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HYDROGELS IN TOPICAL DRUG DELIVERY – A REVIEW

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ABSTRACT

Delivery of drug through topical route represents a most convenient and novel approach. The major difficulty arises while delivering a drug through skin is its action as a natural barrier nature which makes it difficult for most drugs to penetrate into and permeate through it. Conventional topical formulations have not proved to be effective in dermal delivery of drug. Novel drug delivery systems bear great potential for topical delivery. Among them polymeric gels such as hydrogels have been suggested to overcome the problems associated with conventional delivery devices. Hydrogels, the swellable polymeric materials, have been widely investigated as the carrier for drug delivery systems. These biomaterials have gained attention owing to their peculiar characteristics like swelling in aqueous medium, pH and temperature sensitivity or sensitivity towards other stimuli and biocompatability . This review disclose the convenience of hydrogel as a topical drug delivery system anywhere in the body by the route of ophthalmic, rectal, vaginal and skin.

KEY WORDS: Topical drug delivery, Hydrogels, Biocompatibility.

INTRODUCTION

Local application of therapeutic compounds either to the skin, or into the systemic circulation after passage through the skin, offers many advantages over oral and injectable drug delivery. These potential advantages include avoidance of hepatic first-pass metabolism, improved patient compliance and ease of application to the skin [1]. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is that it has ability to deliver drugs more selectively to a specific site (local action). It provides utilization of drugs with short biological half-life, narrow therapeutic window to increase the duration of action [2]. approximately 40% of new chemical entities exhibit poor aqueous solubility and presents major challenge to modern drug delivery systems which leads to poor absorption, poor bioavailability, and lack of dose proportionality. However, in many instances, oral administration is unsuitable when the drug undergoes significant degradation in the gastrointestinal tract or is metabolized to a high degree via the first pass effect in the liver. Formulation of poorly water soluble molecules is a challenging task as they often exhibit low solubility in most topical vehicles. Topical formulation such as ointments, which can solubilize high concentrations of hydrophobic actives, are oily and gritty thus making the formulation less acceptable for patients. A sufficient concentration of a topically applied therapeutic agent must be loaded into the vehicle to ensure an adequate concentration gradient between the formulation and the skin, in order to attain adequate release of the drug into the skin [3,4]. Topical patches do not possess the capability to release the entire amount of the drug incorporated into the skin, and huge quantities of drug are wasted once the patch is peeled off from the skin. Hence what is desired is a combination of aesthetically and cosmetically appealing gel and patch or a film capable of delivering required quantity of drug into the skin without having the disadvantages of a conventional patch. Hence a formulation was attempted which would have the capability of forming a film on topical administration, on the skin. The film-forming polymer may be such as to form a transparent film after the evaporation of a portion of the solvent. The formulation on contact with the skin will form a semi occlusive film over

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the skin, thereby concentrating the active ingredient of the formulation in a matrix of the polymer [5]. At present polymeric gels and hydogels are widely used in drug delivery systems due to their important physical and chemical properties such as controllable and prolonged release of drugs in organisms; as this takes place, high local concentration of medical preparations is maintained in the affected tissues over a long period [6].

ANATOMY OF HUMAN SKIN

The natural barrier for topical delivery is skin, The human skin comprises of three tissue layers (Figure 1): the uppermost being the stratified, avascular, cellular epidermis which is the outermost and non- viable layer of the skin, it acts as a protective barrier for the body and is highly difficult to transverse. The Stratum corneum mainly consists of intercellular lipids which are made up of ceramides, cholesterols, cholesterol esters, and free fatty acids. The organisation and unique chemical composition of these lipids render a high degree of water impermeability to the skin. The barrier function of the stratum corneum is provided by patterned lipid lamel laelocalized to the extracellular spaces between corneocytes which makes it difficult for transversing the membrane for both water and other permeates. The next layer which is the dermis consists of connective tissue, nerves and blood vessles and the lowermost layer is the subcutaneous fat layer which lies beneath the dermis. For therapeutic quantities of drug to permeate through the skin, the barrier properties of the Stratum corneum must be overcome. Because of the selective nature of the skin barrier, a select section of drugs can be delivered to the skin for local action at therapeutic levels. A lipophilic drug, can cross the Stratum corneum, but once it enters the more aqueous lower regions of the epidermis the rate of diffusion decreases. Thus, as the diffusion of a very hydrophobic permeate proceeds into deeper layers of the skin, diffusion slows, and the concentration gradient (from Stratum corneum down to the viable tissue falls) [7].

HYDROGELS

Hydrogels are polymeric material that exhibits the ability to swell and retain a significant fraction of water within its structure, but will not dissolve in water. Hydrogels have received considerable attention in the past 50 years, due to their exceptional promise in wide range of applications. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymeric backbone, while their resistance to dissolution arises from cross-links between network chains [8].

