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EMULGEL – AN INNOVATIVE MODUS OPERANDI FOR FORMULATION OF HYDROPHOBIC DRUGS FOR THE TREATMENT OF DERMATOLOGICAL DISEASES

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ABSTRACT

In this cutting-edge era, there have been a lot of advancements in the medical field to improve the health of individuals suffering from a wide range of diseases either caused by invading microorganisms or by abnormal functioning of body organs. One such example is the formulation of Emulgel, which is a type of topical gel, known to have greater absorptive and therapeutic properties when compared with liquid and solid dosage forms. The main principle applied in the preparation of Emulgel is the incorporation of transparent gel into the emulsion as a means to diminish the adverse effects of dermatological diseases. The amalgamation of an emulsion into gel gives it more stability and henceforth is gaining more popularity as a topical drug delivery system with the sustained-release property as well, in which the drug is released slowly with a specific time interval to give efficient and long-lasting action, along with it can also incorporate hydrophobic drugs, which is a major limitation observed in gel-based formulations. Eventually leads to an opportunity to cure dermatological diseases caused by viruses as well and not only constricted to bacteria or fungal infections.

KEYWORDS: emulgels, hydrophobic drugs, skin, topical gel, drug delivery, in-vitro.

INTRODUCTION

The phenomenon, in which a drug-containing formulation is directly delivered into the systemic circulation when applied to the surface of the skin to cure dermatological ailments, is known as transdermal drug delivery. This path shows a greater therapeutic effect for local and systematic treatment respectively.[1] Skin is the largest organ in the body and acts as an easier accessible target for remedial treatment and diagnosis of hypodermal infections. Topical drug delivery is specifically used when other routes of administration do not seem to function properly with a major disadvantage being first-pass metabolism with oral formulations and risks associated with intravenous/subcutaneous/intramuscular administrations. There are other major drawback occurrences such as gastric emptying rate, pH changes, enzymes metabolism and ADME changes which are repressed by the topical drug delivery system making it an advantageous drug release pathway.[2] Emulgels are a form of a dosage form in which gel and emulsion are combined to give a more therapeutic effect when compared with the traditional ointment form. Emulsifiers and thickeners are employed in the formulation of emulgel, as their gelling capacity allows the formation of stable emulsion with a better surface, interfacial tensions and viscosity characteristics.[3] These days, transparent gels are highly in use for the formulation of emulgel as they entrap large amounts of aqueous or aromatic liquid in a network of colloidal solid particles, which may consist of inorganic salts such as aluminium or organic polymers, permitting greater dissolution and migration of drugs into the systemic circulation. Even though gels have many advantages such as being thixotropic, greaseless, cleansable, spreadable, higher shelf-life and non-staining, delivery of hydrophobic drugs becomes immensely difficult because gels are hydrophilic.[4]

Hence gel and emulsion are incorporated together to overcome this problem so that hydrophobic drugs can also be formulated in gel form for the finest and optimum action.

Composition of the skin

A part of topical drug delivery is also associated with transdermal applications for treating specific dermatological problems such as eczema, herpes labialis and dermatitis. To create an efficient formulation, an understanding of skin anatomy and its physiology is of the utmost requirement. The skin of a healthy adult

conceals the whole body with a surface area of 2 square meters and receives one-third of the total blood systematically circulated.[5] About 40-70 hair follicles are present with 200-300 sweat ducts present at every single square centimetre of the dermal surface.[6] The neutrality of the skin surface is influenced by the sweat and fatty acid secreted by the sebum in the skin.[7]

