuchaudhuari89@gmail.com

How to cite this article:
Chaudhari KD, Ande SN, Bakal RL, Malode GP. Gelling agents: Can they formulate a perfect emulgel? Innov Pharm Pharmacother 2022;10(2):25-29.

Source of Support: Nil.
Conflicts of Interest: None declared.

ABSTRACT

Emulgel is an emulsion, either of the oil in water or water in oil type, which is gelled by mixing with a gelling agent. The main advantage of the emulgel is that lipophilic drugs can be easily formulated as emulgels. Due to solubility problems, the most of the lipophilic drugs cannot be formulated directly as a hydrogel. For this reason, emulgel provides better stability and release of the lipophilic drug in comparison with simple hydrogel base. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickness because the gelling capacity of three compounds allows the formulation of stable microemulsion and opposite creams are decreasing surface and interfacial tension and at the same increasing the viscosity of the aqueous, the water phase converts a classical microemulsion based gel. However, the water content at the swelling equilibrium of into an microemulsion cellulose derivatives hydrogels is influenced basically by the nature of the monomer that makes them up, by the type and density of the cross link and also, by other factors including temperature, pH, and the composition of the hydration medium. As the HLB value increases, the emulsifiers become more soluble in water and their function changes from being W/O emulsifiers to being O/W emulsifiers. Mean particle diameter decreased with increasing HLB value and surfactant concentration. Particles of the emulsion with HLB 12 and surfactant concentration at 15% were distributed in the size of below 500 nm. HLB values are useful for selecting the most appropriate type of emulsifiers for food application.

Keywords: Micro emulsion, Viscosity, pH, HLB value

Introduction

Microemulsion is clear and thermodynamically stable isotropous liquid mixtures of oil, water, and wetter, often times together with cosurfactant. The liquid section could contain salts or different ingredients and "oil" may very well be advanced mixture of various hydrocarbons. The three basic forms of small emulsions are direct coil distributed in water O/W), reversed (Water distributed in oil W/O) and bicontinuous. Microemulsion is outlined as clear dispersion consisting of oil, surfactant, cosurfactant, and water. In O/W microemulsion, wherever in oil droplets are distributed in continuous liquid section. W/O microemulsion wherever in water droplets are distributed in continuous oil section. Bicontinuous small emulsion wherever in microdomains of oil and water are inhume distributed among the system. In all the three types of microemulsion, the interface is stabilized by associate applicable combination of wetter and cosurfactants.[1]

Access this article online	
Website: www.innpharmacotherapy.com	**e-ISSN:** 2321-323X **p-ISSN:** 2395-0781

Gelling agents are the gel forming agents when dissolved in liquid phase as colloidal mixtures forms a weakly cohesive internal structure. They are organic hydro colloidal or hydrophilic inorganic substances. Gelling agents conjointly perform as stabilizers and thickeners to produce thickening without stiffness. These are substances which when added to an aqueous mixtures, increase its viscosity without substantially modifying its other properties. It may be transparent or turbid based on type of gelling agent used, when gels and emulsion are microemulsion base gel.[2] In fact, the presence of gelling agent in water phase converts a classical emulsion in to microemulsion based gel. Gel formulations generally provide faster drug release compared with ointments and creams and pastes. The water insoluble drug is not directly incorporated in to gel base system. Based on physical, chemical structural, and mechanical studies, the gelling agent is used. Gels are generally more rigid because gel contains more covalent crosslinks, higher density of physical bond, or simply less liquid. The gel system could also be clear as water or turbid because the ingredients may not be entirely molecularly dispersed or they may produce aggregates. The concentration of gelling agents is mostly <10%, usually in 0.5–2.0% range. The rigidity of gel is attributed to presence of network formed by complex of gelling agent's particle. The nature of particles and kind of force involve in linkage and determine the structure of network and properties gel.[3]

