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Formulation and evaluation of gels - Review

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ABSTRACT

Gels are getting popularity now a days due to their stability and controlled release when compared with other semisolid dosage preparation like ointments,creams,pastes,etc.Gel formulation provides a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Topical drug delivery has advantages such as applying the drug directly into skin and it also provides prolonged action on the specific site.This review includes fundamental advantages of gel formulation above other semisolid formulation and also other aspects like limitation,classification,formulation,mechanism involved and factors affecting of gel formulation.Gels are an tremendous formulation for several routes of administration . They are useful for oral , topical, vaginal, and rectal administation . Gels can be clear formulation when all of the particles completely dissolve in the dispersion medium. Gels are evaluated by following parameter such as pH, homogeneity, grittiness, drug content, viscosity, spreadability, extrudability, skin irritation studies, invitro and stability study.

Keywords: Gels,Topical,Buccal,Ophthalmic,Vaginal.

INTRODUCTION

GELS[4]

The word “gel” is derived from “gelatin” and both “gel” and “jelly” can be derived from the Latin gelu for “frost” and gel are meaning “freeze” or “congeal”. This origin indicates the essential idea of a liquid setting to a solid like material that does not flow, but is elastic and remains some liquid characteristics.
The USP defines gel as a semisolid system containing either suspensions made up of small inorganic particles, or large organic molecules diffuse by a liquid. The gel mass consists of networks of small separate particles, the gel is classified as a two phase system. In a two phase system, if the particle size of the dispersed phase is comparatively large, the gel mass is sometimes called as magma. Single-phase gels consist of organic macromolecules uniformly circulated throughout a liquid in such a way that no apparent boundaries occur between the dispersed macromolecules as the liquid.
Some gel systems are as clear as water and others are muddy because the ingredients partially molecularly dispersed [soluble or insoluble] or they may form aggregates, which disperse light. The concentration of the gelling agents is mostly less than 10 % usually in 0.5% to 2.0% range, with some exceptions.

Figure 1: GEL

ROUTE OF ADMINSTRATION OF GELS [3]

Gels are an excellent formulation for several routes of administration. They are useful as liquid formulation in oral, topical, vaginal and rectal administration. Gels can be clear formulation when all of the particles completely dissolve in the dispersion medium.

DIFFERENT ROUTES OF ADMINISTRATION OF GEL

Topical routes of administration
Buccal routes of administration
Vaginal routes of administration
Ophthalmic routes of administration

TOPICAL ROUTES OF ADMINISTRATION

Topical preparations are formulation which are applied directly to an external body surface by spreading, rubbing, spraying or instillation. The topical route of administration has been utilized either to produce local effect for treating skin disorder or to produce systemic drug effects within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. E.g. Diclofenac sodium, fluconazole, aceclofenac.

USES

Used in the treatment of a variety of dermatological skin infections like tinea and candidal infection of the skin.

BUCCAL ROUTES OF ADMINISTRATION

Buccal routes have been used to deliverdrugs such as certain antifungal drugs that are subjected to first-pass metabolism. The fluoride rinses and gels used in some oral care regimens are used primarily for antibacterial activity. E.g.Verapamil Hcl,benzydamine hydrochloride for oral ulcers.

USES

Oral gel is used to treat fungal infections in the mouth, throat and gastrointestinal tract, such as oral candidiasis caused by the yeast candida; as well as to prevent spread of infection.

VAGINAL ROUTES OF ADMINISTRATION

Vaginal delivery is an important route of drug administration for both local and systemic diseases. The vaginal route has some advantages due to its large surface area, rich blood supply, avoidance of the first-pass effect, relatively high permeability to many drugs and self-insertion. The traditional commercial preparations, such as creams, foams, gels are known to be inherent in the vaginalcavity for a relatively short period of time owing to the self cleaning action of the vaginal tract, and often require multiple daily doses to ensure the desired therapeutic effect. The vaginal route appears to be highly appropriate for bioadhesive drug delivery systems in order to retain drugs for treating largely local conditions, or for use in contraception. In particular, protection against sexually-transmitted diseases is critical. To prolong the residence time in the vaginal cavity, bioadhesive therapeutic systems have been developed in the form of semi-solid and solid dosage forms. E.g.Nystatin, clotrimazole, miconazole.

