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Gellified Emulsion: A Review of State of Art and Recent Advances

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ABSTRACT:

Gellified emulsion is the emergent dosage form in the topical dosage form which deals with the combination of emulsion and gelling agent. The presence of dual control release system makes it suitable for the topical drug delivery system. gellified emulsion is mainly used to formulate the hydrophobic drugs topically. The efforts given are in the direction of skin disorders and cosmetology. It is beneficial compare to the other dosage form in the terms of drug release as well as it is non greasy, and high patient compliance is obtained. The present review deals with the various factors to be selected while formulating gellified emulsion as well as different methods associated with the formulation. After extensive review we can say that the gellified emulsion is better in terms of drug release, Rheological property and aesthetic appearance compare to the other dosage forms.

KEY WORDS: Topical drug delivery, Emulgel, Gellified emulsion, Advances.

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INTRODUCTION:

Over a last decade treatment of diseases involves administration of drugs via various routes like oral, parental, sublingual, rectal, nasal etc. Generally topical drug delivery systems are used when these systems fails to treat the local infection or diseases[1]. Further this type of drug delivery can also be utilized for the systemic action due to its superiority over other routes. Route of administration is depending upon the severity as well as the type of disease. E.g. for the skin disorders generally topical route is preferred. Topical drug delivery can generally divide into two parts: 1.) Topically applied local drug delivery and 2.) Topically applied systemic drug delivery. Topical drug delivery systems having numerous advantages such as delivery of the drug site specifically, avoidance of first pass metabolism as well as gastric degradation associated with oral drug delivery systems, so increased bioavaibility as well as the drug release can also been obtained for extended period[2]. The release rate of the drug from topical dosage form is directly depends upon the physicochemical characteristic of drug and carriers. The increase in the release rate may increase the rate of percutaneous absorption[3]. In case of the topical delivery systems the drug is released from the system, reaches to the site of action and permeate through the skin.

In topical drug delivery systems, around from late 80's gellified emulsion gets importance. The utilization of the emulsion systems has increased by the use in the dermatological preparations. Gellified emulsions are O/W emulsion or the W/O emulsion which is gellified by incorporated into the gel phase. It provided the dual control release[4].

The emulsion itself acts as a controlled release systems as the drug entrapped in the internal phase will act as a reservoir system. The drug will be released in a controlled manner from the external phase. Further the gelling agent controls the release of the drug because of its cross linked structure. The contact time of the gel can be increased by the use of the mucoadhesive agents. Generally, O/W systems are widely used for the cosmetic purpose and because of ease of washing due to the external aqueous phase. Whereas W/O emulsions are used for the treatment of dry skin and for the emollient action.

The applicability of any topical drug product depends upon its penetration power, oiliness to the skin and disappearance. For the improvement of the emulsion stability and penetration power emulsion is incorporated into the gel phase. Moreover the gellified emulsion is having several favorable properties for the dermatological use such as thixotropic, non greasy, easily spreadable and removable, emollient, and non-staining. The type and concentration of the polymers used as a gelling agent can affect the rate of release of the drug from the gellified emulsion as well as stability of the formulation. Gellified emulsion is having greater patient acceptability. Compare to the creams and ointments it is convenient to apply as it is non-greasy, less thick and does not require excess rubbing. Though there are certain disadvantages of the gellified emulsion system

like less permeation of the macro particles through the skin as well as bubble entrapment during the formulation of gellified emulsion[5].

Now a days biggest problem in the new drug development is poor drug solubility.

Generally BCS type- ii drug can be act as a ideal drug candidate for the gellified emulsion as they are having poor solubility and high permeability. So, the gellified emulsion can be served as a better and stable vehicle for hydrophobic or poorly water soluble drugs.

O/W drug delivery can be used to entrap the lipophilic drug as the drug is present in the oil phase and releases to the skin through the external aqueous phase. Now a days various hydrophobic drugs are delivered by using this system. Gellified emulsions have also been used for various kind of the skin disorders occurred by viral, fungal or bacterial infections.6 Now a day various works has been going on the development of the gellified emulsion for the treatment of candididasis, acne etc.

