Pharmaceutics 1

Chapter 6

Gels

Lecture (9)

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gels

- **Gels** are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jellylike by the addition of a gelling agent
- Among the gelling agents used are

1-Synthetic macromolecules, such as carbomer 934;

2-Semisynthetic macromolecules, e.g. cellulose derivatives… carboxymethylcellulose or hydroxypropyl methylcellulose;

3 Natural gums, such as tragacanth at concentrations of 0.5% to 2.0% in water.

General description

- **Pharmaceutical gels** are semisolid systems in which there is interaction (either physical or covalent) between colloidal particles within a liquid vehicle.
- **The vehicle** is continuous and interacts with the colloidal particles within the three-dimensional network that is formed by the bonds formed between adjacent particles.
- **The vehicle** may be aqueous, hydroalcoholic, alcoholbased or non-aqueous. The colloidal particles may be dispersed solids, e.g. kaolin, bentonite or, alternatively, dispersed polymers.

- **Jellies** is single-phase gels are gels in which the macromolecules are uniformly distributed throughout a liquid with no apparent boundaries between the dispersed macromolecules and the liquid.

- **A magma** is a gel mass consisting of floccules of small distinct particles is termed a *two-phase* system, e.g milk of magnesia (or magnesia magma), which consists of a gelatinous precipitate of magnesium hydroxide, is such a system.

- **Xerogels** are gels in which the vehicle has been removed, leaving a polymer network, e.g. polymer films.

- **Gels** may thicken on standing, forming a thixotrope, and must be shaken before use to liquefy the gel and enable pouring.

- In addition to the gelling agent and water, gels may be formulated to contain a drug substance, solvents, such as alcohol and/or propylene glycol; antimicrobial fo eye, nose, the vagina, and the rectum.

- The nature of the interaction between the particles in the network may be van der Waals interactions (at the secondary minimum), e.g. AL(OH)3 Gel USP.
- However, for certain dispersed solids the nature of the interaction is electrostatic bonding. Examples of the particles that exhibit this type of interaction include kaolin, bentonite and aluminium magnesium silicate.

Gels based on hydrophilic polymers

- **Pharmaceutical gels** are most commonly **(but not exclusively)** manufactured by **dispersing hydrophilic polymers within an appropriate aqueous vehicle.**
- **When dissolved within an aqueous phase**, hydrophilic polymers behave as **lyophilic colloids and their unique physical properties result from the self-association of the dissolved polymer and its interaction with the aqueous medium.**
- There are two types of self-association (termed **irreversible and reversible)** that may be demonstrated by **lyophilic colloids and this allows gels that are manufactured from lyophilic colloids** to be classified as either **type 1 or type 2 gels.**

- The **overwhelming majority of pharmaceutical gels are type 2 gels and typically the following polymers are employed in the formulation of these systems:**

(1) Polyacrylic acid.

(2)Cellulose derivatives;

(3) Polysaccharides derived from natural sources;

(1)Polyacrylic acid

- Poly(acrylic acid) is a synthetic polymer that is produced following the polymerisation of acrylic acid and crosslinking with either allyl sucrose or allyl ethers of pentaerythritol.
- In water, polyacrylic acid exists as aggregated (coiled) colloidal particles of minimal viscosity .
- However, if the pH of the system is neutralised by the addition of an appropriate base, e.g. triethanolamine, triethylamine or sodium hydroxide, the pendant carboxyl groups will ionise, resulting in expansion of the polymer chains due to repulsion of the adjacent ionised groups.

- In so doing the viscosity of the formulation is dramatically increased.
- Typically pharmaceutical gels are produced using 0.5–2.0% w/w poly(acrylic acid) that has been neutralised with an appropriate base.
- Carbomer 940 yields the highest viscosity, between 40,000 and 60,000 centipoises as a 0.5% aqueous dispersion.

