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HYDROGELS- A NOVEL A ND SMART DRUG DELIVERY SYSTEM: AN UPDATED REVIEW

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ABSTRACT

The availability of large molecular weight protein and peptide-based d rugs due to the recent advances in the field of molecular biology has given us new ways to treat a number of diseases. Synthetic hydrogels offer a possibly effective and convenient way to administer these compounds. Hydrogels are hydrophilic, three-dimensional networks, which are able to imbibe large amounts of water or biological fluids and thus resemble to a large extent a biological tissue. Here we discuss recent progress in overcoming these challenges, particularly with regards to effectively delivering hydrogels inside the body without implantation, prolonging the release kinetics of drugs from hydrogels and expanding the nature of drugs which can be delivered using hydrogel-based approaches. Therefore, the precise account of hydrogel behaviour as well as mathematical description of equilibrium swelling, dimensional changes due to solvent uptake, desorption and drug release profiles were the main objectives in many investigations. The objective of this manuscript is to give a brief review on existing mathematical models and theories in the field of hydrogel swelling as well as the description of the drug release mechanism from swelling-controlled networks. The most important properties of hydrogels relevant to their swelling behaviour as well as kinetics and thermodynamic of swelling are also presented.

KEY WORDS: Hydrogels, swelling, diffusion, dimensional.

INTRODUCTION

Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers. Hydrogels can be made from virtually any water-soluble polymer, encompassing a wide range of chemical compositions and bulk physical Properties. Furthermore, hydrogels can be formulated in a variety of physical forms, including slabs, micro particles, nanoparticles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and experimental medicine for a wide range of applications, including tissue engineering and regenerative medicine [(1)], diagnostics, cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions. [(2)]

Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration. Several terms have been coined for hydrogels, such as 'intelligent gels' or 'smart hydrogels'.[(3)] The smartness of any material is the key to its ability to receive, transmit or process a stimulus, and respond by producing a useful effect.[(4)] Hydrogels are 'smart' or 'intelligent' in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behavior, resulting in the release of entrapped drug in a controlled manner.[(5)] The unique physical properties of hydrogels have sparked particular interest in their use in drug delivery applications. Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network. They can also be used for systemic delivery. Hydrogels are also generally highly biocompatible, as reflected in their successful use in the peritoneum.[(6,7)] and other sites *in vivo.*

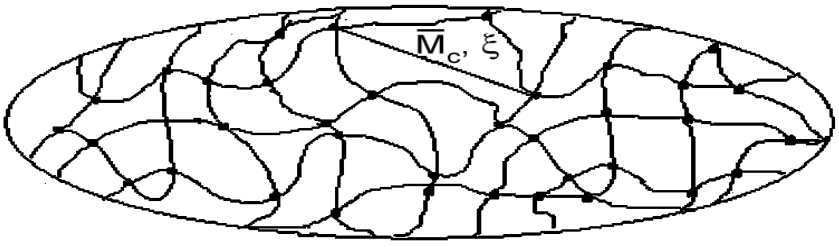

Fig.1: Cross Linked Structure of Hydrogels[(6)]

Biodegradability or dissolution may be designed into hydrogels via enzymatic, hydrolytic, or environmental (e.g. pH, temperature, or electric field) pathways; however, degradation is not always desirable depending on the time scale and location of the drug delivery device. Hydrogels are also relatively deformable and can conform to the shape of the surface to which they are applied. In the latter context, the muco- or bioadhesive properties of some hydrogels can be advantageous in immobilizing them at the site of application.

