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A REVIEW ONFUNDAMENTAL ASPECTS OF HYDROGEL BASED CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

The drug delivery systems of hydrogels presented themselves with a very versatile platform by virtue of their capability for encapsulating therapeutic agents and controlled release. Recent efforts limiting hydrogel-based drug delivery aim at developing systems more responsive toward a change in external stimuli like pH, temperature, or light for targeted and ondemand drug release. Recent advances in polymer chemistry have fabricated hydrogels with improved biocompatibility, mechanical strength, and degradation profiles, thereby yielding a wide range of biomedical applications. Moreover, the combination of nanotechnology with hydrogels has rendered new opportunities not only for drugs but also for the delivery of complex drugs such as proteins, peptides, and nucleic acids, which are difficult to administer by traditional drug delivery methods. Hydrogels, with their distinctive three-dimensional networks of hydrophilic polymers, drive innovations across various biomedical applications. The ability of hydrogels to absorb and retain significant volumes of water, coupled with their structural integrity and responsiveness to environmental stimuli, renders them ideal for drug delivery, tissue engineering, and wound healing. This review delves into the classification of hydrogels based on cross-linking methods, providing insights into their synthesis, properties, and applications.

KEYWORDS: Hydrogels, Biocompatibility, Mechanical strength, Nanotechnology, Hydrophilic Polymer.

INTRODUCTION

Controlled release dosage forms cover a wide range of prolonged action formulation which provides continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration; however, recently such devices have also been introduced for parenteral administration, ocular insertion and for transdermal application. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance. The advantages of controlled release preparation have been summarized in following points**.**

- Decreased incidence and/or intensity of adverse effects and toxicity.
- Better drug utilization.
- Controlled rate and site of release.
- More uniform blood concentrations.
- Improved patient compliance.
- Reduced dosing frequency.
- More consistent and prolonged therapeutic effect.

  In general, controlled delivery attempts to:
- Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.
- Localize drug action by spatial placements of a controlled release system (usually rate-controlled) adjacent to or in the diseased tissue or organ.
- Target drug action by using carriers or chemical derivatization to deliver drugs to a particular “target” cell type.

In most cases, the release system creates constant concentration of drug within the body over an extended period of time. The assumption is that there is a steady state drug levels in plasma and in target tissues or cells are correlated. Ideally, it is desirable to place the drug at the target, be it a tissue, a population of cells, or receptors, leaving the rest of the body drug free. Obviously, this would be quite difficult, especially if the target is sheltered from

systemic circulation by various barriers. For example, drug targeting to the brain via systematic administration is severely limited by selectively of the blood-brain barrier.

In order to maintain a constant drug level in either plasma or target tissue, release rate from the controlled release system should be equal to the elimination rate from plasma or target tissue. The most conventional method to achieve a constant plasma level is the use of intravenous infusion.

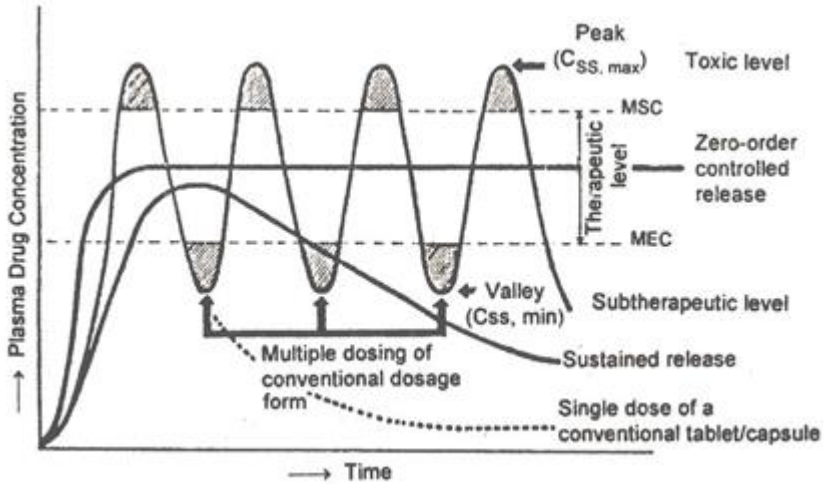


Figure: 1 A hypothetical plasma concentration-time profile from conventionalmultiple dosing and single doses of sustained and controlled delivery formulations.

Pharmacokinetic analysis of controlled delivery systems:

The Pharmacokinetic analysis of controlled release delivery systems involves two primary processes. The first describes the initial diffusion of the drug through the special coating material or polymer membrane of the dosage form into the surrounding body tissue or fluids, and the second is subsequent absorption, distribution, metabolism and excretion of the drug. Since the absorption of the active ingredients is intentionally slowed, the distribution effects usually are obscured and in most cases, a simple one compartment open model can be used to calculate the in vivo release rate constant, as long as the rates of elimination and metabolism are known.

