EMULGEL AS PHARMACEUTICAL FORMULATION: A REVIEW

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Abstract

Topical administration of drugs is delivering medications locally to the eye, skin, rectum and vagina. This route of drug application has many advantages including bypassing the extensive hepatic metabolism, avoiding the invasive parenteral (injection) and others. Emulgel is a semisolid preparation which has advantages of having a high ability to skin penetration than other semisolid formulations, being greaseless, thixotropic, easily spreadable and removable, water soluble, non-staining, emollient and longer half-life. There are many ingredients and constituents of emulgel such as oils, emulsifying agents and gelling agents. Emulgel is prepared as either o/w or w/o type. Many evaluations had been performed to check the properties of emulgel such as organoleptic properties, spreadability, pH, viscosity, rheological study, swelling index, *Ex-vivo* bioadhesive strength measurement of topical emulgel and others.

الخلاصة

التوصيل الموضعي للأدوية هي توصيل الأدوية محليًا للعين والجلد والمستقيم والمهبل. يتميز هذا المسار من استخدام الدواء بالعديد من المزايا بما في ذلك تجاوز التمثيل الغذائي الكبدي الواسع وتجنب الحقن الغازية (الحقن) وغيرها. الايميلجل عبارة عن مستحضر شبه صلب يتميز بقدرته العالية على اختراق الجلد مقارنة بالتركيبات شبه الصلبة الأخرى ، كونه غير دهني، متغير الانسياب سهل الانتشار والإزالة، قابل للذوبان في الماء، غير ملوث وعمر نصفه أطول. هناك العديد من مكونات المستحلب مثل الزيوت وعوامل الاستحلاب وعوامل التبلور. يتم تحضير الايملجل هو اما نوع زيت بالماء أو ماء بالزيت. تم إجراء العديد من التقييمات للتحقق من خصائص المستحضر مثل الخواص الحسية، وقابلية الانتشار، ودرجة الحموضة، واللزوجة، ودراسة الانسيابية، ومؤشر الانتفاخ، وقياس قوة اللاصق الحيوي خارج الجسم الحي للمولجل الموضعي وغيرها.

Introduction

Topical administration of drugs is delivering medications locally to the eye, skin, rectum and vagina [1-3]. These are used for dermatological disease conditions and cosmetic for healthy skin purposes. Additionally, the administered drug could be used for systemic or local action [1, 4]. This route of drug application has many advantages including bypassing the extensive hepatic metabolism, avoiding the invasive parenteral (injection) and others [5]. The applied dosage forms range from liquid through semisolid to solid. However, the favourite one is semisolid. The administered drug could be applied alone or in combination with other medicament(s)[6], in addition to other excipients according to the dosage form and the disease condition [4]. Among the group of the semisolid preparation, gel is the most used form [5, 7, 8].

Gel is a cross-linked three dimensional colloidal solid particles network entrapped aqueous or hydro-alcoholic solution. It has advantages such as releases the drug faster than other topical formulations (ointment and cream). However, gel has limitation in delivering hydrophobic drugs [9]. Therefore, to overcome this limitation of gel preparation, emulgel is developed in order to get advantage of gel and emulsion to formulate both hydrophilic and hydrophobic drugs. The gelling agent presence in the aqueous phase of an emulsion is responsible on transforming it to emulgel [5, 10].

Emulgel is a semisolid preparation which has advantages of having a high ability to skin penetration than other semisolid formulations, being greaseless, thixotropic, easily spreadable and removable, water soluble, non-staining,emollient and longer half-life [4, 5]. Drug molecules penetrate the skin and reach their site of action via stratum corneum, sebaceous follicles and sweat ducts. The drug passage through the stratum corneum is a most limiting and affecting step because of its percutaneous absorption. The concentration gradient of the drug across the cell wall affects mainly its absorption. Additionally, absorption of the drug formulate as emulgel affected by its release from the formula vehicle (i.e., partition coefficient) as well as diffusion through the layers of skin (i.e., diffusion coefficient) [11, 12]. This study was made to explain the comprehensive review of emulgel drug delivery system importance and how it could be formulated and evaluated pharmaceutically.