Advantages of Hydrogels

1. Biocompatible.
2. Can be injected.
3. Easy to modify.
4. Timed release of growth factors and other nutrients to ensure proper tissue growth.
5. Entrapment of microbial cells within polyurethane hydrogel beads with the advantage of low toxicity.
6. Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature or the concentration of metabolite and release their load as result of such a change.
7. Natural hydrogel materials are being investigated for tissue engineering, which include agarose, methylcellulose and other naturally derived polymers.[8]

Disadvantages

1. High cost.
2. Low mechanical strength.
3. Difficult to load.
4. Difficult to sterilize.
5. Nonadherent.
6. In contact lenses - lens deposition, hypoxia, dehydration and red eye reactions.[9]

Classification

On the Basis of the Nature of the Cross Linked Junctions[10]

Chemically cross linked networks having permanent junctions. Physical networks have transient junctions arising from polymer chain entanglements or physical interactions viz. ionic interactions, hydrogen bonds or hydrophobic interactions.

Physical, Chemical And Toxicological Properties Of Hydrogels

Factors Affecting Swelling of Hydrogels

The crosslinking ratio is one of the most important factors that affect the swelling of hydrogels. It is defined as the ratio of moles of crosslinking agent to the moles of polymer repeating units. The higher the crosslinking ratio, the more crosslinking agent is incorporated in the hydrogel structure. Highly crosslinked hydrogels have a tighter structure, and will swell less compared to the same hydrogels with lower crosslinking ratios. Hydrogels containing hydrophilic groups swell to a higher degree compared to those containing hydrophobic groups.

Dynamics of Swelling

The swelling kinetics of hydrogels can be classified as diffusion-controlled (Fickian) and relaxation-controlled (non-Fickian) swelling. When water diffusion into the hydrogel occurs much faster than the relaxation of the polymer chains, the swelling kinetics is diffusion-controlled. A nice mathematical analysis of the dynamics of swelling is presented by Peppas and Colombo.

Mechanical Properties

Mechanical properties of hydrogels are very important for pharmaceutical applications. For example, the integrity of the drug delivery device during the lifetime of the application is very important to obtain FDA approval, unless the device is designed as a biodegradable system. A drug delivery system designed to protect a sensitive therapeutic agent, such as protein, must maintain its integrity to be able to protect the protein until it is released out of the system. Increasing the degree of crosslinking of the system will result in a stronger gel. However, a higher degree of crosslinking creates a more brittle structure. [(11)]

Cytotoxicity and *In-Vivo* Toxicity

Cell culture methods, also known as cytotoxicity tests, can be used to evaluate the toxicity of hydrogels. Three common assays to evaluate the toxicity of hydrogels include extract dilution, direct contact and agar diffusion. Most of the problems with toxicity associated with hydrogel carriers are the unreacted monomers, oligomers and initiators that leach out during application.[(12)] Several measures have been taken to solve this problem, including modifying the kinetics of polymerization in order to achieve a higher conversion, and extensive washing of the resulting hydrogel. The most commonly used technique has been gamma irradiation.[(13)]

Hydrogels of PVA have been also made without the presence of initiators by using thermal cycle to induce crystallization.[14]

Preparation Of Hydrogel

Use of Crosslinkers

Copolymerization of monomers using multifunctional co-monomer, which acts as cross linking agent, chemical initiator initiates the polymerization reaction which can be carried out in bulk, solution or suspension.

Cross linking of linear polymers by irradiation or by chemical compounds. Monomers used here contain an ionizable group that can be ionized or can undergo a substitution reaction after the polymerization is completed. Cross linkers are glutaraldehyde, calcium chloride etc. They impact sufficient mechanical strength to the polymers and thus prevent burst release of the medicaments.[15]

Isostatic Ultra High Pressure (IUHP)

Suspension of natural biopolymers (eg.-starch) are subjected to ultra high pressure of 300-700 MPa for 5 or 20 minutes in a chamber which brings about changes in the morphology of the polymer (i.e. gelatinization of starch molecules occur). Temperature in the chamber varies from 40 to 52^{o}C.[16]

Use of Nucleophilic Substitution Reaction

A pH and temperature sensitive hydrogel viz. hydrogel of N-2-dimethylamino ethylmethacrylamide (DMAEMA) has been prepared using nucleophilic substitution reaction between methacyloyl chloride and 2-dimethylamino ethylamine.[17]

