Overview on transdermal drug delivery by semisolid systems: Emulgel

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ABSTRACT
When gels and emulsions are used in combined form the dosage forms are referred as emulgels. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance.

INTRODUCTION
Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied lotions, creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption of the drugs through the skin, which lead to the idea of TDDS. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. The novel Transdermal drug delivery is defined as self-contained, discrete dosage forms which when applied to the intact skin, deliver the drug through the skin at controlled rate to the systemic circulation.

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEMS

- Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
- Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic “first- pass” effect, formation of metabolites that cause side effects, short half - life necessitating frequent dosing etc.
It is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is required by oral administration.

The simplified medication regimen leads to improved patient compliance and reduced inter & intra – patient variability.

At times the maintenance of the drug concentration within the diphasic not desired. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect.

Self-administration is possible with these systems.

The drug input can be terminated at any point of time by removing transdermal patch.

Provides utilization of drugs with short biological half-lives, narrow therapeutic window.

Improving physiological and pharmacological response.

Avoiding the fluctuation in drug levels.

Maintain plasma concentration of potent drugs.

**DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEMS**

- The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.

- Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin impermeability.

- Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.

- Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.

- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

**HISTORICAL PERSPECTIVE**

Transdermal delivery of medications was foreshadowed in earlier era as by the use of certain plasters and ointments. The mustard plaster, applied as a home remedy for severe chest congestion, may be considered an example. Powdered mustard seeds were mixed with warm water, and the resulting paste was spread on a strip of flannel, which was applied to the patient’s chest with a cloth binding wrapped around the body to hold the plaster in place. The history of plasters has been traced back to antiquity. In addition to mustard plasters, several other plasters were recognized in early 20th century editions of the United States Pharmacopeia (USP) and National Formulary (NF) one time, Belladonna Plaster, containing 0.25 – 0.30% of belladonna root alkaloids, was believed to act transdermally as an analgesic. Perhaps the most remarkable forerunner of modern transdermal medication was Strong Mercurial Ointment, used as a treatment for syphilis when Salvarsan and other arsenicals were in use, before the discovery of penicillin. For the first time use of transdermal drug delivery system was done by the USFDA in December 1979, which administered scopolamine for motion sickness.

**SKIN AS A SITE FOR DRUG DIFFUSION**

The skin of an average adult body covers around 2 m² of surface area and receives approximately one third of all blood circulating through the body. It is one of the extensive and readily accessible organs on the human body. With a thickness of only a fraction of millimeter, the skin separates the underlying blood circulation network from the outside environment and serves as a barrier against physical, chemical and microbial attacks, acts as a thermostat in maintaining body temperature, plays a role in the regulation of blood pressure and protects against the penetration of ultra violet rays. The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers: the epidermis, the dermis and the hypodermis. Microscopically, the epidermis is further divided into five anatomical layers with stratum corneum forming the outermost layer of the epidermis. The stratum corneum consists of many layers of compacted, flattened, dehydrated and keratinised cells. They are dead cells converted to protein and are continuously shed, requiring replacement from the underlying viable epidermal tissues. The stratum corneum has a water content of only ~ 20% as compared to the normal 70% in the physiologically active stratum germinativum (regenerative layer of the epidermis). An average human skin surface is known to contain 40-70 hair follicles and 200-250 sweat ducts on each square centimeter of the skin area. These skin appendages, however, occupy grossly, only 0.1% of the total human skin surface. Even though the foreign agents, especially the water soluble ones may be able to penetrate into the

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skin via these skin appendages at a rate which is faster than through the impact area of the stratum corneum. This transappendageal route of percutaneous absorption has, at steady state, a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore the transdermal permeation of most neutral molecules can, thus, be considered as, process of passive diffusion through the intact stratum corneum in the interfollicular region. For many decades, the skin has been commonly used as the site for the administration of dermatological drugs to achieve a localised pharmacologic action in the skin tissues. Most recently, there is an increasing recognition that the skin can also serve as port of administration for systematically active drugs. In this case, the drug applied topically will be absorbed first into the blood circulation and then be transported to target tissues, which could be rather remote from the site of drug application, to achieve its therapeutic responses. It is exemplified by controlled administration of nitroglycerin for the treatment of angina pectoris and scopolamine for the prevention of motion sickness.

![Figure 1: Anatomy of the skin](image)

**NOVEL ADVANCES IN SEMISOLID DOSAGE FORMS**

**OINTMENTS**

**RECTAL OINTMENT**

It is used for the symptomatic relief against anal and peri-anal pruritus, pain and inflammation associated with hemorrhoids, anal fissure, fistulas and proctitis. Rectal ointment should be applied several times in a day according to the severity of the condition. For intra rectal, use, apply the ointment with the help of special applicator.

**CREAMS**

Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base, usually an oil in-water emulsion or aqueous microcrystalline dispersion of long-chain fatty acids or alcohols that are water-washable and are cosmetically and aesthetically acceptable.