Micro emulsion-based gel

The major limitation of gels is that the lack of ability to convey hydrophobic medication. Microemulsion approach is employed to beat this constraint. The lipotropic drug is with success incorporated directly into the microemulsion and therefore the microemulsion containing the lipotropic drug is then additional into applicable gel. Microemulsion-based gels are the combined indefinite quantity style of microemulsion and gel. Each hydrophilic and hydrophobic medication are ready to be delivered by microemulsion-based gels since hydrophobic medication is often entrapped by the oil in water system whereas the reverse water-in-oil systems are accustomed encapsulate hydrophilic medication. Micoemulsion-based gels may be water-in-oil (organogels) delivery systems or oil-in-water (hydrogels).[4,5]

Optimal characteristics of microemulsion-based gel

Microemulsion-based gel should be non-toxic, economical and efficient, inactive, compatible with other additives, free from microbial contamination maintained all rheological properties of the gel, stable at storage condition, washed with water, and free from staining nature and convenient in handling and its application.[6,7]

Advantages of Micro Emulsion Based Gel

Better stability

The microemulsion-based gel has better stability when compared with other transdermal preparations. It does not show part inversion or breaking as found creams, creaming result as in traditional topical emulsion, rancidity (due to oily base) as in ointment and absorbent properties as in powders.

Greater loading capacity

When compared with other novel approaches such as liposomes and niosomes, gels have comparatively greater loading capacity of the drug due to vast network.

Production feasibility

Production of microemulsion-based gel is distributed in brief and straightforward steps, this will increase the feasibleness of the preparation conjointly within the preparation of microemulsion-based gels, no specialized instruments required for the assembly.

Low production cost

The assembly cost of microemulsion-based gels is low because the materials used are cheap and simply accessible.

Incorporation of hydrophobic drugs

The major problem of incorporating most of the hydrophobic drugs (mainly Biopharmaceutical class 11 drugs) directly into the gel base is solubility. Microemulsion-based gel helps to avoid this constraint. Microemulsion-based gel incorporates these oliophilic drugs into the oil phase and then oily globules are dispersed in an aqueous phase for the formation o/w emulsion. Instances of such drugs are ketoconazole, fluconazole, and so on.

No intensive sonication

Intensive sonication is required within the preparation of sac molecules which can lead to escape and drug degradation. However, this downside is not encountered throughout the preparation of microemulsion-based gel as sonication is not needed.

Avoids first pass effect

Concentration of drugs is reduced as the drug substance moves through the portal circulation following gastrointestinal absorption. The deactivation of the drug by biological process and liver enzymes may be avoided by the employment of microemulsion-based gels.

Controlled release

The effect of drugs having shorter half-lives can be prolonged by the use of microemulsion-based gel. Epithelial duct drug absorption difficulties caused by epithelial duct pH scale and accelerator activity conjointly drug interaction with foods and drinks are often avoided. Chemical reaction and reaction of medicine do not occur since microemulsion-based mostly gel provides protection because it is not exposed to attack by air and water. The effectiveness of a drug will improve by the utilization of microemulsion-based mostly gels as a delivery system, this reduces aspect effects by permitting the entire dose to be faded. The utilization of microemulsion-based mostly primarily based mostly gels as a delivery system ultimately ends up in increase within the rate of absorption and bioavailability of drug as a result of microemulsion-based gel will increase the speed at that drug substances penetrate the skin barrier. Microemulsion-based mostly gel will simply be aloof from the skin since it is less greasy in nature. It is non-invasive and patient compliance is enlarged.[8-10]

Characterization of Microemulsion Gel (MEG)

MEG can be characterized by determining the following factors pH, drug content, viscosity, spreadability, extrudability study, skin irritation studies, *in vitro* release, *in vivo* study, stability, and consistency.

pH

Measurement of pH digital pH meter is used to determine pH of various gel preparations. About 1 g of gel is dissolved in 100 ml distilled water and allowed to stay for 2 h. The measurement of pH of each preparation is normally done in triplicate and average value calculated.[11]

Drug content

100 ml of suitable solvent is mixed with about 1 g of the prepared gel. Suitable dilutions are made to prepare aliquots of different concentrations. After filtering the stock solution, absorbance is measured. The equation, obtained by linear regression analysis of calibration curve, is used to calculate drug content.