USES

This medication is used to treat certain types of bacterial infections in the vagina. It may help to decrease itching, discharge and other symptoms. Vandazole is a vaginal gel used to treat bacterial vaginosis in women who are not pregnant. Vandazole is for vaginal use only and should not be put in the eyes, mouth or on the skin. The use of other vaginal products and vaginal intercourse should be avoided during treatment with vandazole.

OPHTHALMIC ROUTES OF ADMINISTRATION

Drug delivery to the eye can be broadly classified into anterior and posterior segments of eye Conventional systems such as eye drops, suspensions, and ointments cannot be considered optimal in the treatment of vision, threatening ocular diseases. *In situ*-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular *cul-de-sac* to form viscoelastic gel and this provides a response to environmental change. In situ gels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. In situ gel-forming, significant attention hasophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol–gel–sol) and pseudoplastic behavior to minimize interference with blinking. E.g. Pilocarpine hydrochloride, timolol maleate.

USES

Ophthalmic in-situ gel generally more comfortable than insoluble or soluble insertion and less blurred vision as compared to ointment. Increased bioavailability due to increased precorneal residence time decreased naso-lacrimal drainage of the drug which causes undesirable side effects arising due to systemic absorption of the drug through naso-lacrimal duct is reduced. Drug effect is prolonged hence frequent instillation of drug is not required. The principle advantage of this formulation is the possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and moreover promoting pre-corneal retention

STRUCTURE OF GELS[1]

A gel contains a natural or synthetic polymer establish a three dimensional matrix all over a dispersion medium or hydrophilic liquid. After application, liquid evaporate leaving the drug entrapped in a thin film of the gel –forming matrix physically converting the skin. The presence of a network formed by interlocking of particle of gelling agent gives rise to the rigidity of a gel. The nature of the particle and type of form that is responsible for the linkages determine the structure of the network and the property of the gel.

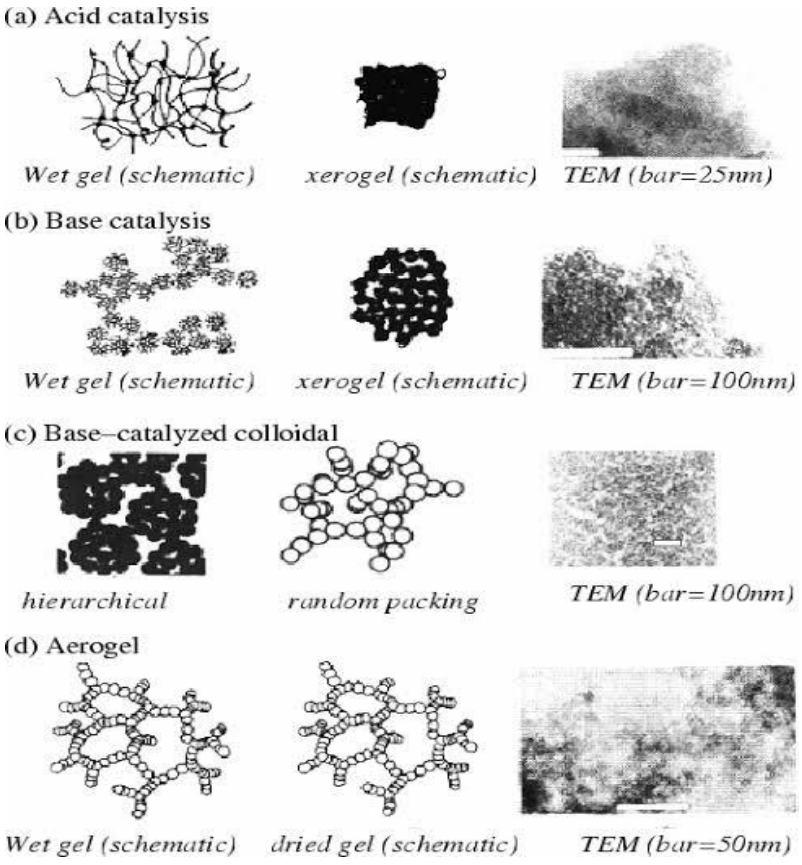

Fig 2: Structure of gel

PREPARATION OF GELS[8]

Gels are normally in the industrial scale prepared under a room temperature. through few of polymers need special treatment before process.