Basic concepts and definitions:

The following paragraphs describe the fundamental Pharmacokinetic parameters and their relationship with the four main physiological processes of absorption, distribution, metabolism and excretion.

Absorption: It is theprocess by which a drug proceeds from the site of administration to the site of measurement within the body. Since the drug cannot be generally measured directly at the site of action, its concentration is measured at an alternative site, the plasma. Apart from being a more accessible site for measurement, the concentration of drug in plasma also reflects the concentration of drug at the site of action. The rate of absorption is then measured as the rate of disappearance of drug in the plasma. It cannot be measured as the rate of disappearance from an extra vascular site of administration as the integrity of the drug moiety may be affected during absorption by one of the several mechanisms described below.

- ✓ Degradation catalyzed by acid in the stomach e.g. penicillin-G, erythromycin.
- ✓ Destruction by the gut flora e.g. sulfasalazine, methotrexate.
- ✓ Enzymatic destruction in the gut, e.g. progesterone, testosterone.
- ✓ Enzymatic destruction in the gut epithelium e.g. isoproterenol, salicylamide.
- ✓ Extensive metabolism by the liver (first pass effect) e.g. propranolol.

The time required for 50% unchanged drug to be absorbed is called the half-life of absorption. The fraction of the percentage of the administered dose that is ultimately absorbed intact is called the bioavailability and is proportional to the total area under the plasma concentration-time curve, irrespective of its shape. The rate and extent of absorption are also reflected in the maximum drug concentrations attained and the time required achieving these concentrations.

Distribution: It refers to the reversible transfer of drugs from one location to another within the body. Distribution occurs at various rates and to various extents. Several factors determine the distribution pattern of a drug. They include:

- ✓ Rate of delivery of a drug to the tissues by the circulation.
- ✓ The ability of a drug to pass through tissue membranes.
- ✓ The binding affinity of drug to plasma proteins, erythrocytes, and tissues.

Since the exact distribution of a drug in the various tissues is difficult to ascertain in vivo, the extent of distribution is determined as a proportionality constant i.e. the volume of distribution (Vd) which relates the observed concentration of drug in the plasma, with the total amount of drug in the body. The volume of distribution is thus a hypothetical space into which the drug is distributed, at equilibrium. A high (Vd) generally implies greater exposure of the body to the drug or a high degree of selective exposure. In general for drugs that are not protein or tissue bound, the volume of distribution varies between the extracellular fluid

volume (16L) and the total body water (42L) depending on the extent to which the drug gains access to the intracellular fluids, for example:

- Antipyrine, caffeine and ethanol distribute in total body water and have a realistic volume of distribution of 40-46 L. evens Blue dye is limited to plasma and has a Vd of 3 L.
- Digoxin is extensively taken up by extra vascular tissue and has a Vd of approximately 500l.
- Salicylic acid and phenylbutazone are extensively bound to plasma proteins, to the extent of 90%respectively. They have Vd of only 10L implying that most of the drug is restricted to the volume of plasma proteins.

Elimination: The process of elimination mainly comprises of:

- Biotransformation or metabolism of the drug primarily by the liver, and
- Renal excretion of both the unchanged drug and its metabolites. Metabolism by the gut epithelium, lungs, blood, kidneys, and other organs and tissues, biliary excretion and excretion through sweat, saliva and breast milk are some of the other modes of elimination.

The time taken for the plasma concentration as well as the amount of drug in the body to fall by one-half is termed as elimination half-life ($t^{1}/2$). Based on the assumption of linear kinetics, elimination is a fist order process and consequently it taken three half-lives for approximately 90% of the drug to be elimination from the body. The loss of drug across an organ of elimination is viewed as clearance (C1). Physiologically, it is defined as the volume of blood or plasma cleared of drug per unit time. Mathematically, it is a proportionality constant that relates the rate of elimination to the plasma concentration. Clearance can be described in term of the eliminating organ e.g. hepatic clearance, renal clearance, pulmonary clearance, etc. total body clearance represents the sum of the individual clearances i.e. both renal and extra-renal.

AN INTRODUCTION TO HYDROGEL

Hydrogels arecross linked polymer networks that can expand substantially and retain large amount of water without being dissolved. The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical cross links, or physical cross links, such as entanglement or crystallites. The latter provide the network structure and physical integrity. These hydrogels exhibit a thermodynamic compatibility with water allows

them swell in aqueous media.