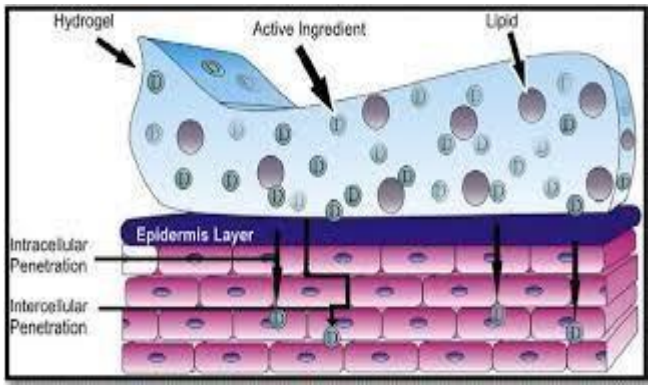

Figure 1 Gellified Emulsion

2. FORMULATION OF GELLIFIED EMULSION:

2.1 OIL PHASE SELECTION:

Gellified emulsions may be either of O/W emulsion or W/O emulsion depending upon use incorporated into the gel phase. In the formulation of emulsion the type of oil phase is the most important criteria. The oil phase material and its amount is primarily depend upon the use of the product. In case of the pharmaceutical and cosmetic products the oil phase is generally lipids of natural or synthetic origin as it is used as an active ingredient.

The consistency of the lipids varies from the mobile liquid to the high solids. Depending upon the application, utilization and properties different types of oils are used.

Oils derived from the medicinal plants have a wide scope for the formulation of gellified emulsion as the effective formulation can be made for the particular disease. There are various oils which possess the medicinal values. One such oil is geranium. Geranium is used in bleeding, ulcers, healing of wounds as well as in the treatment of skin disorders, dysentery, diarrhea and colic. Geranium also possess anti bacterial and insecticidal properties.7 The plants like arnelia nobilis, garciana indica, boehavia diffusa, solanum albicaule, vitex nigundu, bunium persicum, acacia concinna and albizia lebbeck were investigated for the anti microbial properties. Ethanolic extracts of the above plants shows the anti microbial property agains selected bacterias and fungi. Some herbal drugs like camtothecin, brucea javanica oil, coixenolide oil and zedoary oil are attempted to make into emulsion.[8,9]

The emulgel for the buccal administration was prepared by perioli et al. In that neutral lipid glycerol behenate (Compritol®888ATO) was used as an oil phase which is generally used as an excipient in the sustained release tablets and capsules. The various studies on the gellified emulsion shows that most effective formulation can be prepared by the low to medium oil phase content in the range of 0.3-0.4% w/w of aqueous phase. The formulations with the optimum viscosity are supposed to be compatible with the delivery trough pre- filled syringe[10]. Generally light liquid paraffin is used as a vehicle for the many of the gellified emulsion formulations. also carried the research work for emulgel containing novel oil jojoba oil. The final formulation was the clotrimazole emulgel with jojoba oil as an oil phase. The jojoba oil is responsible to reduce the inflammation associated with fungal infections. This was effective in several experimental animal models[11]. also developed the gellified emulsion of clotrimazole by using lavender oil as oil phase because lavender oil is reported to possess antifungal, antiseptic, and anti inflammatory property. Various factorial designs were also applied to the formulation for the investigation of the effect of the various factors like concentration of gelling agent and emulsifying agent as well as oil phase concentration. The prepared emulgel was generally evaluated for the physical appearance, swelling index, viscosity, drug release etc[12].

The carbopol based gel with low oil phase concentration and high emulsifying agent is the formula of the choice. But the factors may vary depending upon the nature and type of the agents used. The vaginal emulgel had also been prepared with the use of cetosteryl alcohol as an oil phase. The formulation contains benzydamine (0.5% w/w) and characterized based on the mucoadhesive force, viscosity and release behavior. The final formulation was compared with the marketed vaginal cream. The cetosteryl alcohol provides highest mucoadhesive force as well as it provides stability to the emulsion system because of the emulsification property.

Caifu Li studied the characteristics of the submicron emulsion prepared by emulsion inversion point method. It was found that the oil droplets formed were solid with having irregular shape, which was better for the emulsion stability.

Table 1 Oil phase

Chemical	Quantity (%)	Dosage Form
Light liquid paraffin	7	**Emulsion and emulgel**
Isopropylmyristate	7-7.5	**Emulsion**
Isopropyl stearate	7-7.5	**Emulsion**
Isopropyl palmitate	7-7.5	**Emulsion**
Propylene glycol	**3-5**	**Gel**

2.2 EMULSIFYING AGENTS SELECTION:

Emulgels are the O/W or W/O emulsions incorporated in the gel phase. As the emulsion systems are thermodynamically unstable system, suitable emulsifying agents are employed to decrease the interfacial tension, and hence to enhance the stability of the system up to significant extent. The emulsifier should be capable of producing the stable emulsions by maintaining the hydrophilic- lipophilic balance13. Generally, non ionic surfactants like spans, tweens are having HLB values greater than 8 and hence are used to formulate O/W emulsion. Whereas mineral oils like liquid paraffin is having HLB values less than 8 and hence are used to formulate W/O emulsions.