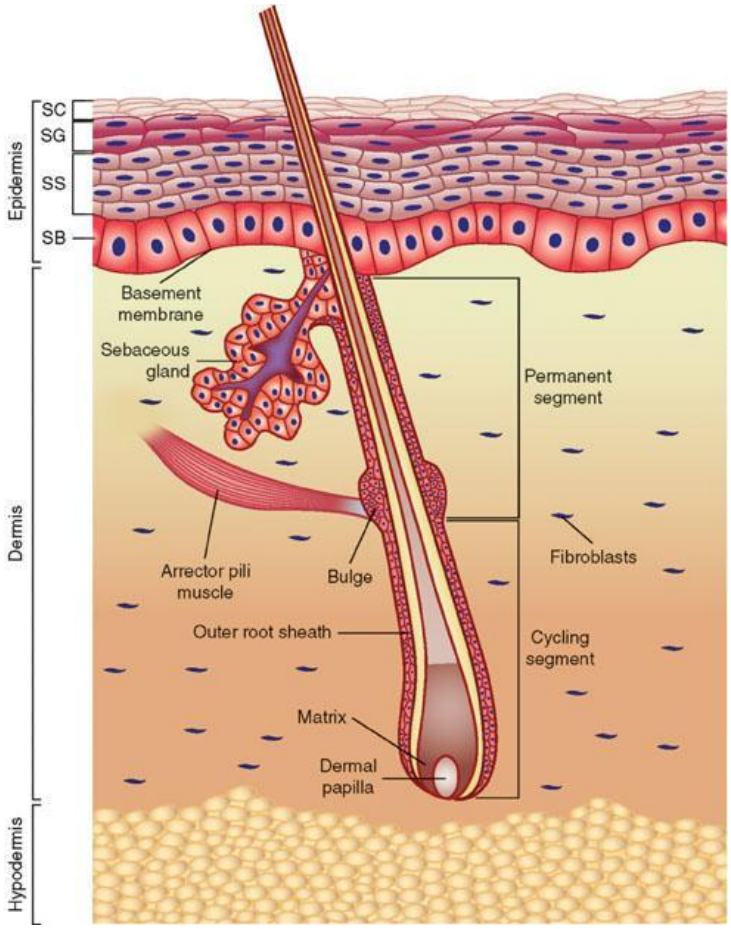

Fig 1: a pictorial representation of skin layers.

The skin consists of three distinct layers through which the drug is absorbed into the systemic circulation-

Epidermis- It consists of a detailed assemblage of cells identified as keratinocytes, which function to synthesize keratin, a long, delicate protein with a self-protective role. Furthermore, the epidermis is composed of stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum with stratum basale and stratum corneum being the deeper layers and peripheral layers of the epidermis respectively.[8]

Stratum basale is the deepest layer of the epidermis, also known as stratum germinativum. This layer is responsible for producing colour to the skin due to the presence of melanocytes. The basement membrane distinguishes this layer from the dermal layer and is attached to it by special stem cells that rapidly produce keratinocytes.[9]

Stratum spinosum is also identified as a prickle layer due to the presence of polyhedral cells in the form of spines with cytoplasmic processes, bridging the nearby desmosomes. They play a major role in maintaining the cohesion of the epidermis. Dendrite cells are present in this layer. It's composed of 8 to 10 cell layers.[10]

Stratum granulosum is a zone of intense biochemical activity and morphological change due to the presence of keratohyalin granules and lamellar granules. Keratohyallin granules have keratin precursors that separate, crosslink and form bundles, these are stained for studying their structure. Lamellar granules contain glycolipids, which act as the glue in binding the cells together.[11]

Stratum lucidum comprises 2-3 cell layers and is a thin transparent layer entailing a metabolised product of keratohyalin, eleidin. It is situated in the denser skin located in the soles and palms of the feet and hand. Cells in this layer are non-nuclear.[12]

Stratum corneum is the foremost layer of the epidermis made up of anucleate squamous cells which are keratin horny scales, these produce host defence peptides also otherwise called defensins as part of the first immune defence response. This layer adapts for weight-bearing

function in the soles and palms of the feet and hand, the horny pads present in them are 40 times thicker than the membranous horny layer giving rise to their inexplicable durability to external factors.[13]

Dermis- it is the inner region, lying between the epidermis and subcutaneous tissue. This area contains a dense network of structural protein fibres (collagen, elastin and reticulum embedded in the matrix of ground substance made up of mucopolysaccharides**.** The connective tissue is divided into the papillary layer and reticular layer, with the former being the thinnest layer and the latter being the thickest. Dermis gives the area for the establishment of hair follicles, muscles, sensory neurons and blood vessels and gives elasticity to the skin due to the existence of the gel structure of the cells.[14]

Subcutaneous tissue: this tissue lies below the dermis layer containing adipose tissues. It is also identified as sub-cutaneous fascia due to the presence of fat-rich areolar tissue, attaching itself to the principal structure. Large arteries and veins along with hair follicles and muscles and sensory neurons are present in this region of the skin.[14]