Their classification may be based on the source: natural or synthetic gels; on the nature of the cross linking: covalent or physical gels; on the nature of the network: homopolymer networks, copolymer networks, interpenetrating networks, or double networks; on the presence of pores: homogeneous hydrogels, microporous and macroporous hydrogels and on their fate in an organism: degradable and no degradable hydrogels.

Type of hydrogel:

Hydrogel based on their nature, can be classified as pH sensitive, temperature sensitive, enzyme sensitive and electrical sensitive hydrogels etc.

pH sensitive hydrogel:

Hydrogels exhibiting pH-dependent swelling behavior can be swollen from ionic networks. These ionic networks contain either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize, developing fixed charges on the gel. As a result of the electrostatic repulsion the uptake of solvent in the network is increased.

Ionic hydrogels are swollen polymer networks containing pendent group, such as carboxylic or sulfonic acid, which show sudden or gradual changes in their dynamic and equilibrium swelling behavior as a result of changing the external pH. In these gels, ionization occurs when the pH of the environment is above the pka of the ionizable group. As the degree of ionization increases, the number of fixed charges increases, resulting in increased electrostatic repulsion between the chains, this in turn, result in an increased hydrophilicity of the network, and greater swelling ratio. Conversely, cationic materials contain pendent groups such as amines. These groups ionized in media which are at a pH below the pkb of the ionizable species. Thus, in a low pH environment, ionization increases, causing increased electrostatic repulsions. The hydrogel becomes increasingly hydrophilic and will swell to an increased level.

Properties of pH-sensitive hydrogels:

Hydrogels made of cross linked polyelectrolyte's display big differences in swelling properties depending on the pH of the environment. The pendant acidic or basic groups on polyelectrolytes undergo ionization just like acidic or basic groups of monoacids or

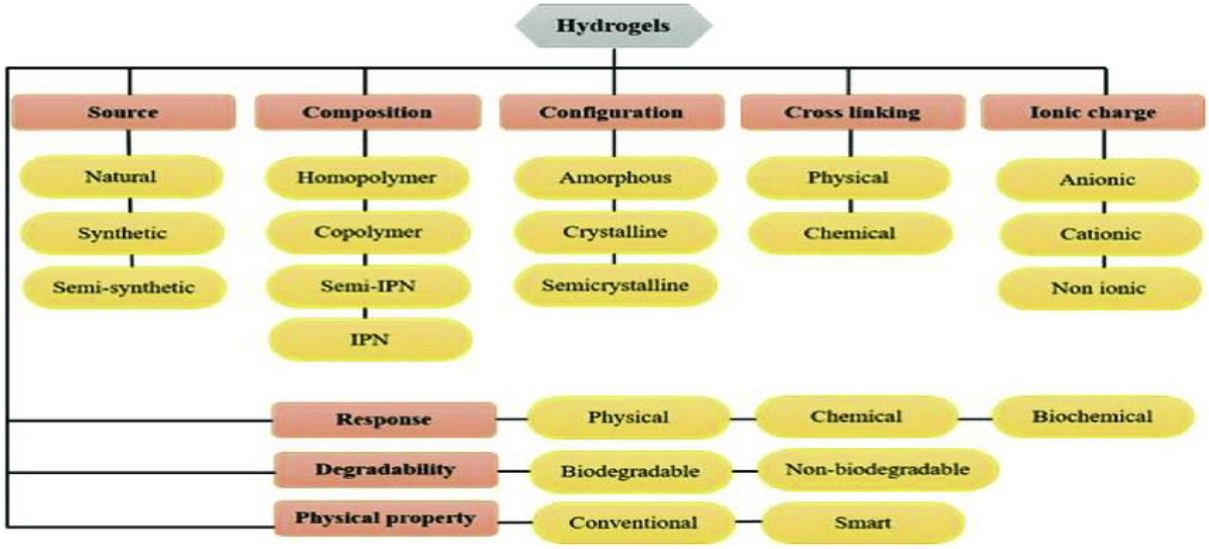
monobases. Ionization on polyelectrolytes, however, is more difficult due to electrostatic effects exerted by other adjacent ionized groups. This tends to make the apparent dissociation constant (ka) different from that of the corresponding monoacid or monobase. The presence of ionizable groups on polymer chains results in swelling of the hydrogels much beyond that can be achievable by nonelectrolyte polymer hydrogels. Since the swelling of polyelectrolyte hydrogels is mainly due to the electrostatic repulsion among charges present on the polymer chain, the extent of swelling is influenced by any condition that reduce electrostatic repulsion, such as pH, ionic strength, and type of counterions. The swelling and pH-responsiveness of polyelectrolyte hydrogels can be adjusted by using neutral co monomers, such as 2-hydroxyethyl methacrylate, methyl methacrylate and maleic anhydride. Different co monomers provide different hydrophobicity to the polymer chain, leading to different pH-sensitive behavior.