Table 1: Gelling agent and polymer used in emulgel

Ingredients	Viscosity	pH	Density	M.P.	Properties
Carbopol® 910	3000–7000 cP	3.3	1.2 g/ml	95°C	Effective in low fixations will give a low consistency formulation
Carbopol® 934	30,500–39,400 cP	3.2	1.2 g/ml	12.5°C	It offers excellent stability at high viscosity and produces thick formulations
Carbomer 941	4000–11,000	6.49	1.2 g/ml	12.5°C	Produces low viscosity gels. Very good clarity
Carboxymethyl cellulose	1500–3000 cP	6.5–9.0	1.6 g/cm^3	274°C	It is capable to absorb large amounts of water and swells to form superabsorbent hydrogels that exhibit superior mechanical properties and viscoelasticity
Methyl cellulose	1500–3000 cP	4.2–9.2	1.33g mL^{-1}	290–305°C	Forming thermally reversible hydrogels on heating and important surface activity, decreasing the surface tension of water from 72.8 dyn/cm to 45–55 dyn/cm for a 0.1% (w/v) solution at 20°C
Hydroxy propyl cellulose	250–800 cP	6–8	0.5 g/cm^3	190–195°C	Surface activity; aqueous thickening and stabilizing properties
Hydroxy ethyl cellulose	250–450 m Pas	5–8.5	0.6 g/mL	5–8.5	Thickening and the gelling agent used in capsules containing hydrophobic drugs to improve dissolution of drugs
Polaxomer	0.0091 poise	5.0–7.5	1.06 g/cm^3	53–57°C	Poloxamers usually have an efficient thermoreversible property with characteristic sol-gel transition temperature that is used widely in the thermogelling system
Polyacrylamide	5.5–9 cP	4–6		84°C	Good adhesiveness, proper hygroscopicity, high hydrophilicity, and non-toxicity
Agar	10–100 cps	4.5–9	0.81g/cm^3	85°C	As encapsulating agents of microparticles of β-galactosidae, also used in the preparation of alginate hydrogels
Alginic acid	305–402 mPas	2–3.4	1.601 g/cm^3	300°C	As encapsulating agents of microparticles of β-galactosidae, also used in the preparation of alginate hydrogels
Tragacanth	400–4000 mPas	4–8	1.25-1.384	115–118°F	Tragacanth provides thixotrophy to a solution. The maximum viscosity of the solution is achieved after several days, due to the time taken to hydrate completely

Viscosity study

Brookfield viscometer is used to measure the viscosity of the prepared gel. The gels are rotated at 0.3, 0.6, and 1.5 rotations/min. The corresponding dial reading is noted at every speed. Multiplication of the dial reading with factor given in the Brookfield viscometer catalogues is carried out to obtain the viscosity of the gel.[12]

Spread ability

Good spread ability is one of the criteria; a gel must possess in order to be effective. The extent of area to which a gel readily spreads when applied to skin or affected part is known as spreadability. The spreading value of a formulation greatly affects its therapeutic efficacy. It is expressed in terms of time in seconds taken by two slides to slip off from gel placed in between the slides under the direction of certain load. Spreadability will be better if the time taken to separate the two slides is small.[13] It is determined using the formula:

$$S = \frac{M.L}{T}$$

Where,
M = Weight tied to upper slide
L = Length of glass slides
T = Time taken to separate the slides.