2)Cellulose derivatives

- The most commonly used examples from this series that are used to formulate pharmaceutical gels include:
- ■ Methylcellulose **(MC)**
- ■ Hydroxyethylcellulose **(HEC)**
- ■ Hydroxypropylcellulose **(HPC)**
- ■ Sodium carboxymethylcellulose **(Na CMC)**

(3)Polysaccharides

- Polysaccharides that have been derived from natural sources are commonly used as the basis for pharmaceutical gels. Examples of these include:

(1) Carrageenan; (2) Alginic acid/sodium alginate.

(A) Carrageenan

- This is a family of polysaccharides that is derived from red seaweed. There are three chemically related carrageenans, termed lambda, iota and kappa which differ according to the location of sulphate groups and the presence or absence of anhydrogalactose

(b)Alginic acid/sodium alginate

- Alginic acid is a polysaccharide that is derived from algae (Phaecophyceae family).
- Addition of calcium ions to a solution of alginic acid will result in an electrostatic interaction, producing a viscous gel at low concentrations of calcium and a cross-linked polymer at higher concentrations.
- Alginic acid is incompatible with basic drug molecules.

Factors affecting gelation of type 2 gels

- Gelation in type 2 gels occurs whenever a sufficient number of polymer–polymer interactions (junction zones) occur.

(1) Concentration of polymer

- As the concentration of polymer increases, the number of polymer–polymer interactions increases an eventually, at a defined polymer concentration, the flow properties of these systems become non-Newtonian (termed the gel point).

- Further increases in the concentration of polymer lead to an increase in the number of junction zones and hence the resistance to deformation from an applied stress (the viscosity) increases.

- Therefore, the physicochemical and rheological properties of a pharmaceutical gel may be readily manipulated by altering the concentration of hydrophilic polymer

(2) Molecular weight of the polymer

- As the **molecular weight of the hydrophilic polymer increases** (at a defined concentration of polymer), there are **a greater number of available sites on the polymer chains that may engage in polymer–polymer interactions**.
- As a **result the viscosity of the formulation increases.**

(3)Nature of the solvent

- In solvents that are described as 'good solvents', **the chains of a polymer will exist in the expanded state**.
- Conversely, **in the presence of a poor solvent, the polymer chains will exist in a nonexpanded (coiled) state.**
- **The viscosity of a polymer solution is dependent on the expansion of the polymer chains.**
- Therefore, **the concentration of polymer that results in gel formation and the physicochemical (rheological) properties of the gel** are **dependent on the solvent system** into which the hydrophilic polymer is dissolved.
- **In poor solvents gelation will not occur.**

(4) pH of the solvent

- The pH of the solvent **directly affects the ionisation of acidic or basic polymers** which, in turn, **affects the conformation (expansion) of the polymer chains.**

- In the **non-ionised state acidic and basic polymers exist in a coiled (non-expanded) state and gelation does not occur. The rheological properties of ionic polymers are optimal with a range of pH values at which maximum expansion of the polymer chains occurs.**

- The **rheological properties of non-ionic polymers are unaffected by the pH of the solvent**, usually over a large pH range.

(5)Temperature

Certain hydrophilic polymers may undergo a thermally induced transition that results in an increase in the rheological properties.

One examples of this is solution of methylcellulose(and hydroxypropylcellulose(HPC) which have been reported to undergo gelation at elevated temperatures (50–60C).

At temperatures below this (sol–gel) transition temperature (*T*sol/gel), solutions of this polymer exhibit Newtonian flow and low viscosity (the sol state). Conversely, above *T*sol/gel the polymer sol is converted into a gel with pronounced elasticity and viscosity.