Hydrogels made of poly (methacrylic acid) (PMA) grafted with poly (ethylene glycol) (PEG) have unique pH-sensitive properties. At low pH, the acidic protons of the carboxyl groups of PMA interact with the ether oxygen of PEG through hydrogen bonding, and such complexation results in shrinkage of the hydrogels. As the carboxyl groups of PMA become ionized at high pH, the resulting decomplexation leads to swelling of the hydrogels. The same principle can be applied to IPN systems where two different types of polymer chain interact through pH-dependent hydrogen bonding.

Temperature-sensitive hydrogels:

Temperature-sensitivehydrogels have gained considerable attention in the pharmaceutical field due to the ability of the hydrogels to swell or deswell as a result of changing the temperature of the surrounding fluid. Numerous researchers studied various applications of these hydrogels, such as on-off drug release regulations, biosensors and intelligent cell culture dishes.

Thermo sensitive hydrogels can be classified as positive or negative temperature sensitive systems. A positive temperature-sensitivehydrogel has an upper critical solution temperature (UCST). Such hydrogels contract upon cooling below the UCST. Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST). These hydrogels contract upon heating above the LCST.

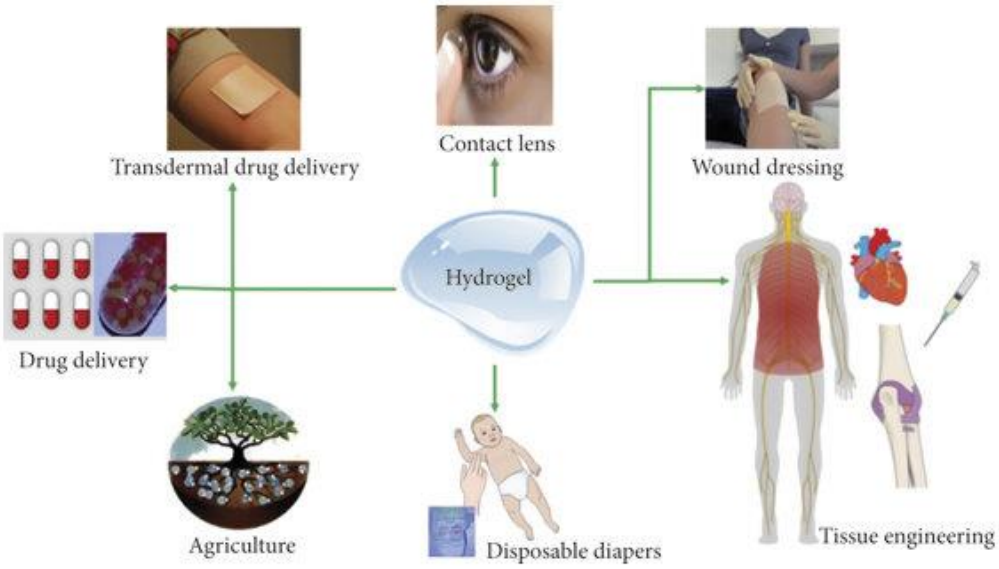


Basic Principles of Hydrogel

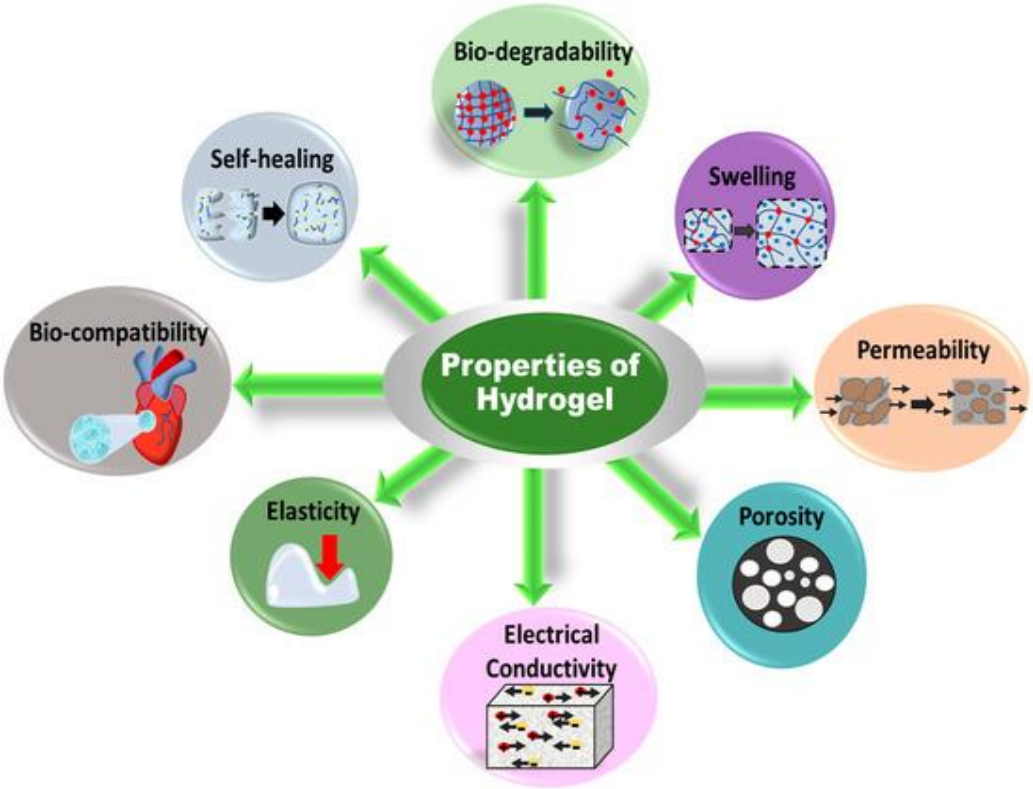