GELS CAN BE PREPARED BY FOLLOWING METHODS

- Thermal changes
- Flocculation
- Chemical reaction

THERMAL CHANGES

Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reducing, the degree of hydration is reduced and gelatin occurs. (Cooling of a concentrated hot solution will produce a gel). E.g.: -Gelatin, agar sodium oleate, guar gummed and cellulose derivations etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.

FLOCCULATION

Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is essential to ensure quick mixing to avoid local high concentration of precipitant.E.g.: solution of ethyl cellulose, polystyrene in benzene can be gelled by quick mixing with suitable amounts of a non-solvent such as petroleum ether. The adding of salts to hydrophobic solution brings about coagulation, gelation is infrequently observed. The gels formed by flocculation method are Thixotropic in behaviour. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to “salt out”, the colloidal and gelation doesn’t occur.

CHEMICAL REACTION

In this method gels are formed by chemical interaction between the solute and solvent. E.g.: aluminium hydroxide gel can be prepared by interchange in aqueous solution of an aluminium salt and sodium carbonate an increased concentration of reactants will produce a gel structure.

FORMULATION CONSIDERATIONS FOR PHARMACEUTICAL GELS[5]

- The choice of vehicle/solvent
- Inclusion of buffers
- Preservatives
- Antioxidants
- Flavours of sweeting agents

THE CHOICE OF VEHICLE/SOLVENT

Normally purified water is used as a solvent. To enhance the solubility of the therapeutic agent in the dosage form and/or to improve drug permeation across the skin, co-solvents may be used,E.g., alcohol, glycerol, PG, PEG 400.

INCLUSION OF BUFFERS

Buffers may be involved in aqueous and hydroalcoholic-based gels to control the pH of the formulation. The solubility of buffer saltsis reduced in hydroalcoholic-based vehicles. E.g., Phosphate, citrate.

PRESERVATIVES

Certain preservatives cooperate with the hydrophilic polymers used to prepare gels, thereby reducing the concentration of free (antimicrobially active) preservative in the preparation. Therefore, to compensate for this, the initial concentration of these preservatives should be improved. E.g., Parabens, phenolics.

ANTIOXIDANTS

It may be involved in the formulation to improve the chemical stability of therapeutic agents that are prone to oxidative degradation. Its choice is based on the nature of the vehicle used in the preparation of gel. Water-soluble antioxidants are generally used as the majority of gels are aqueous-based. E.g., Sodium metabisulphite, sodium formaldehyde sulfoxylate.

FLAVOURS/SWEETING AGENTS

Flavors and sweetening agents are only incorporated in gels that are designed for administration into the oral cavity (E.g., for the treatment of infection, inflammation, ulceration, etc.). E.g., Sweeteners: Sucrose, liquid glucose, glycerol, sorbitol, saccharin sodium, aspartame, etc.

FLAVORS

Butterscotch, apricot, peach, vanilla, wintergreen mint, cherry, mint, anise, citrus flavors, raspberry.

EXCIPIENT USED FOR GEL FORMULATION[2]

- Polymer **(** Carbopol 934 p , HPMC)
- Triethanolamine
- Glycerine
- Methyl paraben
- Propyl paraben
- Purified water

CARBOPOL

Carbopol is used as thickener in lotion,creams and gels.it is used to stablize suspend and control the release of pharmaceutical products at low concentration.

Formula :$(C_3H_4O_2)_n$
Melting point:111 ◦C

HPMC

HPMC is used as a thickening agents,binder,film former and hydrophillic matrix material.HPMC is available in various viscosity grades ranging from 4000 to 100000 mpa s . HPMC matrices shows sustained release pattern by two mechanism are diffusion and erosion of gel layer.

TRIETHANOLAMINE

The triethanolamine neutralize fatty acid adjust and buffers the pH,solubilize oils and other ingredients that are not completely soluble in water.it is safe for the skin and does not have any side effects.