Use of Gelling Agent

Gelling agents like glycophosphate1-2propanediol, glycerol, trehalose, mannitol etc have been used in the preparation of hydrogels. However, presence of negative charged moieties and turbidity are the problems associated with the method.[18]

Use of Irradiation and Freeze Thawing

Irradiation method is suitable as well as convenient but the processing is costly along with the poor mechanical strength of the product. Freeze thawing method imparts sufficient mechanical strength and stability to the hydrogels except that they are opaque in appearance

with little swelling capacity. However, hydrogels prepared from microwave irradiation are more porous than conventional methods.[19]

Synthesis of Hydrogel in Industry

Formulation of monomer along with initiators and additives lead to polymerization which forms the gel. The gel is dried, sieved and mixed with other additives and post treatment is done if needed. The final formulation is packed and dispatched.

Hydrogel-Network Design And Structure

Mathematical understanding of various properties viz. interaction parameters, material properties, kinetic profile and transport mechanisms aids in designing the network of complex hydrogel systems by identifying the determining parameters which decides the rate and extent of drug release.[20]

Table. 1: Hydrogel Structure with Release Mechanism

STRUCTURE	RANGE	RELEASE MECHANISM
Macroporous	0.1-10 µm	Depends on drug diffusion coefficient
Microporous	100-1000 µm	Molecular diffusion and convection
Nonporous	10-100 µm	Diffusion

The deciding parameters that describe the nanostructure of cross linked hydrogel networks are

1. Polymer volume fraction in swollen state.
2. Number average molecular weight between crosslinks.
3. Network mesh size. Number average molecular weight between two adjacent crosslinks gives the degree of cross linking of the hydrogel networks. [21]

Factors affecting mesh size are

1. Degree of cross linking of the gel
2. Chemical structure of the constituting monomers
3. External stimuli viz. temperature, mesh size dictates the physical properties of the hydrogels (mechanical strength, degradability and diffusivity of the releasing molecules.[22]

Theoretical Description Of Swelling

During the past decades, modelling of polymeric networks swelling has been conducted on different scales, based on global macroscopic to microscopic theories.[23] For instance, the

global swelling ratio of polyelectrolyte gels is well explained through statistical theory. Based on this macroscopic theory, the equilibrium state is achieved by a minimum of the Gibbs free energy, ΔF. This theory is applied for chemical and also thermal stimulations.[24] As an example, the experimental results of swelling of *N*isopropyl acrylamide (NIPAAm) hydrogels in water and aqueous solutions of ethanol and acetone are well analyzed by statistical theory.[25]

Theory of porous media is an example of macroscopic or mesoscopic continuum theories. This theory is based on the theory of mixtures extended by the conception of volume fractions.[26] This theory is formulated simply by conservation equations for the different constituents, while the local porous micro-structure and the real geometrical distribution of all the elements are unknown.[27]

Multi-field formulation, which is a chemoelectro- mechanical model, is formulated by different balance equations.[28] The chemical, electrical and mechanical fields are formulated by the diffusion, the Poisson and the momentum equations, respectively.

The hydrogel network is characterized by distributed particles interacting with each other mechanically.[29] The mechanical behaviour is obtained by solving the Newton's equations of motion, while the chemical field is described by diffusion equations for the different mobile particles.

Recently, the swelling behaviour of polyelectrolyte gels under electrochemical stimulation was investigated by Wallmersperger et al., applying different modelling strategies. Based on the works of Wallmersperger, a chemoelectro- mechanical model is developed by Li et al., to simulate the swelling and shrinking of hydrogel. The ionic fluxes within both the hydrogel and solution, the coupling between the electric field, ionic fluxes and mechanical deformations of the hydrogel are well accounted in this model.[30]

Lai's group developed a triphasic chemoelectro- mechanical model to describe the behavior of soft tissues, such as charged-hydrated tissues.[31] This theory was verified for the one dimensional equilibrium results of swelling, while neglecting geometrical non-linearities. In this model, an assumption of "electroneutrality" condition is made thereby constraining the application range to a few particular cases.[32]