Preparation Hydrogels are three-dimensional, hydrophilic polymer networks capable of storing large amounts of water or biological fluids within their structure. Thus, the ability to absorb and retain water in their structures, with maintenance of integrity, places the material in acquiring position of high value in several fields such as medicine, agriculture, and environmental sciences. Hydrogels are prepared via complex interplays of chemical and physical processes, which, in turn, would dictate the properties and functionalities of the final product.

Polymerization and Cross-Linking Mechanisms

The principle of forming hydrogels is based on the polymerization-cross-linking of monomers or polymers. Polymerization is a process in which small molecules combine chemically to form long chains or networks called polymers. Within the preparation of hydrogels, the polymer network has to be cross-linked in order to get a stable structure with swelling ability in water without dissolving. The method of cross-linking has immense effects on the mechanical properties, swelling behaviour, and degradation rate of the hydrogel. For example, covalently cross-linked hydrogels are relatively more stable and less degradable than physically cross-linked hydrogels, which may show reversible or temporary network formation.

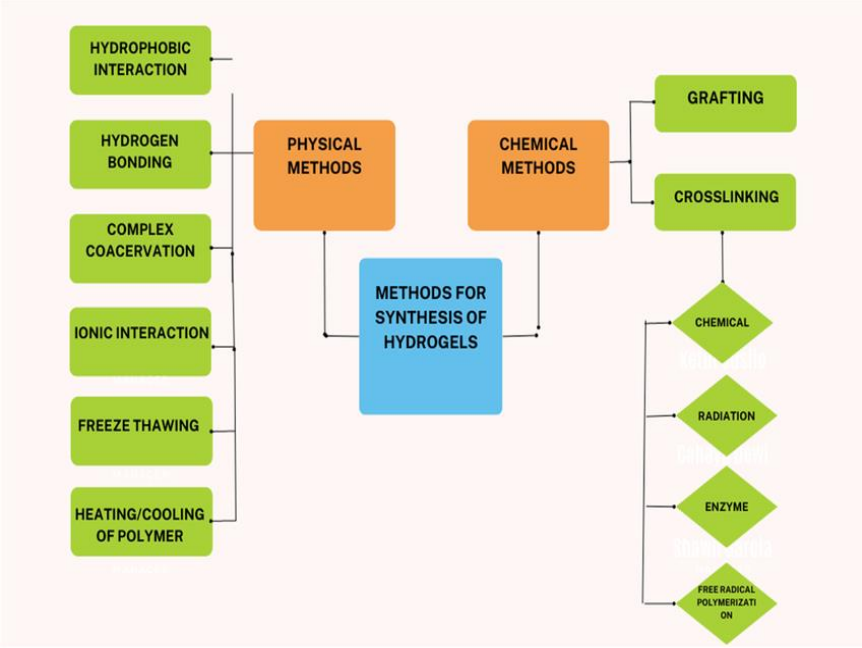


APPLICATION OF HYDOGEL IN VARIOUS INDUSTRIES



PREPARATION OF HYDROGEL

Hydrogel is produced using both chemical and physical cross-linking techniques. Either noncovalent or covalent interactions result in the formation of the cross-linking. Hydrogel Physical gels are the result of processing non-covalent contact, whereas chemical gels are the result of processing covalent interaction.