Boiling point:335.4◦c
Formula:$C_6H_{15}NO_3$

Methyl paraben

Methyl paraben is the type of paraben. parabens are chemicals that are often used as preservative to give products a longer shelf life.

Boiling point: 275°C
Formula : $C_8H_8O_3$
Appearance: colorless crystals

PROPYL PARABEN

It is a stable, non volatile compound used as an antimicrobial preservative. Propyl paraben is relatively non toxic by both oral and parenteral.

FACTORS AFFECTING GEL FORMULATION[5]

A number of factors are known to affect gel preparations. Some major factors have been enlisted as follows

i. Concentration of the gelling agent.
ii. Molecular weight of the gelling agent.
iii. Solubility and affinity of gelling agent to the solvent being used.
iv. Nature of the solvent.
v. pH of the solution.
vi. Ionic strength of the solution.
vii. Temperature at which the gel is being formulated.
viii. Humidity and other environmental conditions.

Table 1: Gelling concentrations for substance used in pharmaceutical products.

Substances	Gel-forming concentrations
Collagen	0.2-0.4
Gelatin	2-15
Agar	0.1-1
Alginates	0.5-1
K-carrageenan	1-2
Gellum gum	0.5-1
Carboxy methyl cellulose	4-6
Hydroxyl propyl cellulose	8-10
Hydroxyl propyl methylcellulose	2-10
Aluminium hydroxide	3-5
Bentonite	5
Laponite	2
Poloxamer	15-50

Table 2: Gel forming substances.

Semisynthetic polymers	Synthetic polymers	Inorganic substances	surfactants
Cellulose derivatives	**Carbomer:** Carbopol-934 Carbopol-940 Carbopol-941	Bentonite	Brij-96
Methylcellulose	Polyacrylamide	Aluminium hydroxide	Cetostearyl alcohol
Hydroxyethylcellulose	Poloxamer		Sodium lauryl sulphate
Hydroxypropyl cellulose	Polyvinyl alcohol		Dodecyl pyridinium iodide
Carboxymethyl cellulose	Polyethylene and its co-polymers		Sorbitan mono-oleate
Hydroxypropyl methyl cellulose			Lecithin

MECHANISM OF GEL FORMATION[7]

Gels are formed via three types of cross linking

- chemical cross-linking
- physical cross – linking
- ionic cross- linking

CHEMICAL CROSS- LINKING

Chemical cross-linkage is found also with polymer possessing bonded group in their assembly. When cross-linkage compounds are bringing together such polymers cause an irreversible reaction among the added compound and free group. After attaining a specific concentration viscosity increases in this type of reaction and results in gel formation. Eg: Polyacrylic acid (with multiple carboxylic acid).

PHYSICAL CROSS- LINKING

By hydrogen bond formation solution to gel transition can be obtain also in cases like concentration variation, temperature variation transition, crystalline component solubilisation. Physical cross-linking is shown in Eg: Cellulose gels, Dextran gels.

ION CROSS- LINKING

Here cross-connecting occur by making charge on polymer(S) or different particles (Solvent) that attract one another resulting in gel. Charges on the molecules result in Ionic bonds formation. Eg: Polysaccharide alginate produce gel matrix in company of calcium ions result in gel matrix of calcium ions result in gel matrix that encapsulates some compounds (enzymes).

EVALUATION PARAMETERS OF GEL[7]

- Measurement of pH
- Drug content
- Viscosity study
- Spread ability
- Extrudability study
- Skin irritation study
- In-vitro dissolution studies
- Stability
- Homogeneity
- Grittiness

MEASUREMENT OF PH

PH can be determined by using digital pH meter.

DRUG CONTENT

Mix 1g of the gel formulation with 100 ml of suitable solvent. Filter the stock solution. Then prepared the aliquots of different concentration by suitable dilutions and measure the absorbance. Linear regression analysis of calibration curve is used to calculate the drug content.

VISCOSITY STUDY

It is carried out by using Brookfield viscometer. Rotate the gels at 0.3, 0.6 and 1.5 RPM. Note down the corresponding dial reading at each speed. The viscosity was obtained by dial reading × factor given in the Brookfield viscometer catalogues.