Drug delivery across the skin

Medicament delivery through the skin is considered to be the most effective way for therapeutic effectiveness. There are two potential routes for penetration of the drug across/into the intact skin, the trans-epidermal and trans-appendage pathways. In the trans-epidermal pathway, drug molecules travel through the stratum corneum which acts as a multi-cellular layer and then through the corneocytes, these corneocytes also allow the transport of hydrophilic /polar solvents. The trans-appendage route focuses on the transport of drug molecules through the sweat glands and the hair follicles.[16]

The drug delivery across the skin is affected by physiological and physiochemical factors such as the thickness of the skin and hair follicles, lipid content, skin pH, blood flow, hydration of skin, inflammation of the skin, partition coefficient, molecular weight (>400 Dalton), degree of ionisation and effect of vehicles, these properties help in characterising a formula for the drug to be delivered to the target site.[16]

Therefore, reviewing the drug delivery process profoundly is important to bring out an effective and non-toxic drug delivery form that would give maximum therapeutic effect to the affected site in action.

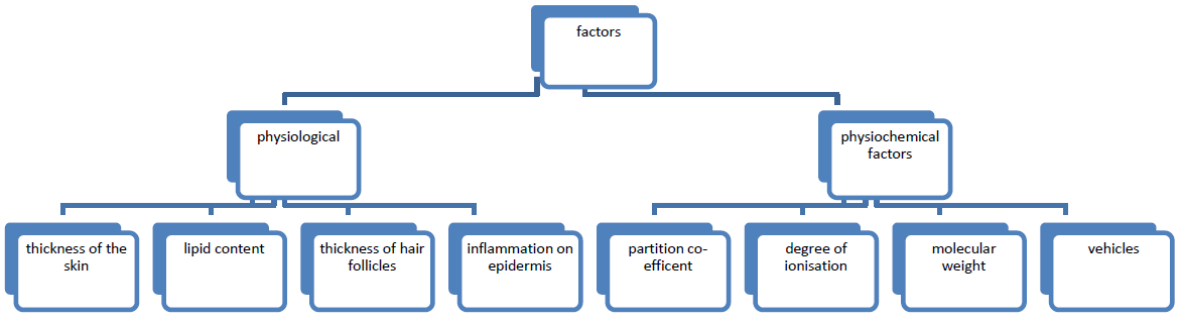

Fig 2: factors affecting drug delivery to the dermal layer.

Emulgel

In the mid-1980 emulgel has been increasing its significance in pharmaceutical topical semisolid dosage forms. As the name implies emulgels are the combinations of emulsion and gel. The emulsion is gelled by mixing with a gelling agent to form an emulgel. Their wide usage as a pharmaceutical dosage form comes from the wide use of emulsion systems, especially for dermatological formulas.[17]

Emulgels are controlled release systems. Emulsions are of two types, oil-in-water type and water-in-oil type, which are immiscible. The drug particles get entrapped in the internal phase and pass through the external phase and get absorbed into the skin to give its controlled effect 4. Water-in-oil emulsions are used for emollient actions and the treatment of dry skin, whereas oil-in-water emulsions are useful in general cosmetics.[18]

According to USP Gel is defined as a semisolid system containing either suspension made of either small inorganic particles or large organic molecules interpenetrated by a liquid. The amalgamation of gelling agent in the aqueous phase, turns a traditional emulsion into an emulgel. Most of the jellified emulsions function as a better vehicle for water-insoluble drugs.[19]

Emulgels have a better choice for the class-II of drugs as per BCS Classification systems that shows poor solubility and high permeability. While the emulsion owns the property of thixotropic, the process of penetration into the skin has become complicated. So, to enhance its penetration and stability it is assimilated into a gel.[20]

Emulgels are extensively used for patients. Because of its non-greasy property, it can be applied to the skin. It also

has many positive properties for dermatological use such as being thixotropic, easily spreadable, bio-friendly, easily removable, non-staining, pleasing appearance, emollient and has a longer shelf life.[20]