The selection of the emulsifiers and its concentration has been done based on the trial and error method and also a matter of experience. In the formulation of emulgel spans are added in the oil phase and tweens are added in the aqueous phase. Tweens and spans provide greater stability in combination rather than used as pure span or pure tween14. Other emulsifiers like pamulen was also reported to use as an emulsifier in the formulation of emulgel intended for the buccal administration. Pamulens can act both as primary emulsifiers for O/W emulsions as well as viscosity increasing agent. They tend to stabilize O/W emulsion because of their short lipophilic chain integrates into oils droplets while long hydrophilic part forms the microgel around the oil droplet15. The emulsifier pamulen is also having mucoadhesive property so that it is preferable for the formulation of gellified emulsion.

Surfactant generally toxic in nature and also creates problems regarding health and environment. So, to avoid this biosurfactants can also be used as an

alternative. They are produced by the microbes and they are sometimes species specific. Biosurfactants are hydrophilic and hydrophobic as well as they are sticky in nature because of their short fatty acid tail and long polar head groups. They are having same mechanism for lowering the surface and interfacial tension as that of chemical surfactants. Therefore they are the best alternative to the chemical surfactants as they are less toxic, highly biodegradable and hence more eco-friendly. They also possess better foaming property and stable activity even at the extreme pH and temperature. These features make them efficient commercial alternative to the chemical surfactants.

2.3 GELLING AGENTS SELECTION:

Gelling agents are the major component in the formulation of the gellified emulsion for providing controlled release as well as to provide the optimum viscosity. They ate basically are of two types: natural and synthetic. Incorporation of gelling agent to the emulsion system makes them thixotropic. Thixotropy is the phenomenon which shows the reversible changes i.e. gel-sol-gel due to the time dependent change induced by pH, temperature etc. without any change in the volume of the system16. These thixotropic behaviors of the gel impart stability as well as improve bioavaibility of the system.

The stability of the system depends upon the polymer concentration, pH, temperature as well as the polymer modification or combination, addition of cation or anion. There are several polymers tried for the formulation of the efficient gellified emulsion system like HPMC, Carbopol etc. hydroxyl methyl cellulose is the synthetic modification of the cellulose which is used in the tablet binder, film coating, thickening agent, and modified release. Carbomers are the polymers of the acrylic acid crosslinked with the polyalkenyl ethers or divinyl glycol. Every particle can be seen as a cross linked structure of the polymer chains. Carbomers absorbs water, hydrated and swells. Though it is a hydrophilic polymer but it is insoluble in the water. This characteristic make it ideal candidate for the controlled drug delivery system. Every particle is having average diameter of around 0.2-0.6 µm.

Quantity and quality of the carbopol is having major effect on the consistency of the formulation. Effect of the gelling agents on the release rate from the gellified emulsion has also been studied. It has been seen that there is an inverse relationship between the concentration and the release rate. The final formulation of the gellified emulsion shows non- Newtonian sheer thinning behavior with little or no thixotropy. The stability testing of various gellified emulsion shows that the low carbopol concentration or the combination of two gelling agents shows better stability. Shen et al. formulated the cyclosporine A emulgel for the ocular drug delivery by the use of polycarbophil as an gelling agent. The results shows that the polycarbophil based emulgel can be a potential hydrophobic drug carrier for the ocular drug delivery[17].

Neutralization of the aqueous dispersion is done with the NaOH or with triethanolamine (TEA) results into the clear stable gel. For the complete polymer hydration the gels are supposed to be stored at 40C for 24 hours before the addition of the emulsion. The novel gelling agents are also employed like pamulen and benzydamine. Pamulen based emulgel was intended for the buccal administration where as benzydamine based emulgel was formulated for the vaginal drug delivery18,19. Mucoadhesivity is the important criteria for the prolonged retention time which leads to the less number of administrations. In case of the vaginal drug delivery NaCMC (3%) shows best performance where as hydroxyl ethyl cellulose shows good release but low mucoadhesion.

There are so many gelling agents applied in the formulation of gellified emulsion from synthetic, semisynthetic and natural category. The natural gelling agents have a major disadvantage of microbial growth. Now a days so many synthetic and semisynthetic agents replace the natural gelling agents. In case of cellulose derivatives NaCMC is the agent of choice for the formulation of the sterile jellies because it can withstand with the autoclaving without major deterioration.

Table 2 Gelling agent

Gelling agent	Quantity (%)	Uses
Carbolpol-934	1	Emulgel
Carbopol-940	1	Emulgel
HPMC	3.5	Gel
Sodium CMC	1	Gel

3. FORMULAITON METHOD SELECTION:

There are various methods reported for the formulation of the gellified emulsion with the aid of different ingredients. Mohamed et al. formulated the emulgel bu formulating O/W emulsion, followed by the addition of suitable gelling agent. The first step involves the preparation of O/W emulsion by dissolving span 20 in the oil phase. Aqueous phase was prepared by addition of tween 20 in the water. Propylene glycol solution was prepared by dissolving methyl paraben and propyl paraben in it. Drug was dissolved in the ethanol. The solution was mixed to form aqueous phase. Both the aqueous and oily phase were heated up to 70-80 0c and mix with constant stirring until cooled at room temperature.