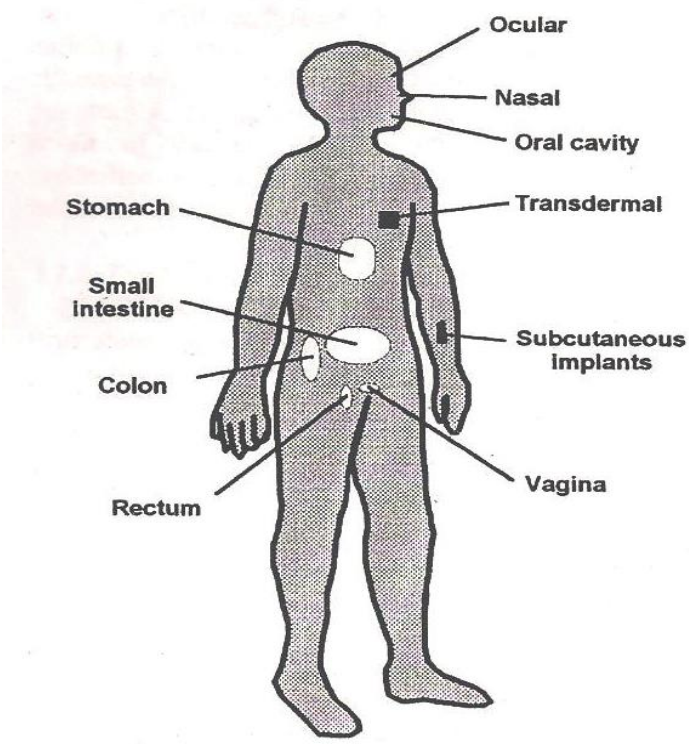


Applications of hydrogels in drug delivery:

A number of strategies have been proposed to achieve drug delivery systems for efficient therapy. Among them, hydrogels have attracted considerable attention as excellent candidates for controlled release devices, bioadhesive devices, or targetable devices of therapeutic agents. Hydrogel-based delivery devices can be used for oral, rectal, ocular, epidermal and subcutaneous application.

Drug delivery in the oral cavity:

Drug delivery to the oral cavity can have versatile applications in local treatment of diseases of the mouth, such as peridonatal disease, stomatitis, fungal and viral infections, and oral cavity cancers. Long-term adhesion of the drug containing hydrogel against copious salivary flow, which bathes the oral cavity mucosa, is required to achieve this local drug delivery. For this purpose, many types of bioadhesive hydrogel systems have been devised since the early 1980s. Some of these are already on the market. For example, a bioadhesive tablet developed by Nagai et al. is commercially available under the brand name attach. This product is composed of a double layer, with a bioadhesive layer made of hydroxypropyl cellulose and poly (acrylic acid) and a lactose non-adhesive backing layer. It is a local delivery system of triamcinolone acetonide for the treatment of aphthous ulcers.



Tissue locations applicable for hydrogel-based drug delivery systems.

Petelin et al. investigated the pharmaceutical performance of three different hydrogel-based ointments as possible vehicles for liposome delivery into the oral cavity tissues by electron paramagnetic resonance (EPR). The vehicles employed were or abase (a sodium carboxymethylcellulose, pectin and gelatin combination in a polyethylene-paraffin base), Carbopol 934P and neutralized poly (MAA-co-methyl methacrylate (MMA). Liposome containing mucoadhesive ointments were prepared by simply mixing multilameller liposome's with each ointment prediluted with phosphate-buffered saline of pH 7.4 in the volume ratio of 1:4. An EPR study showed that P (MAA-co-MMA) was the most appropriate ointment in terms of liposomal stability in the ointment, transport of liposome entrapped molecules from the ointment into the oral soft tissues, and washing-out time from oral mucosa or gingvia.

The oral cavity can also provide a useful location as a transport route for heavily metabolized drugs, since the drugs absorbed from this route bypass first-pass hepatic metabolism. Kitano et al. proposed a hydrogel ointment containing absorption enhancers for the buccal delivery of 17 β-estradiol (E2) to treat osteoporosis. It is well known that the oral administration of E2 results in very low availability due to its high first-pass effect. Ethanol solution containing E2, and glyceryl monolaurate as an absorption enhancer, and an aqueous solution of a

commercial carboxyvinyl polymer and triethanolamine were mixed together to produce the hydrogel ointment. In-vivo studies using hamsters demonstrated that the buccal administration of E2 with this formation allowed the maintenance of the E2 plasma level at over 300 µg/ml per cm3 for 7 hr, while no primary morphological change of buccal membrane was observed 7 hr after application.