**CREAMS CONTAINING MICROSPHERES**

Albumin microsphere containing vitamin A can be administered by using creams topically. 222 ± 25 μm size of microsphere of vitamin A were produced by emulsion method. The in-vitro and in-vivo drug release of a microencapsulated and non-microencapsulated vitamin A cream was studied. The in vivo study in six volunteers revealed that these microspheres were able to remain on the skin for a long period of time, and as a consequence they were able to prolong the release of vitamin A.

**LAMELLAR FACED CREAMS**

They are liquid paraffin in water emulsion prepared from cetrimide / fatty alcohol like mixed emulsifiers and ternary system formed by dispersing the mixed
emulsifier in require quantity of water. The cationic emulsifying wax showed phenomenal swelling in water and this swelling was due to electrostatic repulsion which can be suppressed by addition of salt and can be reduced by changing surfactant counter ion.

CREAM CONTAINING LIPID NANOPARTICLES
Occlusion of cream is important criteria since it increases the penetration of topical drugs. This can be achieved by using oils and fats like liquid and semisolid paraffin in large quantities. However, such formulations have the limitations of poor cosmetic properties since they have greasy feel and glossy appearance. The development of a water-in-oil cream containing small paraffin particles was studied. A high degree of occlusivity was obtained with smooth, flexible films prepared by drying aqueous dispersions of solid paraffin particles with a mean size of 200 nm (nanoparticle dispersion). However, this nanodispersion revealed a rough texture when applied. The development of a water-in-oil cream wherein the aqueous phase was divided into small droplets solved this problem. Nanoparticles were incorporated in the aqueous phase. Hence, the oil phase in which the water droplets were dispersed served as a lubricant for nanoparticles, thereby preventing a rough feel during application.

GELS
Gels are defined as semisolid system in which a liquid phase is constrained within a polymeric matrix in which a high degree of physical and chemical cross-linking introduced.

CLASSIFICATION OF GELS
Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.

BASED ON COLLOIDAL SYSTEMS
SINGLE-PHASE SYSTEM
These consist of large organic molecules existing on the twisted strands dissolved in a continuous phase. This larger organic molecule either natural or synthetic polymers are referred as gel formers, they tend to entangle with each other their random motion or bound together by Vander walls forces.

TWO PHASE SYSTEM
If partial size of the dispersed phase is relatively large and form the three-dimensional structure throughout gel, such a system consists of flocules of small particles rather than larger molecules and gel structure in this system is not always stable. They must be thixotropic-forming semisolids on standing and become liquid on agitation.

BASED ON NATURE OF SOLVENT
HYDRO GELS (WATER BASED)
Here they contain water as their continuous liquid phase. e.g.: bentonite magma, Gelatin, cellulose derivatives, carpooler, and poloxamer gel.

ORGANIC GELS (WITH A NON-AQUEOUS SOLVENT)
These contain a non-aqueous solvent on their continuous phase. E.g.: plastibase (low molecular wt polyethylene dissolved in mineral oil & short Cooled) Olag (aerosol) gel and dispersion of metallic stearate in oils

XEROGELS
Solid gels with low solvent concentration are known as xerogels. These are produced by evaporation of solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid, they swells and can be reconstituted. E.g. Tragacanth ribbons, acacia tear β-cyclodextrin, dry cellulose and polystyrene.

BASED ON RHEOLOGICAL PROPERTIES
PLASTIC GELS
Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.

PSEUDO-PLASTIC GELS
The viscosity of these gels decreases with increasing rate of shear, with no yield value. The rheogram results from a shearing action on the long chain molecules of the linear polymers. As the shearing stress is increased the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from gel matrix. E.g.: Liquid dispersion of tragacanth, sodium alginate, Na CMC etc. exhibits pseudo-plastic flow.
THIXOTROPIC GELS
The bonds between particles in these gels are very weak and can be broken down by shaking. The resultant solution will revert back to gel due to the particles colliding and linking together again. (The reversible isothermal gel-sol-gel transformation). This occurs in colloidal system with non-spherical particles to build up a scaffold like structure.
E.g.: Kaolin, bentonite and agar.

BASED ON PHYSICAL NATURE
ELASTIC GELS
The fibrous molecules being linked at the point of junction by relatively weak bonds such as hydrogen bonds and dipole attraction. If the molecule possesses free –COOH group then additional bonding takes place by salt bridge of type –COO-X-COO between two adjacent strand networks. Gels of agar, pectin, Guar gum and alginites exhibit an elastic behavior.

RIGID GELS
This can be formed from macromolecule in which the framework linked by primary valance bond. E.g.: In silica gel, silic acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

EMULGEL
When gels and emulsions are used in combined form the dosage forms are referred as emulgels. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance.

RATIONALE OF EMULGEL AS A TOPICAL DRUG DELIVERY SYSTEM
Numbers of medicated products are applied to the skin or mucous membrane that either enhance or restore a fundamental function of skin or pharmacologically alter an action in the underlined tissues. Such products are referred as topical or dermatological products. Many widely used topical agents like ointments, creams lotions have many disadvantages. They have very sticky causing uneasiness to the patient when applied. Moreover they also have lesser spreading coefficient and need to apply with rubbing. And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelatin substance present. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels.