Skin irritation study

Skin irritation study is carried out using guinea pigs (400–500 g) of either sex. The animals are held under standard conditions and are maintained on standard animal feed and had free access to water. The guinea pig's hair is shaved from back and area of 4 cm^2 is marked on both the sides, one side served as test and the other side as the control. Gel is applied (500 mg/guinea pig) twice a day for 7 days and the site is observed for any sensitivity. The reaction if any is graded as 0, 1, 2, and 3 for no reaction, slight patchy erythema, and slight but confluent or moderate but patchy erythema and severe erythema with or without edema, respectively.[14,15]

In vitro drug release study

The *in vitro* drug release studies of the emulgel were carried out on diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1 g) was applied onto the surface of egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer. The samples (1 cubic centimeter aliquots) were collected at appropriate amount sample and were analyzed for drug content by ultraviolet-visible photometer once acceptable dilutions. Additive corrections were created to get the full quantity of drug free at every time interval. The additive quantity of drug release across the egg membrane was determined as a function of time. The additive proportion drug release was calculated mistreatment customary standardization curve.[16]

Gelling Agents in Microemulsion-based Gel Formulation

Gelling agents are gel forming agents when dissolved in liquid phase as colloidal mixtures form a weakly cohesive internal structure. They are organic hydrocolloids or hydrophilic inorganic substance.

In semisolid dosage forms, gelling agents are used at concentration at 0.5–10%. Gelling agents additionally perform as stabilizers and thickeners to supply thickening while not stiffness. Recently, polymer has been widely used as gelling agents. Gelling agents are substance that are used to impart viscosity or to stabilize the formulations. This may be obtained from natural, synthetic, or semi-synthetic sources.

Examples of Gelling Agents for Emulgel

- Polymeric gelling agent: Carbomer (Carbomer 934 P, carbomer 940, carbomer 941)
- Cellulose-based gelling agent: Hydroxypropyl cellulose (HPC), carboxymethyl cellulose and hydroxyethyl cellulose (HEC)
- Natural gelling agent: Xanthan gum, gellan gum, guar gum, and gelatin more examples of gelling agents are given in Table 1.

Variety of Polymers Acting as Gelling Agent

Natural polymers as gelling agent

Gelatin, casein, collagen, egg white, polysaccharides like guar gum, acacia, tragacanth, bug bean gum, pectin, starch, xanthan gum, dextran, succinoglucon etc are examples of some natural polymers acting as gelling agent.

Semi synthetic polymers as gelling agent

Subordinates include carboxymethyl cellulose, ethyl cellulose, HEC, HPC, magnesium aluminum silicate methylcellulose, and sodium alginate.

Synthetic polymers as gelling agent

Agar, alginate, carrageenan, sodium pectate these are some synthetic polymers acting as gelling agent.[17,18]

Gelling Agents and Polymer Used in Emulgel[19]

The aim of this work was to develop emulgel formulation of chlorophensin using Carbopol 934, HPMC as gelling agents. The influence of the type of the gelling agent and the concentration of both the oil phase and emulsifying agent on the drug release from the prepared emulgels was investigated using a 23 factorial design. It was found that the emulsifying agent concentration had the most pronounced effect on the drug release from the emulgels followed by the oil phase concentration and finally the type of the gelling agent. The drug release from all the emulgels was found to follow diffusion-controlled mechanism.[20]

The present study was aimed to prepared and characterize gel formulations of mimosa pudica using different polymers as gelling agents in various concentrations and also to evaluate anti-inflammatory activity of gel. For the study, polymers such as carbopol 940 (0.2–1.0%w/v), carboxy methyl cellulose (3.5%w/v), and hydroxy propyl methyl cellulose (0.5–1.0%w/v) were selected for preparation of different gel formulations. Formulation A with 0.5% carbopol 940 was the best formulation, having good *in vitro* activity; the formulated gels were evaluated for gross visual appearance, pH, and extrudability, spreadability drug content, and anti-inflammatory.[21]