- Formulation considerations for pharmaceutical gels. There are several formulation considerations open to the pharmaceutical scientist concerning the formulation of pharmaceutical gels. These include:
- **(1) The choice of vehicle;**
- **(2) The inclusion of buffers;**
- **(3) Preservatives;**
- **(4) Antioxidants;**
- **(5) Flavours/sweetening agents**
- **(6) Colours.**

The choice of vehicle

- **Purified water is the normal solvent/vehicle used in the formulation of pharmaceutical gels.**

- However, **Co-solvents may be used**, e.g. **alcohol, propylene glycol, glycerol, polyethylene glycol** (usually **polyethylene glycol 400**) to **enhance the solubility of the therapeutic agent in the dosage form and/or (in the case of ethanol) to enhance drug permeation across the skin.**

- If the drug has poor chemical stability and/or poor solubility in water or water-based vehicles, pharmaceutical gels may be formulated using polyhydroxy solvents, e.g. **propylene glycol, glycerol, polyethylene glycol 400 and polyacidic polymers, e.g. poly(acrylic acid).**

- In these **systems gelation is facilitated by hydrogen bonding between the hydroxyl and carboxylic acid groups and this results** in:

(1) Expansion of the pendant groups on the polymer chain

(2) non-covalent cross-linking of adjacent polymer chains.

The inclusion of buffers

- As in other pharmaceutical formulations, buffers (e.g. phosphate, citrate) may be included in aqueous and hydroalcoholic-based gels to control the pH of the formulation.

- It should be noted that the solubility of buffer salts is decreased in hydroalcoholic-based vehicles.

Preservatives

- Pharmaceutical gels require the inclusion of preservatives and, in general, the choice of preservatives is similar to that described for ointments and pastes in the early .
- It should be remembered that certain preservatives, e.g. parabens, phenolics, interact with the hydrophilic polymers used to prepare gels, thereby reducing the concentration of free (antimicrobially active) preservative in the formulation.
- Therefore, to compensate for this, the initial concentration of these preservatives should be increased.

Antioxidants

- As in other formulations, **antioxidants may be included in the formulation to increase the chemical stability of therapeutic agents that are prone to oxidative degradation.**

- The **choice of antioxidants is based on the nature of the vehicle used to prepare the pharmaceutical gel**.

- Therefore, **as the majority of pharmaceutical gels are aqueous-based, water-soluble antioxidants**, e.g. **sodium metabisulphite, sodium formaldehyde sulphoxylate,** are commonly used.

Flavours/sweetening agents

- **Flavours and sweetening agents are only included in pharmaceutical gels that are designed for administration into the oral cavity**, e.g. for the treatment of infection, inflammation or ulceration.
- As before, **the choice of sweetener/flavouring agents is dependent on the required taste, the type and concentration** selected to mask the taste of the drug substance efficiently.
- Examples of **flavours/sweetening agents** used for this purpose Colours, e.g. added into pharmaceutical gels.

Manufacture of pharmaceutical gels

- In the manufacture of pharmaceutical gels, generally the **water soluble components/excipients are initially dissolved in the vehicle in a mixing vessel with mechanical stirring.**
- **The hydrophilic polymer** must be added to **the stirred mixture slowly to prevent aggregation** and **stirring is continued until dissolution of the polymer has occurred**.
- It should be noted **that excessive stirring of pharmaceutical gels results in entrapment of air.**
- Therefore, to **prevent this, the mixing rate must not be excessive or a mixing vessel may be used to which a vacuum may be pulled, thereby removing air.**

Transdermal preparations

- This is often accomplished by addition of penetration enhancers to the topical vehicle.
- Penetration enhancers include dimethyl sulfoxide, ethanol, propylene glycol, glycerin, PEG, urea, dimethyl acetamide, sodium lauryl sulfate, the poloxamers, Spans, Tweens, lecithin, terpenes, and many others.

- A transdermal preparation commonly compounded is Pluronic lecithin organogel.
- It consists of a Pluronic (Poloxamer) F127 ge (usually 20% or 30% concentration) mixed at a ratio of approximately 1:5 with a mixture of equal parts of isopropyl palmitate and lecithin.