Drug delivery in GI tract:

The GI tract is unquestionably the most popular route of drug delivery because of the facility of administration of drugs for compliant therapy, and its large surface area for systemic absorption. It is, however, the most complex route, so that versatile approaches are needed to deliver drugs for effective therapy.

Like buccal delivery, hydrogel-based devices can be designed to deliver drugs locally to the specific sites in the GI tract. For example, Patel and Amiji proposed stomach-specific antibiotic drug delivery systems for the treatment of Helicobacter pylori infection in peptic disease. For localized antibiotic delivery in the acidic environment of the stomach, they developed cation hydrogels with pH-sensitive swelling and drug release properties. The hydrogels were composed of freeze-dried chitosan-poly (ethylene oxide) (PEO) IPN. pH-dependent swelling properties and the release of two common antibiotics, antibiotics, amoxicillin and metronidazole, entrapped in the chitosan-PEO semi IPN were evaluated in enzyme-free simulated gastric fluid (SGF; pH 1.2) and simulated intestinal fluid (SIF;pH 7.2).

Oral insulin delivery using pH-responsive complexation hydrogels was reported by Lowman et al. The hydrogels used to protect the insulin in the harsh acidic environment of the stomach before releasing the drug in the small intestine were crosslinked copolymers of PMAA with graft chains of polyethylene glycol (P(MAA-g-EG)). The insulin-containing P(MAA-g-EG) microparticles demonstrated strong dose-dependent hypoglycemic effects in in-vivo oral administration studies using both healthy and diabetic rats. The blood glucose levels in these animals were decreased significantly for at least 8 hr due to the absorption of insulin in the GI tract. It is worth nothing that these effects were observed without the addition of additives, such as absorption enhancers or protease inhibitors.

Due to a lower proteolytic activity in comparison to that in the small intestine, the colonic region has also been considered as a possible absorption site for orally administered peptides

and proteins. Several hydrogels are currently being investigated as potential devices for colon-specific drug delivery. These include chemically or physically crosslinked polysaccharides, such as dextran, amidated pectin, guar gum and insulin, and azocross-linked poly (acrylic acid). They are designed to be highly swollen or degraded in the presence of colonic enzymes or microflora, providing colon-specific city in drug delivery.

Rectal delivery:

The rectal route has been used to delivery many types of drugs, although patient acceptability is variable due to the discomfort arising from administered dosage forms. Its primary applications have been for local treatment of diseases associated with the rectum, such as hemorrhoids. Additionally, it is well known that drugs absorbed from the lower part of the rectum drain into the systemic circulation directly. Thus, the rectal route is a useful administration route for drugs suffering heavy first-pass metabolism. Conventional suppositories hitherto adapted as dosage forms for rectal administration are solids at room temperature, and melt or soften at body temperature. A problem associated with rectal administration using conventional suppositories is that drugs diffusing out of the suppositories in an uncontrolled manner are unable to be sufficiently retained at a specific position in the rectum, and sometimes migrate upwards to the colon. This often leads to a variation of the bioavailability of certain drugs, in particular, for drugs that undergo extensive first-pass elimination.

Certain dosage forms, such as suspension and ointments, can be retained in the eye, although these sometimes give patients an unpleasant feeling because of the characteristics of solids and semi-solids. Due to their elastic properties, hydrogels can also represent an ocular drainage-resistant device. In addition, they may offer better feeling, with less of a gritty sensation to patients. In particular, in-situ-forming hydrogels are attractive as an ocular drug delivery system because of their facility in dosing as a liquid, and their long-term retention property as a gel after dosing.

Cohen et al. developed an in-situ-gelling system of alginate with high guluronic acid contents for the ophthalmic delivery of pilocarpine. This system significantly extended the duration of the pressure-reducing effect of pilocarpine to 10 hr, compared to 3 hr when pilocarpine nitrate was dosed as a solution. Rheological evaluation of Gelrite, deacetylated gellan gum which gels upon instillation in the eye due to the presence of cations was carried out by Carlfors et al. Their study indicated that a high rate of the sol/gel transition of Gelrite in-situ

gels results in long precorneal contact time.

Transdermal delivery:

Drug delivery to the skin has been traditionally conducted for topical use of dermatological drugs to treat skin diseases, or for disinfection of the skin itself. In recent years, a transdermal route has been considered as a possible site for the systemic delivery of drugs. The possible benefits of transdermal drug delivery include that drugs can be delivery for a long duration at a constant rate, that drug delivery can be easily interrupted on demand by simply removing the devices, and that drugs can bypass hepatic first-pass metabolism. Furthermore, because of their high water content, swollen hydrogels can provide a better feeling for the skin in comparison to conventional ointments and patches. Versatile hydrogel-based devices for transdermal delivery have been proposed so far. Sun et al. devised composite membranes comprising of cross linked PHEMA with a nonwoven polyester support. Depending on the preparation conditions, the composite membranes can be tailored to give a permeation flux ranging from from 4 to 68 μg/cm^2 per hr for nitroglycerin.