The aim of this work was to prepare and evaluate the topical carbopol gel formulation containing ketoconazole encapsulated liposomes. Ketoconazole-loaded liposomes were prepared by thin film hydration technique. The prepared liposomes were incorporated into 1% carbopol gel and the systems were evaluated for *in vitro* drug release, drug retention into skin and *in vitro* antifungal activity. The release of ketoconazole from liposomal gel was much slower than from non-liposomal formulations. Gel containing liposomal ketoconazole showed maximum antifungal activity after 30 h over plain ketoconazole gel and cream formulations.[22]

The aim of this work was to prepare and evaluate topical liposomal gel for fluconazole. Gels containing liposomes (optimized batch) were prepared in Carbopol® 934 NF and were characterized for rheology, spread ability, permeation, and drug deposition in the rat skin. Results of regression analysis revealed that vesicle size and entrapment efficiency were dependent on the cholesterol and lipid concentration. Liposomal dispersion and gels were found to increase the skin permeation and deposition compared to control and marketed gel.[23]

In this study, miconazole nitrate was formulated as topically applied emulgel; different formulas were prepared using sodium carboxymethylcellulose and carboxypolymethylene (carbomer 941) as gelling agents. Emulsifying agent has pronounced effect on drug release from emulgel followed by the oil phase concentration and finally the type of gelling agent. The incorporation of gelling agent gives emulgel a proper consistency and exhibit shear-thinning behavior with thixotropy.[24]

The objective of the study was to prepare emulgel of mefenamic acid, a NSAID, using carbapol 940 as a gelling agent. Mentha oil and clove oil were used as penetration enhancers. *In vitro* release of the tests formulations was performed to determine drug release from emulgel rate and duration of drug release. From the *in vitro* studies, formulation F4 showed maximum release of 56.23% in 240 min.[25]

The aim of the study was to formulate and evaluate aceclofenac gel. A gel provides a successful approach in delivering combination products; hence, for the present study, a gel system has designed to deliver the drug aceclofenac and also improve physical appearance of the gel. The most significant part is the high performance polymer Carbopol-934 that was used as the gelling agent; also cremophor as base maker, as well as for improving spreadability and PVP K-90 is used as a thickening agent.[26]

Ibuprofen gel formulations, incorporating various permeation enhancers, were prepared using chitosan as a gelling agent. The formulations containing 5% of either menthol or glycerol as permeation enhancers gave drug release patterns comparable to that of the reference product. Propanol increased the apparent viscosity of the test gels to the same extent as that of the reference.[27]

Conclusion

Emulgel is helpful in enhancing spreadability, grasp, consistency, and ejection, it will wind up being a surely understood movement structure for topical application in the future. Gelling agent is being developed record of their massive inclinations and flexibility in their use. Such hydrophobic drugs where such solutions can be combined into its smooth stage and passed on to skin. These novel polymers are playing an imperative and fabulous part in the definition of different novel medication conveyance frameworks like emulgel.

Acknowledgment

We are thankful to Principal & Management of Dr. Rajendra Gode institute of Pharmacy, Amravati.