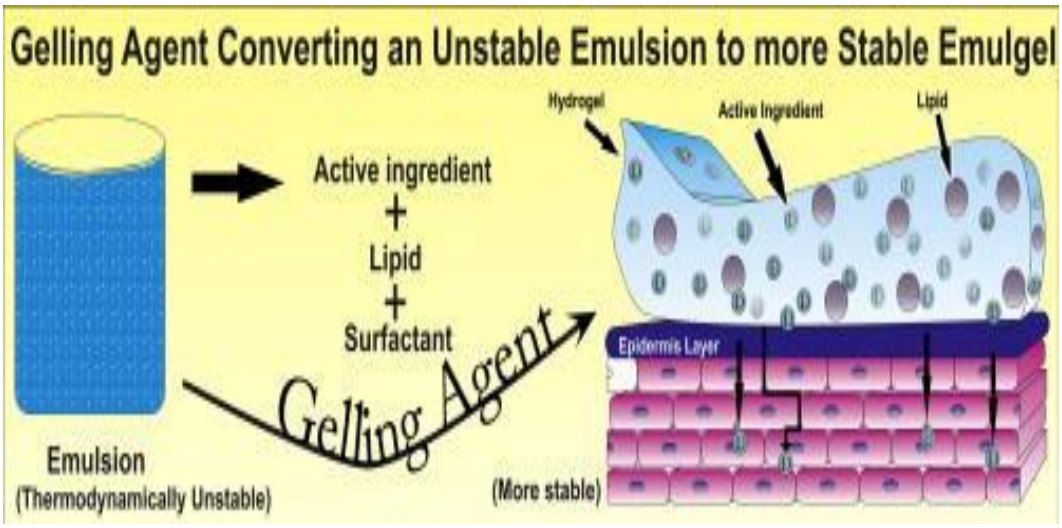

Fig.3: The action of emulgel on dermal layer.

Types of emulgel[21]

Emulgels are emulsions that are divided into two types:

- Water-in-oil
- Oil-in-water

Both oil-in-water and oil-in-water are gelled by mixing with a gelling agent to form emulgel.

Constituents of emulgel[22,23,24]

1. Vehicle

The vehicle such as water and alcohol transports the drug to the selected site of action and accurately deposits the drug on the skin and distributes it evenly.

2. Aqueous phase

The most commonly used agents are water and alcohol which form the aqueous phase of the emulsion.

3. Oils

Oils form the oily phase of the emulsion, as mentioned in *table (1)*. Mineral oils either single or combined with soft or hard paraffin are used for externally applied emulsions.

For internal use, the widely used oils are mineral oil, castor oil, fish-liver oil, Arachis oil, cottonseed oil and maize oil.

4. Emulsifiers

These agents are used for emulsification at the time of preparation and also help in maintaining stability during a shelf life that can change from days to years

Ex: Polyethylene glycol stearate, Sorbitan monooleate (span80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.

5. Gelling agents

Polymers that are essential to give the structural complex for the preparation of gels are known as gelling agents.

Gelling agents may be natural, synthetic or semi-synthetic.

These agents are used to elevate the consistency of the dosage form. They are also used as thickening agents as given in *table (2).*

6. Permeation enhancers

These are the agents that separate into and interact with skin constituents and get a temporary and reversible increase in skin permeability, as given in *table (3).*

Ex: Oleic acid, Methanol, Clove oil, Lecithin, Urea, Linoleic acid, Cinnamon oil. Etc.

- Properties of permeation enhancers:
  - ❖ They should not have pharmacological activity within the body.
  - ❖ They should work ideally and rapidly
  - ❖ They must be non-toxic, non-irritating and non-allergic.
  - ❖ Penetration enhancers should work unidirectionally.
  - ❖ They must be cosmetically allowable with a suitable skin feel.
- Mechanism of permeation enhancers:

They may act by one or more of 3 main mechanisms:

- Disturbs the extremely ordered structure of stratum corneum lipid.
- Interaction with intercellular protein.
- Improved partition of the drug, co-enhancer or solvent into the stratum corneum.[20]

7. Preservatives

These are the agents which stop or reduce the growth of micro-organisms and prevent the spoilage of the product.

Ex: Propylparaben, Methylparaben, Benzalkonium chloride, Benzoic acid, Benzyl alcohol.