Drug characteristics for topical delivery

The molecular mass of the drug should be 600 Da or less. It must have oil and water solubility with high partition coefficient, except for water soluble ions, very small particle drug, and drug molecules with polar properties which unable to penetrate intact stratum corneum [12].

Advantages of Emulgel [1, 4, 13]

1. Hydrophobic drug incorporation

The hydrophobic drug can not be directly incorporated in the gel formulation since it is insoluble in the hydrogel. While emulgel able to use for lipophilic drug delivery because of the oil phase of the emulsion (oil in water) which involve in the emulgel formula. Then this emulsion incorporated with gel base to make it more stable than emulsion alone [14].

2. High drug loading capacity

The emulgel has better drug loading capacity than other topical formulations since the medicaments could integrated in both gel base and the emulsion.

3. Better formula stability

Most other topical formulations than emulgel are less stable. Cream (as emulsion) could suffer from phase inversion while ointment undergoes oil phase rancidity.

4. Low production cost

Emulgel formulation could be considered unexpansive in comparison with other available drug deliveries since its formulated materials are available and cheap as well as there is no need for complicated and especial instruments.

5. Controlled release

Emulgel composition as emulsion incorporated in gel base allows it to deliver short half-life drugs for long time (controlled release).

6. No intensive sonication

Preparation of emulgel do not need sonication. This could avoid the degradation and leakage of drugs related to sonication in vesicular molecules production.

Factors affecting topical drug absorption [15, 16]

1. Physiological factors: these factors include;

- Thickness of the skin
- Lipid content
- Density of skin hair follicles
- Density of the available sweat glands in the skin
- The skin pH
- Hydration of the skin
- Blood flow
- Inflammation of the skin

2. Physicochemical factors

- Drug molecular weight (of less than 400 Dalton)
- Partition coefficient
- Degree of ionization of the drug (only the unionized drugs are absorbed efficiently)
- Vehicles properties effect

3. Factors affecting choosing a topical preparation

- Vehicle effect, the occlusive vehicle could enhance the drug penetration, then its effect. It may have drying, cooling, protective or emollient action.
- Matching the type of the skin condition with the preparation method and the method of the preparation with the application site of the skin.
- Sensation or irritation potential, i.e. ointment and oil in water cream are less irritating than gel.

The most important ingredients and constituents of emulgel

1. Aqueous materials

This represents the aqueous phase or water of the emulsion. Generally, water or hydroalcoholic solution are used for this phase [17, 18].

2. Oils

The oil phase of the emulsion represents by these agents. For internally used emulsion, various fixed oils of vegetable origin, fish liver oils non-biodegradable mineral oils were used [5, 19].

3. Emulsifying agents

Emulsifying agents are substances used both to control stability of the emulsion during shelf life and to promote emulsification of the product at manufacturing. There are many emulsifying agents including sorbitan mono-oleate, sodium stearate, polyoxyethylene sorbitan mono-oleate, stearic acid and others [20].

4. Gelling agent

These substances are responsible for gel thickness consistency of emulgel form. Many natural and synthetic gelling agents were used for emulgel formation including xanthan gum, carbopol and hydroxypropyl methyl cellulose [21].

5. Permeability enhancers

Penetration enhancer could be added to emulgel to promote permeability of poorly penetrated medications. There are many natural and synthetic enhancers used in emulgel involving oleic acid, lecithin clove oil, menthol and others [22].

Method of emulgel preparation

First step in the preparation is emulsion formulation either it is o/w or w/o type which stabilized by utilizing emulsifier. Oil soluble ingredients are incorporated in oil phase, while water soluble ingredients in aqueous phase. Then, gel base forms which generally contain the gelling agent and water. Finally, the emulsion incorporated to gel base to form emulgel [23-25], as shown in Figure 1.