Kinetics Of Hydrogel Swelling

Swelling is a continuous process of transition from unsolvated glassy or partially rubbery state to a relaxed rubbery region. It is well known that sorption processes for polymer solvent systems frequently do not conform to the behaviour expected from the classical theory of diffusion. Although penetrant sorption by rubbery polymers may be described by Fickian transport with a concentration dependent diffusion coefficient, this description usually is not successful for glassy polymers.[33] Fickian or Case I transport, which appears when the Tg of polymer is well below the medium temperature. Case I diffusion is characterized by a linear increase of polymer weight gain as a function of the square root of sorption time.[34] Depending on the relative rates of chain relaxation and diffusion, they commonly classified the non- Fickian diffusion to two subsections: "Case II transport" and "anomalous transport". Case II transport is dominated when the diffusion is very rapid compared to relaxation (Rdiff >> Rrelax), with relaxation occurring at an observable rate. The anomalous transport is observed when the diffusion and relaxation rates are comparable (Rdiff ≈ Rrelax).

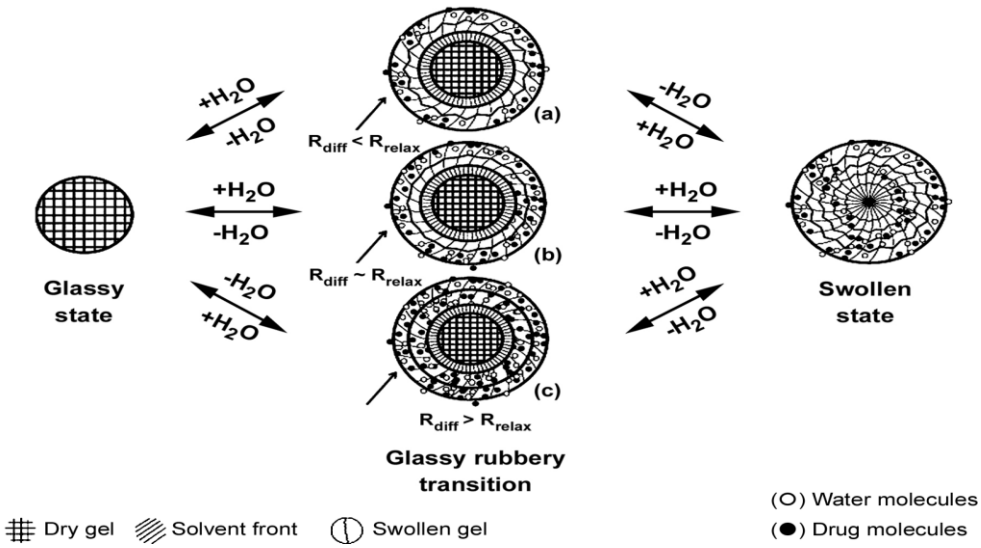

Fig. 2: The mechanisms of Case II and anomalous diffusion [35]

Drug Release Mechanisms From Hydrogel Devices

Hydrogels imbibe more water than 90% of their weight due to hydrophilicity, thus differing in their release mechanisms from hydrophobic polymers. Various models have been developed to predict the release of an active agent from a hydrogel device as a function of time. These models are based on the rate limiting step for controlled release and are divided into three categories viz.

1. Diffusion controlled
2. Swelling controlled

3. Chemically controlled

Diffusion Controlled

It is most widely applicable mechanism relating to drug release. Fick's law of diffusion is commonly used in modeling this release.[36] For reservoir system, drug depot is surrounded by a polymeric hydrogel membrane. Fick's first law of diffusion describes drug release through the membrane. For matrix system (drug uniformly dispersed throughout the matrix), unsteady state drug diffusion may be described using Fick's second law of diffusion.[37]

Swelling Controlled

It occurs when diffusion of drug is faster than hydrogel swelling. In this condition the modeling of drug involves moving boundary, where molecules are released at the interface of the rubbery and glassy phases of swollen hydrogels.[38] Korsmeyer and Peppas introduced a dimensionless swelling interface number Sw, to correlate the moving boundary phenomena to hydrogel swelling.[39]