ADVANTAGES OF EMULGEL AS A DRUG DELIVERY SYSTEM
HYDROPHOBIC DRUGS CAN BE EASILY INCORPORATED INTO GELS USING W/O/W EMULSIONS
Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

BETTER STABILITY
Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.
OTHER NOVEL APPROACHES LIKE NIOSOMES AND LIPOSOMES ARE OF NANO SIZE AND DUE TO VESICULAR STRUCTURES MAY RESULT IN LEAKAGE AND RESULT IN LESSER ENTRAPMENT EFFICIENCY. BUT GELS DUE TO VAST NETWORK HAVE COMPARATIVELY BETTER LOADING CAPACITY.

PRODUCTION FEASIBILITY AND LOW PREPARATION COST
Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

NO INTENSIVE SONICATION
Production of vesicular molecules needs intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

CONTROLLED RELEASE
Emulgels can be used to prolong the effect of drugs having shorter t1/2.

IMPORTANT CONSTITUENTS OF EMULGEL PREPARATION
AQUEOUS MATERIAL
This forms the aqueous phase of the emulsion. Commonly used agents are purified water, alcohols.

OILS
These agents form the oily phase of the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics.

EMULSIFIERS
Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations. eg Polyethylene glycol 40 stearate, Sorbitan mono-oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.

GELLING AGENT
These are the agents used to increase the consistency of any dosage form and can also be used as thickening agent. Some of the examples are HPMC, HPMC K-100, carbopol 940, carbopol 934, sodium carboxy methyl cellulose, xanthun gum etc.

PERMEATION ENHANCERS
These are agents that partition into, and interact with skin constituents to induce a temporary and reversible increase in skin permeability. Some of the examples are oleic acid, lecithin, urea, DMSO, linolic acid etc.

EVALUATION PARAMETERS
PHYSICAL APPEARANCE
The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency and phase separation.

PH EVALUATION
PH evaluation is an important criterion especially for topical formulations. The pH of emulgel should be in between 5-7 to mimic the skin conditions. If the pH of prepared emulgel is acidic or basic, it may cause irritation to the patient. PH of prepared emulgel was measured using digital pH meter by dipping the glass electrode into the emulgel. The measured pH of each formulation was done in triplicate and average values were recorded.

RHEOLOGICAL STUDIES
The viscosity of gel during handling, transport and storage is an important criterion. The viscosity of different emulgel formulations was determined at 25°C using Brook field viscometer. The emulgels were rotated using spindle 6 at10 rpm and viscosities were measured.

SPREADABILITY TEST
One of the criteria for a dermatological preparation is to meet the ideal qualities is that it should possess good spread ability. Spread ability is the term expressed to denote the extent of area to which the gel readily spreads on application to skin or the affected area. The therapeutic efficacy of the formulation also depends on the spread ability values. Hence determination of spread ability is an important emulgel evaluation parameter, spread ability is measured as:
$S = M \times \frac{L}{T}$

Where,
- $M =$ weight to be taken
- $L =$ length of the slide
- $T =$ time taken

The spreadability if each sample was evaluated in triplicate by using fabricated spreadability apparatus which consists of two glass plates. 0.5g of the sample was placed on lower plate and upper plate was placed on the top of the sample. Force was generated by adding increasing weight slowly at 1 minute interval into the pan connected to the upper plat, each sample was tested three times at constant temperature and exerted weight and the mean values of the spread surface area on lower plate were calculated.

**DRUG CONTENT DETERMINATION**

Drug concentration in emulgel was measured by UV-Visible spectrophotometer. celecoxib content in emulgel was measured by dissolving accurately 5ml of emulgel in 6.8pH phosphate buffer by Sonication and diluted to 10 folds prior to absorbance. Absorbance was measured at 231nm using UV-Visible spectrophotometer 1700 (Shimadzu, Japan). The test was conducted in triplicate and the average % drug content was determined.

**ISOLATION OF EGG MEMBRANE**

Egg was taken and made a small hole on the tip portion of the egg. The contents of the egg were removed via that hole. Then egg shell was washed internally with water and dipped into 0.1N Hcl solution for four hours. The outer shell of the egg would dissolve and egg membrane was isolated from it.

**IN-VITRO DRUG PERMEATION STUDY**

In-vitro permeation study was carried out using keishary chein cell having capacity of 18ml volume. Egg membrane was isolated and used for the study. 5ml of emulgel was spread evenly on to the egg membrane. The egg membrane was clamped between donor and receptor compartment. The receptor compartment was filled with 16ml of 6.8pH phosphate buffer maintained at 37ºC and stirred by using magnetic stirrer. The sample (2ml) was collected at suitable time intervals and analyzed for drug content by UV-Visible Spectrophotometer 1700 (Shimadzu, Japan) at 231nm after appropriate dilutions as discussed earlier.

**BIBLIOGRAPHY**