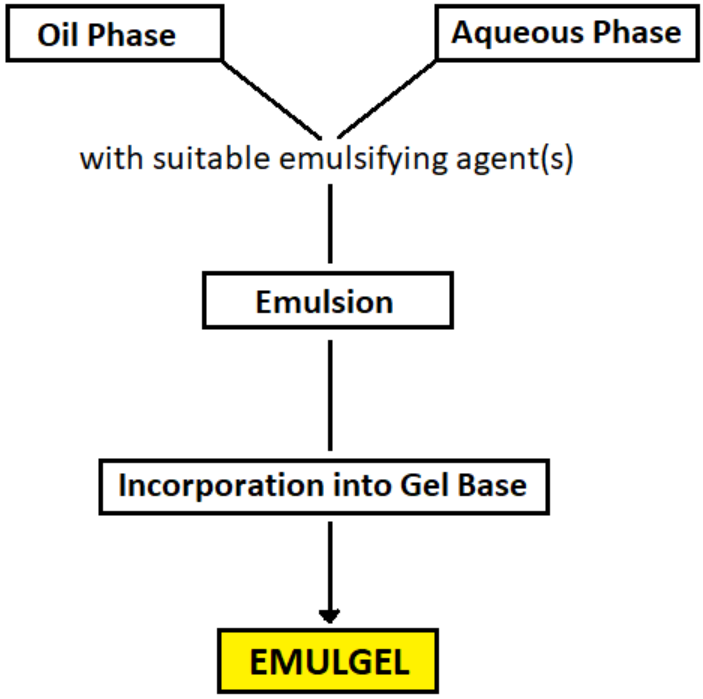

Figure 1. Steps of emulgel preparation.

Characterization and evaluation of emulgel

1. Organoleptic properties

The prepared emulgel formulations were checked for the general appearance characteristics including colour, consistency and homogeneity by eye visually [26].

2. Emulgel pH

Emulgel formulas were tested to insure that they were not irritant for skin due to its pH were different than skin one. This test performed by measuring their 1% aqueous solution using pH meter [26].

3. Spreadability

Emulgel spreadability had been studied (on the basis of emulgel SLIP and DRUG properties) using wooden block that at one end was supplied with a pulley. A slide made with glass is fixed onto the block on which emulgel in excess is put. Between this used glass slide and another one (has hook) the emulgel formula sandwiched. A heavy weight of 1Kg is put onto the slides for few minutes to ensure that all the air is discarded and uniform emulgel film produced inside these two slides. Then, the upper plate subjected to 80 gm pull with aid of string that fastened to the hook. The time required in order to cover a distance of 7.5 cm by the upper slide be noted and recorded. The shorter time interval demonstrated better spreadability for the formula. This parameter for the emulgel was measured by the following equation below [21, 27]:

$$S = M.L/T$$

Where 'S' is spreadability, 'M' is the weight tied of the upper slide, 'L' is the glass slide length, 'T' time required for slides separation.

4. Extrudability study

This test measures the time needed in order to eject the formula material from a tube. The method used to determine the applied shear in a specific region of the rheogram instrument correlate to a shear rate surpassing the value of yield and manifesting consequent plug flow. Recently, this procedure used to evaluate extrudability of emulgel depend on the percent of emulgel or quantity and that extruded from lacquered aluminium collapsible tube by force resulted from the used weight (in grams) that needed to eject event small amount (at least 0.5 cm/10 sec emulgel). The more quantity ejected is better extrudability for the evaluated formula. It is calculated according to the formula below [28]:

Extrudability = The weight applied to eject emulgel from the used tube (g)/ Area (cm)

5. Emulsion globule size and its distribution in gel base

These two tests are performed using zetasizer. A 1 g of emulgel diluted with distilled water, then this sample is injected in the instrument photocell. The mean of the globule size and distribution were obtained [5].