References

1. Singla V, Saini S, Joshi B, Rana AC. Emulgel: A new platform for topical drug delivery. Int J Pharma Bio Sci 2012;3:485-98.
2. Kuller R, Saini S, Seth N, Rana AC. Emulgel: A surrogate approach for topical used hydrophobic drugs. Int J Pharma Bio Sci 2011;1:117-28.
3. Kute SB, Saudagar RB. Emulsified gel - A novel approach for delivery of hydrophobic drugs: An overview. J Adv Pharm Technol Res 2013;3:368-76.
4. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev 2000;45:89-121.
5. Patel CJ, Tyagi S, Gupta AK, Sharma P, Prajapati PM, Potdar MB. Emulgel: A combination of emulsion and gel. J Drug Discov Ther 2013;1:72-6.
6. Piyusha D, Jain A, Vyas N, Khambete H, Jain S. Gellified emulsion for sustain delivery of itraconazole for topical fungal diseases. Int J Pharm Pharm Sci 2010;2:104-12.
7. Hosny KM, Rambo SM, Al-Zahrani MM, Al-Subhi SM, Fahmy UA. Ketoprofen emulgel: Preparation, characterization, and pharmacodynamic evaluation. Int J Pharm Sci Rev Res 2013;20:306-10.
8. Kotta K, Sasikanth K, Sabareesh M, Dorababu N. Formulation and evaluation of diacerein cream. Asian J Pharm Clin Res 2011;4:93-8.
9. Jain A, Gautam SP, Jain S. Development and characterization of Ketoconazole microemulsion based gel for topical drug delivery. Pharm Sin 2010;1:221-31.
10. Chandel A, Parashar B, Gupta N, Kumar A, Sharma V. An overview on the gel formulation. Int J Pharm Rev Res 2013;3:18-22.
11. Corswant CV, Engesterom S, Soderman O. Microemulsion based on soyabean phosphotidylcholin and triglycerides. Phase behavior and microstructure. Langmuir 1997;13:5061-70.
12. Shahin M, Hady SA, Hammad M, Mortada N. Novel jojoba oil-based emulsion gel formulations for clotrimazole delivery. AAPS Pharm Sci Tech 2011;12:239-47.
13. Jones DB, Woolfson AD, Brown AF. Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers. Int J Pharm 1997;151:223-33.
14. Dreher F, Walde P, Luisi PL, Elsner P. Human skin irritation studies of a lecithin microemulsion gel and of lecithin liposomes. Skin Pharmacol 1996;9:124-9.
15. Zhua W, Guo C. Microemulsion-based hydrogel formulation of pencyclovir for topical delivery. Int J Pharm 2009;378:152-8.
16. Patel MR, Patel RB, Parikh JR, Solanki AB, Patel BG. Effect of formulation components on the *in vitro* permeation of microemulsion drug delivery system of fluconazole. AAPS Pharm Sci Tech 2009;10:917-23.
17. Raymond CR, Paul JS, Marian EQ. Hand Book of Pharmaceutical Excipients. 6th ed. London, Chicago: Pharmaceutical Press; 2009. p. 110-4.
18. Singh S, Gajra B, Rawat M, Muthu MS. Enhanced transdermal delivery of ketoprofen from bioadhesive gels. Pak J Pharm Sci 2009;22:193-8.
19. Jain A, Deveda P, Vyas N, Chauhan J, Khambete H, Jain S. Development of antifungal emulsion based gel for topical fungal infections. Int J Pharm Res 2011;2:784-90.
20. Mohamed MI. Optimization of chlorphenesin emulgel formulation. AAPS J 2004;6:81-7.
21. Kumar V, Kumar S. Formulation and evaluation of mimosa Pudica gel. Int J Pharm Pharm Sci 2011;3:55-7.
22. Patel R, Patel H, Baria A. Formulation and evaluation of carbopol gel containing liposomes of ketoconazole. (Part-II). Int J Drug Deliv Technol 2009;1:8839.
23. Mitkari BV, Korde SA, Mahadik KR, Kokare CR. Formulation and evaluation of topical liposomal gel for fluconazole. Indian J Pharm Educ Res 2010;44:324-33.
24. Sabri LA, Sulayman HT, Khalil YI. An investigation release and rheological properties of miconazole nitrate from Emulgel. Iraqi J Pharm Sci 2009;18:26-31.
25. Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery. Saudi Pharm J 2012;20:63-67.
26. Debnath SK, Sarkar S, Janakiraman K, Chakraborty S. Formulation and evaluation of aceclofenac gel. Int J Chem Tech Res 2009;1:204-7.
27. Rasool BK, Abu-Gharbieh EF, Fahmy SA, Saad HS, Khan SA. Development and evaluation of ibuprofen transdermal gel formulations. Trop J Pharm Res 2010;9:355-63.