8. Antioxidants

These protect cells against free radicals

E.g.: Butylated hydroxytoluene, Ascorbyl palmitate, butylated hydroxyl anisole.

9. Humectant

These are used to reduce the water loss from the formulation

Ex: Glycerin, Propylene glycol, etc.

Table 1: Quantity of chemicals used for different dosage forms.[25]

Sr. No	Chemical	Quantity (%)	Dosage forms
1	Light liquid paraffin	7.5	Emulsion and emulgel
2	Isopropyl myristate	7-7.5	Emulgel
3	Isopropyl stearate	7-7.5	Emulsion
4	Isopropyl palmitate	7-7.5	Emulsion
5	Propylene glycol	3-5	gel

Table 2: Quantity of gelling agents used in different dosage forms.[25]

Sr. No	Gelling agent	Quantity%	Dosage form
1	Carbopol-934	1%	emulgel
2	Carbopol-940	1%	Emulgel
3	HPMC-2910	2.5%	Emulgel
4	HPMC	3.5%	Gel
5	Sodium CMC	1%	Gel

Table 3: Quantity of penetration enhancers used in different dosage forms.[25]

Sr. No	Penetration Enhancer	Quantity	Dosage form
1	Oleic acid	1%	Gel
2	Lecithin	5%	Gel
3	Isopropyl myristate	5%	Gel
4	Clove oil	8%	Emulgel
5	Menthol	5%	Emulgel

Emulgel Preparation[26,27,28]

1. Preparation of Gel Base

Primarily the gel base was prepared by mixing the carbopol/hydroxypropyl methylcellulose (HPMC) with purified water in a beaker with continuous agitation.

2. Preparation of Emulsion

The emulsion was prepared in either oil in the water phase (or) water in the oil phase. The span 80 was dissipated in light liquid paraffin to prepare the oil phase. The Tween 80 was dissolved in distilled water to prepare the aqueous phase. Both the phases (oil &aqueous) are heated individually at 70-80oc. The drug was dispersed in the oil phase. Later the oil phase is added to the aqueous phase by gentle stirring and allowed to cool.

3. Combination of Emulsion into Gel Base

The prepared emulsion is combined with a gel base with continuous agitation. Thus, an emulgel was prepared.

Characterization of Emulgel[29,30,31]

1) Physical examination

The formulation was visually inspected for its colour, homogeneity, appearance, consistency, grittiness and phase separation.

2) Determination of PH

The digital PH meter is used for the determination of PH. The PH should be in the range of 5-6, similar to that of skin.

3) Spreadability

Spreadability can be determined by the slip and drag method which is put forward by a multimeter.

2gm of formulated emulgel was placed on the lower ground slide. The other slide is used to cover the ground slide as a sandwich type. 500 mg weight is placed on the upper slide for 5 minutes. Note the time taken to cover a 5cm distance by an upper slide which is used to calculate the spreadability by using the formula

$$\text{Spreadability (s)} = M*L/T$$

Where S = spreadability
M = weight bound to upper slide
L = Length of glass slide
T = time taken to cover the distance by upper slide.

4) Globule size and its distribution in emulgel

Globule size and its distribution in emulgel are usually determined by calibrating the eyepiece micrometre with a stage micrometre and calculating the factor. A sample is dispersed in distilled water and is stirred to get

homogenous dispersion. Mean globule diameter and its distribution are obtained.

5) Swelling index

For determination of swelling index a porous aluminium foil containing 1gm of the prepared formulation is placed in a 50 beaker containing 10ml of 0.1N NaOH. At different time intervals, the sample was taken and it is reweighed. The swelling index can be calculated premeditated by using the formula

Swelling index per cent (sw%) = [(wt-wo)/wo*100]

Where

Wo = initial weight of emulgel at zero time

Wt = final weight of emulgel after time t

SW% = per cent swelling index

6) Drug content determination

0.1gm of the prepared formulation was dissolved in 50ml of methanol. UV spectrophotometer is used to determine its absorbance. Thus drug content is determined by using a standard plot.

7) Microbial assay

The technique used in the microbiological assay is the ditch plate technique. This technique is used for the estimation of the bacteriostatic (or) fungi-static activity of a compound. Culture loops that are freshly prepared were streaked across the agar at a right angle from the ditch to the edge of the plate. The fungal growth was observed after incubating for 24 hours at 25^0C.