$S_W = V\partial(t)/D$----------(1)

V = Velocity of the hydrogel swelling front

D = Drug diffusion coefficient in the swollen phase

Chemically Controlled

It characterizes molecule release based on reactions occurring within a delivery matrix. Most commonly occurring reactions are- Cleavage of polymer chains via hydrolytic or enzymatic degradation. Reversible or irreversible reactions occurring between the polymer network and releasable drug.[40]

Purely–kinetic – controlled release

Polymer degradation (bond cleavage) is the rate determining step while diffusion contributes almost negligible to the drug release.[41] It is of two types viz.

1. Pendant chain (prodrugs)
2. Surface eroding systems

In pendent chain systems, drugs are covalently linked to the hydrogel network device through cleavable spacers and drug release is controlled by the rate with which spacer bond cleavage occurs.[42] Nevertheless due to the inherently high water content of hydrogels, surface erosion occurs slowly in enzymatic degradation systems where the transport of enzyme into the gel is

slower than the rate of enzymatic degradation.[43] Models focusing on the release mechanisms are based on hydrolytic degrading polymers.[44]

Gel Versus Hydrogel

Technically, gels are semi-solid systems comprising small amounts of solid, dispersed in relatively large amounts of liquid, yet possessing more solid-like than liquid-like character.[45] Sometimes, hydrogels are also described as aqueous gels because of the prefix 'hydro'. Although the term 'hydrogel' implies material already swollen in water. Dorothy Jordan Lloyd aptly described gels as; true sense hydrogels are a cross-linked network of hydrophilic polymers. They possess the ability to absorb large amounts of water and swell, while maintaining their three-dimensional (3D) structure.[46]

Hydogels For Ocular Delivery

One of the main problems encountered in ophthalmic drug delivery is the rapid and extensive elimination of conventional eye drops from the eye. This process results in extensive drug loss.[47] The reason for this inefficient drug delivery includes rapid tear turnover, lachrymal drainage and drug dilution by tears.[48] The higher drainage rate is due to tendency of the eye to maintain its residence volume at 7-10 µl permanently, whereas volumes of topically instilled range from 20-50µl. It has been demonstrated in vivo that 90% of the dose was cleared within 2 min. for an instilled volume of 50µl.[49] Consequently, the ocular residence time of conventional solution is limited to few minutes, and the overall absorption of a topically applied drug is limited to 1-10%.[50]

Previous studies on rabbits by Robinson et al [51] established that the rate of drainage from the eye of an instilled solution is markedly reduced as the viscosity of the solution is increased. More recently, the approach to improve pre-corneal retention is based on the use of mucoadhesive polymers that are able to interact with the mucin-coating layer present at the eye surface.[52] It is generally well accepted that the instillation of a formulation should influence tear behavior as little as possible.[53]

Ph Sensitive Hydrogels

Gelling of the solution is triggered by a change in the pH. Cellulose acetate phthalate (CAP) latex, cross linked acrylic, and derivatives such as Carbomer are used. [54] The gelled system constitutes a micro-reservoir of high viscosity First preliminary investigations of pH sensitive latexes for ophthalmic administration began in early 1980s and have been extensively studied

by Boye.[55] He proposed the preparation of latexes containing Pilocarpine with Cellulose acetate phthalate (CAP).

Cellulose acetate phthalate latex is a polymer with potentially useful properties for sustained drug delivery to the eye because latex is a free-running solution at a pH of 4.4, which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The use of pH sensitive latex nanoparticles has been described by Gurny.[56] Carbomer (Carbopol) a crosslinked acrylic acid polymer (PAA) also shows pH induced phase transition as the pH is raised above its pKa of about 5.5. Different grades of Carbopol are available. The manufacturer states that Carbopol 934 gel has the lowest cross-linking density, while Carbopol 981 intermediate and Carbopol 940 have the highest.