SPREADABILITY

It indicates the extent of the area to which gel readily spreads on application to the skin or affected part. The therapeutic potency also depends upon spreading value. The time in sec taken by two slides to slip off from gel which is placed in between the slides under the direction of certain load is expressed as spreadability. Lesser the time taken for the separation of two slides, better the spreadability. The following formula is used to calculate the spreadability:

Spreadability (S) = M × L / T

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

EXTRUDABILITY STUDIES

The formulations are filled in the collapsible tubes, after it was set in the container. Extrudability is determine in terms of weight in gm required to extrude a 0.5 cm ribbon of gel in 10 second.

SKIN IRRITATION TEST

For skin irritation study, Guinea pigs (400-500g; either sex) were used. The animals were maintained on the standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from the back. Five ml of each sample was withdrawn periodically at 1,2,3,4,5,6,7 and 8h and each sample was replaced with an equal volume of fresh dissolution medium. Then analyzed the samples for drug content by using phosphate buffer as guinea pigs and an area of 4 cm was marked blank on both the sides, one side served as control while the other side was test. The gel was applied (500 mg/ guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any. It was graded as.

0	**No reaction**
1	Minor patchy erythema
2	Minor but confluent or modest but patchy erythema
3	Severe erythema with or without edema

IN-VITRO DIFFUSION STUDIES

It is done by using Franz diffusion cell todetermine the dissolution release of gels through a cellophane membrane. 0.5 of gel sample occupied in cellophane membrane. Diffusion studies were done at 37±1°C using pH buffer (pH7.4) 250 ml as dissolution medium.

IN-VIVO STUDIES

It is done in 6 male Wister albino rats divided into 3groups.

Rubbing 100mg of prepared gel carefully twice at 1 and 2 h on each paw and calculate the percentage of inhibition by using mercury plethysmo meter**.**

STABILITY

It is done by freeze-thaw cycling. The products are kept under temperature of 4°c for 1 month again 25°C for 1 month and next at 40°C for one month, and syneresis have being detected. The gels are kept under room temperature and find the liquefied exudates separately.

Table 3: Patentable Formulations.

Sr. No.	Patent No.	Formulation
1	US 5939090 A	Gel formulations for topical drug delivery
2	EP 1304992 B1	Topical gel delivery systems for treating skin disorders
3	US 5914334 A	Stable gel formulation for topical treatment of skin conditions
4	EP 0183322 A2	Gel-form topical antibiotic compositions
5	WO 0187276 A1	Hydrogel composition for transdermal drug delivery
6	US 2014363498 A1	Hydrogel polymeric compositions and methods
7	US 8771734 B2	Sustained-release hydrogel preparation
8	US 2200709 A	Organogel

Advantage of Gels [6]

- It is used externally
- possible side effect can be reducing
- Local action
- Suitable dosage form for bitter drugs

First pass gut and hepatic metabolism is avoided.

Disadvantages of Gels[6]

- There is no dosage accuracy in this type of dosage form.
- The base which is used in the semi-solid dosage form can be easily oxidized.
- May cause irritation or allergy to some patient

Limitation of gel[5]

i) The effect of gels is comparatively slowerand sustained.
ii) The additives or the gelators may induce irritation.
iii) The water content may increase the chancesof microbial or fungal attack in gels.
iv) Syneresis (expulsion of solvent from the gel matrix) may occur in gels during storage.
v) Solvent evaporation from the formulation may result in drying of the gel.
vi) Covalent bonds present in some gels may render them unbreakable thus sealing the medicament inside the gel matrix.
vii) Flocculation in some gels may produce an unstable gel.
viii) Rheology of some gels may alter due to the effect of temperature, humidity and other
environmental factors.
ix) The gelling agents may precipitate and result in salting out.
x) Some drugs may degrade in gel formulation due to the presence of polymers.

CONCLUSION

The study clearly revealed about the detailed view on gel formulation including its excipients, preparation, mechanism involved in gel formation and their Evaluation. Gels are getting more popular nowadays because they are more stable and also can provide controlled release than other semisolid preparations like creams, ointments, pastes, etc. The gel preparation can gives a better absorption and enhance bioavailability of the drug.

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