Gel phase was prepared by soaking the carbopol or HPMC in water. HPMC is required to soak overnight for the complete hydration where as carbopol has to just disperse in the water with constant stirring. Both the gel phase and emulsion phase were mixed in 1:1 ratio for the emulgel preparation. 20 The other method was described by perioli et al. for the preparation of buccal emulgel.

They describe the formation of emulgel in three steps: 1.) Formation of polymer dispersion. 2.) Neutralization of polymer dispersion. 3.) Emulsification of oil phase. For the first step different quantities of polymers were dispersed in the water and stirred continuously for 20 min. at 900 rpm by the use of mechanical stirrer. The dispersion was neutralized with the use of NaOH (18%) to form the gel. Further the gel is stored at 40C for 24 hours for the complete hydration of the gel phase. Then different quantities of O/W emulsion were added in the gel phase with continues stirring at 800C at 800 rpm. The prepared emulgel is cooled down and pH is measured.19

Shahin et al. described a method for formulating the emulgel for the delivery of clotrimazole. In this method oil phase was prepared by the addition of span 60 in the jojoba oil with the help of magnetic stirrer at 750C with subsequent cooling followed by addition of carbopol to the oil phase. The aqueous phase was prepared by the dissolving brij-35 in propylene glycol. Then the oil phase and aqueous phase were mixed with the aid of overhead mixer for 10 min. at 1400 rpm and then introduced in homogenizer for 5 min. at 10000 rpm. Gellified emulsion was formed by neutralizing agent triethanolamine to the emulsion using over head mixer at 200 rpm for 45 min to get the pH of 5.5-6.5. 21

The prepared emulgels are intended to be delivered via vaginal, buccal as well as topical routes.

4. FUTURE PROSPECTIVE:

Delivery of hydrophobic drugs is the major challenge in the formulation and development department. Hydrophobicity also responcible for the poor solubility and low bioavaibility. To overcome this various formulations had been tried like creams, ointment, lotion etc. These products generally utilize the oleaginous base like petroleum or bees wax or vegetable oils which are hydrophobic in nature. This provides excellent emollient property but it also hinders the drug release from the formulation and makes the product thick and greasy. Whereas gels provides aqueous environment to the drug and hence provides faster drug release compare to other formulations. Therefore gellified emulsion is act as a ideal drug delivery system for hydrophobic drugs in which the drug is incorporated in the oil phase and delivered to the skin. These properties may be used in future for many hydrophobic drugs delivered in the form of gellified emulsion.

5. CONCLUSION:

From the extensive review of literature we can conclude that the gellified emulsion is the ideal dosage form for the topical drug delivery of the hydrophobic drugs because of its dual release properties as well as its favorable properties. Further the problems associated with the emulsion systems like creaming, phase separation are solved by gellified emulsion system and stability is also increases. This system mainly deals with the treatment of skin disorders and in the case of dermatology. Further it can also be utilized for the systemic drug delivery of the hydrophobic drugs.

6. MARKETED PREPARATIONS:

Table 3 Marketed preparations

Sr.No.	Product name	Drug	Manufacturer
1.	Voltaren emulgel	Diclofenac-diethyl-ammonium	**Novartis pharma**
2.	Miconaz-H-emulgel	Miconazole nitrate, Hydrocortisone	**Medical union pharmaceuticals**
3.	Excex gel	Clindamycin, Adapalene	**Zee Laboratories**
4.	Pernox gel	Benzoyl peroxide	**Cosme Remedies Ltd.**
5.	Lupigyl gel	Metronidazole, Clindamycin	**Lupin Pharma**
6.	Clinagel	Clindamycin phosphate, Allantion	**Stiefel Pharma**
7.	Topinate gel	Clobetasol propionate	**Systopic Pharma**
8.	Kojivit gel	Kojic acid, Dipalmitate Arbuti	**Micro Gratia Pharma**
9.	Acent gel	Aceclofenac	**Intra Labs India Pvt. Ltd.**
10.	Avindo gel	Azithromycin	**Cosme Pharma Lab.**
11.	Cloben gel	Clotrimazole, Beclomethasone	**Indoco Remedies**
12.	Nadicin cream	Nadifloxacin	**Psycho remedies**
13.	**Zorotene gel**	**Tezarotene**	**Elder Pharmaceuticals**

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