Combination PAA with a suitable viscosity-enhancing polymer e.g. Hydroxy propyl methyl cellulose or Methyl Celluloseallows a reduction in the PAA concentration without comprising the in situ gelling properties.[57] Polycarbophil-based in situ gelling systems were developed by Robinson and Miynek[58] Polycarbophil is insoluble in water, but its high swelling capacity in a neutral medium permits the entanglement of the polymer chains with the mucus layer.

Ion-Sensitive Hydrogels

Ion-sensitive polymers mainly used in situ gelling materials for ocular drug delivery. It is therefore likely that the osmolality of the solution might have an influence on the rate of the solgel transition occurring in the eye. One example is Gelrite, an anionic extra cellular polysaccharide, low acetyl Gellan gum secreted by pseudomonas elodea. Gelrite formulations in aqueous solutions form a clear gel in the presence of the mono or divalent cations typically found in the tear fluids.[59]

The precorneal contact times for drugs can thus be extended up to 20-h.[60] Gellan containing formulations of pilocarpine HCl allowed reduction of drug concentration from 2% to 0.5% obtaining the same bioavailability. Rozier et al[61] found an improvement in the ocular absorption of timolol in albino rabbits compared with an equiviscous solution of hydroxyl-ethyl cellulose. Sanzgiri et al[62] compared various systems of Methyl prednisolone (MP); esters of MP with Gelrite eye drops, Gellan-MP film and Gellan film with dispersed MP. Gellan eye drops provided better performance because they afforded the advantage of faster gelation over a high surface area in eye, whereas the results obtained with the Gellan-MP film

seemed to indicate that the gelation at the surface of the film occurred very slowly, and the release was not controlled.

Mourice and srinivas[63] measured a two fold increase in the permeation of the fluorescein in humans when using Gellan gum compared to isotonic buffer solution. Presence of this polymer significantly extended the duration of the pressure reducing effect of pilocarpine to 10-h and carteolol to 8-h[64] allowing only once a day administration in case of carteolol.
The extent of alginate gelation and consequently the release of Pilocarpine were found to be dependent upon the percentage of Glucuronic Acid residues in the polymer backbone. Alginates with G content more than 65%, such as Manugel DMB[65], instantaneously formed gels upon their addition to STF. Silver et al compared the commercial product Timoptic XE 0.5% with a timolol mealeate gel forming solution with xanthan gum as the gelling polymer (Timolol GFS 0.5% Alcon Research). The xanthan gum preparation was developed for once-daily dosing. The reported data indicated equivalent efficacy in the reduction of intraocular pressure [66].

Evaluation Of The Hydrogels

Rheological Studies

Viscosity determinations of the prepared formulation are determined using Brookfield viscometer LVDV II. The viscosities of the hydrogel are measured at different rpm. The correct viscosities of the hydrogel are noted at particular spindle at which it shows maximum percent torque value. The Literature suggests that the viscosity value in the range of 15 cps to 50 cps significantly improves the contact time of the formulation on the corneal surface and higher viscosity values offers no significant advantage and have a tendency to leave a noticeable residue on the lid margin.[67]

Drug Polymer Interaction Studies

Drug polymer interaction studies are carried out by Infrared spectral analysis. Infrared spectra of pure drug & formulation are scanned by using Perkin elenmeyer FTIR 1600, by a thin film method. The increased viscosity leads to a broadening of peak.[68]

***In-Vitro* Drug Release**

In vitro release rate of the drug from the stimuli sensitive hydrogels are determined by the diffusion process. 1 ml of the formulation are kept in the donar compartment over a cellophane membrane which are rinsed and soaked for the 24 hours in the diffusion medium.