8) In-vitro drug release study

An in-vitro drug release study is conducted using the Franz diffusion cell method.100mg of the formulation was applied on the surface of the egg membrane. The egg is placed between the donor and the receptor chamber of the diffusion cell. The receptor chamber was filled with buffer solutions made up of NaOH and KH2P to soluble the drug. A magnetic stirrer is present in the receptor chamber. At regular time intervals, the sample is collected. UV spectrophotometer is used for the sample analysis after appropriate dilutions. The amount of drug released was determined.[32]

9) Stability studies

The prepared emulgel formulation was packed in aluminium collapsible tubes and subjected to stability studies at 5^0C, 25^0C /60%RH, 30%C/65%RH, and 40%C/75% RH for 3 months. At particular time intervals, the sample is withdrawn to evaluate physical appearance, pH, drug content and drug release profile.[33]

Advantages of emulgel[34]

1. Emulgel is an easy and more cost-effective preparation.
2. Emulgel provides targeted drug delivery.
3. Improve patient compliance.
4. Convenient & easy to apply.
5. No first-pass metabolism.
6. Gastrointestinal incompatibility eradicated.
7. Penetration of the skin is enhanced due to both hydrophilic & hydrophobic nature.
8. Drug loading capacity is better in emulgel.
9. More stable than other transdermal preparations.
10. emulgels are used to prolong the effect of drugs having a short half-life(T1/2)

Disadvantages

1. Skin irritation on contact dermatitis.
2. During the formulation of emulgel bubbles may form.
3. Poor permeability of some drugs through the skin.
4. Possibility of allergenic reactions.
5. Large particle size of a drug is not easy to absorb through the skin**.**

Marketed Preparations

SR.NO.	BRAND NAME	ACTIVE INGREDIENT	MANUFACTURER	USES
1	Voltarol (1.16% emulgel)	Diclofenac Diethylammonium salt	Novartis	Antiinflammatory
2	Diclomax emulgel	Diclofenac sodium	Torrent pharma	Antiinflammatory
3	Miconaz-H-emulgel	Miconazole nitrate, Hydrocortisone	Medical union pharmaceuticals	Topical corticosteroid and antifungal
4	Dermafeet emulgel	Urea40%	Herbitas	Intense moisturizing and exfoliation activity
5	Denacine emulgel	Clindamycin phosphate	Beit Jala pharmaceutical company	antiacne
6	Isofen emulgel	Ibuprofen	Beit Jala pharmaceutical company	anti-inflammatory
7	Diclona emulgel	diclofenac diethylamine	Kuwait Saudi pharmaceutical industries co.	anti-inflammatory
8	Dosanac emulgel	Diclofenac dimethylammoniummmm	Siam bheasach	anti-inflammatory
9	Diclon emulgel	diclofenac diethylamine	med pharm	anti-inflammatory
10	Cataflam emulgel	Diclofenac potassium	Novartis	anti-inflammatory

Future Prospective

Hydrophobic behaviour of drugs is one of the most common problems faced during formulation. Because of the hydrophobic nature of many drugs delivery to these to the biological system have been challenging creams, lotion & ointments are of different types of drug delivery system which has been applied topically have excellent emollient properties but retards the release of drugs due to the presence of oleaginous bases such as beeswax or vegetable oils those themselves are hydrophobic in nature.

It makes them an excellent emollient but retards the release of drugs & makes the product thick & greasy. Emulsion based gel provides a suitable medium for delivery of such hydrophobic drugs where such drugs can be incorporated into its oily phase & delivered to the skin. All such points of interest of emulgel over other topical drug delivery systems make them more effective & profitable. Subsequently, these properties will be utilized to deliver further topical medications in the form of emulgel.

CONCLUSION

After a through literature survey, we reached the conclusion that emulgels are the most convenient, better, and effective delivery system. As they are non–greasy and have a gel-like property that serves as an aqueous environment for the drug, which helps in stress-free dissolution for the emulgel to produce better drug release when compared to the other topical drug delivery systems. Since emulgel displays improved adhesion, spreadability, extrusion and viscosity, it can be reflected as a promising novel drug delivery system with enhanced characteristics and advantages.

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