6. Rheological study

The emulgel viscosity is determined using a cone and plate viscometer with spindle which connected to controlled water bath [21].

7. Swelling index

Swelling index of the emulgel is measured weighing 1 g of emulgel using porous or permeable aluminium foil which afterwards put in 10 ml 0.1N sodium hydroxide. Samples are taken at different time intervals then put in dry place then re-weighed. Swelling index is determined using the equation:

$$\text{Swelling Index} = [(Wt - Wo)/Wo] * 100$$

Where 'Wt' is the swollen formula weight and 'W_0' is the original emulgel weight at zero time [29].

8. *Ex-vivo* bioadhesive strength measurement of topical emulgel

The animal fresh skin is divided into specific required size pieces then washed in alkali 0.1N sodium hydroxide. Two skin pieces are put and fasten to two glass slide. One of these slides was tied to wooden piece and the another with the right side of a balance. The two pan sides of the used balance are balanced adding weight to its left side. A weight of 1 g of the tested formula is placed between the two slides, next the weight added to the left side of the balance is removed to discard the presence air by the applied pressure and to sandwich the skin pieces. The balance is stayed in this position for 5 min, then weight is added (200 mg/min) to the left side pan of the balance till the patch detached from the skin surface. The strength of bioadhesion is measured using the equation [30]:

$$\text{Bioadhesive Strength} = \text{Weight Required in g/ Area in } cm^2$$

9. Determination of drug content

The amount of the drug formulated as emulgel is measured using spectrophotometric instrument or other methods depending on the formulated drug chemical properties by solubilizing a specific amount of the formula in a buffer. A sample from the solution is tested with the specified method for quantification [31, 32].

10. *In-vitro* drug release study

This test is made using Franz diffusion cell. An amount of 200 mg of emulgel is placed onto the membrane (synthetic or natural) evenly which fixed between the receptor and donor chamber of the used cell. The chamber of receptor is filled with release medium (phosphate buffer solution) that stirred with magnetic stirrer. Samples form the receptor are collected at specific time intervals according to the drug and the type of the formulated emulgel, then analysed for the drug. Finally, the percent of drug release represented with time [4].

11. Drug release kinetic study

The mechanism of release for the drug from the formula is analysed and its release could be fitted to the one of following styles [33]:

Zero order equation: $Q = K^o t$

Where 'Q' is drug released amount at 't' (time), 'K_o' release rate constant.

First order equation: $\ln (100 - Q) = \ln 100 - K_1 t$

Where 'Q' is the drug released percentage at 't' (time), 'K_1' is release rate constant.

Higuchi's equation: $K_2 \sqrt{t}$

Where 'Q' is the drug released percentage at 't' (time), 'K_2' is the release rate constant.

12. Microbiological assay

This assay is performed using Ditch plate method to evaluate the fungistatic and bacteriostatic activity of materials. Three grams of the formulated emulgel are put onto ditch cut in the Sabouraud's agar plate. Freshly prepared culture loops which are lined across this agar at a specific angle from ditch to the plate edge. Then, it is incubated for 24 h at 25^{o}C. The inhibition zone is measured as follow:

$$\%\text{Inhibition} = L2/ L1 \times 100$$

Where 'L1' is the streaked culture total length and 'L2' is inhibition length [34].

13. Irritation of the skin

This study is made by placing the formulated emulgel on a shaven area of rat skin and observing the skin area for the colour changes and morphology for 24 h [33, 35].

14. Stability study

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines are used for this study. The emulgel formulations are stored in different temperatures of 37, 45 and 60^{o}C for 90 d. Then, formulas samples are analysed for the incorporated drug content every 14 d as well as the pH of the formulas is checked frequently during this interval [33, 35].

Conclusion

Emulgel is one of the popular and widely used dosage form which used mainly for topical application. It improve the patient compliance since it is applied topically and has good texture, spreadability, extrusion and viscosity. In addition, wide range from hydrophilic and hydrophobic drugs can be incorporated into this delivery system.

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