The donar compartment are immersed in the receptor compartment containing 50 mlb of the phosphate buffer of pH 7.4, the beaker containing diffusion medium (receptor compartment) are maintained at 37ºC with the constant stirring at 22 rpm using the magnetic stirrer. One ml aliquots are withdrawn from the diffusion medium every hour for the 8 hours and same quantity of fresh, pre warmed diffusion medium are replaced for the amount withdrawn. The sample swith drawn are analysed spectrophotometrically using Shimazdu Double beam UV-Visible spectrophotometer.[69]

Sterlity Testing

The sterlity testing of the hydrogels were performed for the aerobic, anaerobic bacteria and fungi by using alternative thioglycolate medium and soyabean casein digest medium. The positive control (growth promotion), negative control (sterlity) test are also carried out. *Bacillus subtilis* are used as a test organism in the case of aerobic bacteria test. *Bacteriodes vulgatus* are used as a test organism in case of anaerobic bacteria test *& candida albicans* in fungi test. Thus the hydrogels are sterile in nature.[70]

***In Vivo* Evaluation**

Glaucoma are induced in the rabbit by the method of Bonomi et. al. In this method, six albino rabbits of both sexes weighing between 1.8 kg to 2.2 kg were used in the study. During the experiment food and water was provided *ad libitum*. The increase in the intraocular pressure was achieved by the subconjuctival injection of the Betamethasone. The formulation X_2 was instilled in the conjuctival Cul de sac and the lowering in the intraocular pressure was measured by using schiotz tonometer. The marketed eye drops suddenly lowers the intraocular pressure to the minimum and afterwards there was a sudden increase in the intraocular pressure to the original reading, where as the hydrogels lowers the intraocular pressure slowly to the minimum and thereafter a gradual increase in the intra ocular pressure. Thus a sustained effect was maintained with this stimuli sensitive hydrogels.[71]

Ocular Eye Irritation

In the measurement of injury to the eye, a modification of the scoring system of Friedenwald, Hughes and Herrmann (Modified Draize Technique) was used. Six albino rabbits of both sexes weighing 1.8 to 2.2 Kgs were used for the study. 0.1 ml of selected formulation was instilled in the conjunctival sac of each rabbit and readings were made at 1, 24 and 48 hours after instillation of the formulation into the eye and were evaluated on the guidelines of scale of weighted scores for grading the severity of ocular lesions.

APPLICATIONS

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.[72]

Peroral Drug Delivery

Drug delivery through the oral route has been the most common method in the pharmaceutical applications of hydrogels. In peroral administration, hydrogels can deliver drugs to four major specific sites; mouth, stomach, small intestine and colon. By controlling their swelling properties or bioadhesive characteristics in the presence of a biological fluid, hydrogels can be a useful device for releasing drugs in a controlled manner at these desired sites.

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 periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers. Some of these are already on the market. For example, a bioadhesive tablet developed by Nagai et al[73] is commercially available under the brand name Aftachw.

RemunaÂn-LoÂpez[74] reported new buccal bilayered tablets containing nifedipine and propranolol hydrochloride intended for systemic drug administration. As a result of the crosslinking effect, the tablets showed controlled swelling and prolonged drug release with an adequate adhesiveness.

Drug Delivery in the 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.[75]

Undoubtedly, peroral delivery of peptides and proteins to the GI tract is one of the most challenging issues, and thus, under much investigation. Akiyama[76] reported novel peroral dosage forms of hydrogel formulations with protease inhibitory activities using Carbopol (C934P), a poly(acrylic acid) product, which has been shown to have an inhibitory effect on the hydrolytic activity of trypsin, and its neutralized freeze-dried medication (FNaC934P).

They demonstrated that two-phase formulations, consisting of the rapid gel-forming FNaC934P and the efficient enzyme-inhibiting, but more slowly swelling, C934P, had the most profound effect on trypsin activity inhibition.

Rectal Delivery

The rectal route has been used to deliver 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.

Ocular Delivery

In ocular drug delivery, many physiological constraints prevent a successful drug delivery to the eye due to its protective mechanisms, such as effective tear drainage, blinking and low permeability of the cornea. Thus, conventional eye drops containing a drug solution tend to be eliminated rapidly from the eye and the drugs administered exhibit limited absorption, leading to poor ophthalmic bioavailability. Additionally, their short-term retention often results in a frequent dosing regimen to achieve the therapeutic efficacy for a sufficiently long duration. These challenges have motivated researchers to develop drug delivery systems that provide a prolonged ocular residence time of drugs.