A Carbopol 934-based formation containing phosphatidylcholine liposome's (liposome-gel) was prepared by Kim et al. in their study; the skin absorption behavior of hydrocortisone-containing liposome-gel was assessed. Gayet and Fortier reported hydrogels obtained from the copolymerization of bovine serum albumin (BSA) and PEG. Due to their high water content over 96%, allowing the release of hydrophilic and hydrophobic drugs, their use as controlled release devices in the field of wound dressing was proposed as the potential application of the BSA-PEG hydrogels. Comprehensive studies on in-situ photopolymerizable hydrogels made from terminally diacrylated ABA block copolymers of lactic acid oligomers (A) and PEG (B) for barriers and local drug delivery in the control of wound healing have been carried out by Hubbell.

Recent research trends in transdermal application are focusing on electrically-assisted delivery, using iontophoresis and electroporation. Several hydrogel-based formulations are being investigated as vehicles for transdermal iontophoresis to obtain the enhanced permeation of luteinizing hormone releasing hormone, sodium nonivamide acetate, nicotine and enoxacin. On the other hand, a methyl cellulose-based hydrogel was used as a viscous ultrasonic coupling medium for transdermal sonophoresis assisted with an AC current, resulting in an enhanced permeation of insulin and vasopressin across human skin in vitro.

Subcutaneous delivery:

Posses a wide variety of possible pharmaceutical applications. Among them, their substantial application may be found in implantable therapeutics. Subcutaneously inserted exogenous materials may more or less evoke potentially undesirable body responses, such as inflammation, carcinogenicity and immunogenicity. Therefore, biocompatibility is a prerequisite that makes materials implantable. Due to their high water content, hydrogels are generally considered as biocompatible materials. They also provide several promising properties: (1), minimal mechanical irritation upon in-vivo implantation, due to their soft, elastic properties; (2), prevention of protein adsorption and cell adhesion arising from the low interfacial tension between water and hydrogels; (3), broad acceptability for individual drugs with different hydrophilicities and molecular sizes; and (4), unique possibilities (crosslinking density and swelling) to manipulate the release of incorporated drugs. Some of these may offer an advantage for the delivery of certain delicate drugs, such as peptides and proteins.

Giammona et al 1996. developed new hydrogels originating from the chemical reticulatin of α, β-polyasparthydrazide (PAHy) by glutaraldehyde. PAHy is new water soluble by reaction with hydrazine. Histological analysis revealed that this hydrogel was inert when implanted subcutaneously into rats.Several hydrogel formulations for the subcutaneous delivery of anticancer drugs have been also proposed. For example, cross linked PHEMA with good biocompatibility was applied to cystabine (Ara-C) and methotrexate. Poly (AAm-co-monomethyl or monopropyl itaconate) developed by Blanco's group was employed for the controlled release of Ara-C and 5-fluorouracil.

Current studies on implantable hydrogels have been directed towards the development of biodegradable systems requiring no follow-up surgical removal once the drug supply is depleted. A bioerodible hydrogel based on a semi-IPN structure composed of a poly(ε-caprolactone) and PEG macromere terminated with acrylate groups was devised by Cho et al. long-term constant release over 45 days of clonazepam entrapped in the semi-IPN was achieved in vivo. Recently, two types of novel degradable PEG hydrogels for the controlled release of proteins were developed by Zhao and Harris. One type is prepared by a polycondensation reaction between difunctional PEG acids and branched PEG polyols. Upon hydrolysis of the resulting ester linkages, these gels degrade into only PEG and PEG derivatives. The other is PEG-based hydrogels having functional groups in which protein drugs can be covalently attached to the gel network via ester linkage. Thus, the release of the

protein drugs immobilized would be controlled by the hydrolysis of the ester linkage between the gel and protein, followed by the diffusion of the protein out of the gel, and by the degradation of the gel. Extensive research efforts on degradable dextran hydrogels have been carried out by hennink and his coworkers. These hydrogels are based on acrylate derivatives of dextran. In their studies, the application of the hydrogels to the controlled release of protein was thoroughly investigated. Biodegradable cross linked dextran hydrogels containing PEG (PEG-Dex) were reported by moriyama and Yui. Insulin release from these hydrogels was regulated by the surface degradation of PEG-Dex microdomain-structured.

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