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 delivered 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. Gayet and Fortier reported hydrogels obtained from the copolymerization of bovine serum albumin (BSA) and PEG.

Subcutaneous Delivery

Hydrogels 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 in 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.

Protein Drug Delivery

Interleukins conventionally administered as injection are now given as hydrogels which show better compliance and form *in-situ* polymeric network and release proteins slowly.

Cosmetology

Hydrogels when implanted into breast accentuate them for aesthetic reasons. These implants have silicon elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gel.

Hydrogel for Gene Delivery

Modification of hydrogel composition leads to effective targeting and delivery of nucleic acids to specific cells for gene therapy. Hydrogel versatility has potential application in the treatment of many genetic and/or acquired diseases and conditions.[6]

Novel Hydrogel for Controlled Drug Delivery

HYPAN is the novel hydrogel having properties useful controlled drug delivery. Physical network of crystalline clusters distinguishes HYPAN hydrogels from others

Tissue Engineering

Micronized hydrogels are used to deliver macromolecules (phagosomes) into cytoplasm of antigen-presenting cells. This property is also utilized in cartilage repairing. Natural hydrogel

materials used for tissue engineering include agarose, methylcellulose and other naturally derived products.

Soft Contact Lenses (silicon hydrogels and polyacrylamides)

The first commercially available silicon hydrogels adopted two different approaches. First approach by Bausch and Lomb was a logical extension of its development of silicon monomers with enhanced compatibility in hydrogel forming monomers. The second by Ciba vision was the development of siloxy monomers containing hydrophilic polyethylene oxide segments and oxygen permeable polysiloxane units.

Table .2: Marketed Products of Hydrogel

Product	Product manufactured by/marketed by	Hydrogel composition	Indication	Remarks
SQZ gel oral release systems	Macromed(Sandy,UT,USA)	Chitosan and Polyethylene glycol	Hypertension	pH-sensitive
Hycore-V™ and Hycore-	™CeNeSDrug delivery (Irvine,UK)	-	Vaginal and rectal infections	Localized delivery of metronidazole
Cervidil vaginal	Controlled herapeutics UK;marketed by insert Forest pharmaceuticals	Poly(ethylene oxide) and urethane	Initiation and/or continuation of cervical ripening	Product contains 10 mg diniprostone
Smart **C** Hydrogel	Medlogi Global™ (Plymouth,UK)	Liquid poly (acrylic acid)	Used for development of ophthalmic, vaginal and transdermal.	Mucoadhesive composition that undergoes sol-gel transformation

CONCLUSIONS

Drug delivery has undergone a revolutionary advancement in the past few years. With the advent of novel delivery systems, various drug molecules have been revived of their therapeutic and commercial benefits. The introduction of stimuli-responsive systems has further strengthened the link between therapeutic need and drug delivery. A lot of research is ongoing in various laboratories to explore stimuli- responsive hydrogels as drug delivery systems for better patient care. The success of hydrogels as delivery systems can be judged by several marketed preparations (Table 2). In the present scenario, the major considerations during the formulation of hydrogel-based drug products are their mechanical strength and response-time in a physiological environment. Fast-responding hydrogels releasing maximal drug in less time while maintaining the structural integrity in a biological system will be the more appreciated delivery systems. Moreover, a high level of *in vitro–in vivo* correlation in

their performance will determine their future success. The most widely developed drug delivery system is represented by the polymeric hydrogels. Hydrogels generally offer a moderate improvement of ocular drug bioavailability despite their favorable bioadhesive properties. One of the disadvantages is that hydrogel may result in blurred vision as well as foreign body sensation to patients. In situ activated gel-forming systems seem to be preferred as they can be administered in drop form and create significantly less problems with vision. Moreover, they provide good sustained release properties. Over the last decades, an impressive number of novel temperature, pH, and ion induced in situ forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use.

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