ADVANTAGES

- Hydrogel is more elastic and stronger than available hydrogels of similar softness. Poly (methyl acrylate-cohydroxyethylacrylate) hydrogel implant material of strength and softness.
- Hydrogel-based micro valves have a number of advantages over conventional micro-valves, including relatively simple.
- Fabrication, no external power requirement, no integrated electronics, large displacement (185μm), and large force generation (22 mn).
- Environmentally sensitive hydrogels. These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a changes.
- Natural hydrogel materials are being investigated for tissue engineering. These materials include agarose, methylcellulose, and other naturally derived polymers [9, 10].

Desired physicochemical properties of drug which required for formulation of topical hydrogels are

I) Drug should have a molecular weight of less than 500 Daltons.

ii) Drug must have adequate hydrophilicity.

iii) A saturated aqueous solution of the drug should have a pH value between 5 and 9.

iv) Drug highly acidic or alkaline in solution is not suitable for topical delivery [11]

STRUCTURE OF HYDROGEL IN DRUG DELIVERY

Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers. 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 skin [11].

Film forming hydrogels

The film-forming hydrogel (FFH) is a hydrogel dosage form which transform from the hydrogel to film type by solvent evaporation after application to the wound site. This formulation has the advantages of both hydrogel and film types. Compared with wound dressing forms, it offers easier use and application, and simpler manufacture. Furthermore, the FFH system can be freely applied to any wound site, even though the wound is curved and shaped [13].

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 [13]

- Diffusion controlled
- Swelling controlled
- 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

Drug Diffusion Coefficients

Types of diffusion - controlled hydrogel delivery systems are as follows

- Reservoir system
- Matrix system

For *reservoir system*, drug depot is surrounded by a polymeric hydrogel membrane. Fick's first law describes drug release through the membrane.

For *matrix system* (drug uniformly dispersed throughout the matrix), unsteady state drug diffusion in a one dimensional slap- shaped matrix may be described using Fick's second law of diffusion [14].

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. Transition occurs from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules rapidly diffuse. Release of small molecule drugs from HPMC hydrogel tablets are based on this mechanism. For example, Methocel matrices (a combination of methylcellulose and HPMC).

Chemically controlled

It characterizes molecule release based on reactions occurring within a delivery matrix. Most commonly occuring reactions are-

- Cleavage of polymer chains via hydrolytic or enzymatic degradation.
- Reversible or irreversible reactions occurring between the polymer network and releasable drug.

It can be categorized on the basis of reactions occurring during drug release [15].

1. Purely–kinetic – controlled release Polymer degradation (bond cleavage) is the rate determining step while diffusion contributes almost negligible to the drug release.

It is of two types viz.

- Pendant chain(prodrugs)
- 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. In specific applications where a more targeted delivery approach is desired, it is advantageous to design enzymatically cleavable spacer bonds [16].

In *surface eroding systems*, drug release is mediated by the rate of surface erosion of the polymer matrix. In hydrophobic polymer networks, surface erosion occurs when the rate of water transport into the polymer is much slower than the rate of bond hydrolysis. 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. Models focusing on the release mechanisms are based on hydrolytic degrading polymers [17].

2. Reaction – diffusion-controlled release Reaction (polymer degradation, protein – drug interaction) and diffusion both contribute to the drug release. Action is the production of relatively pure and initiator-free hydrogels [18].

APPLICATIONS OF HYDROGELS

Perfume delivery

The role of hydrogels in the process revolves around, once again, their swelling properties that can be exploited inmaterials "wherein release of a perfume smell is triggered by dynamic swelling force of the polymer when the polymer is wetted". These devices release volatile particles thanks to osmotic diffusion of the specie from the swollen hydrogel to new water in the environment.

Cosmetics

For a product to be approved in cosmetics, the most important parameter to be assessed is Primary Irritation Index (PII). This index is simple to obtained and exist both for skin and eyes, indeed for each level of PII corresponds a determinate effect. Considering that the majority of hydrogels used in this field are suitable for cells culture and for other biomedical applications, is not surprising that their Irritation Index is among the lowest. Thus, with a relatively small investment, companies are able to launch on the market new cosmetic products based on hydrogels, such as so called "beauty masks". Usually made with engineered collagen (Masqueology TM by SEPHORA USA Inc., Bio Collagen Cosmeceuticals by NOVOSTRATA UK Ltd.), hyaluronic acid (SEPHORA USA Inc.), or polyvinyl pyrrolidone (Pecogel®), these masks claim to hydrate the skin, restore its elasticity and promote anti-aging actions. Pecogel by Phoenix Chemicals Inc., is a wide selection of hydrogels, based on polyvinyl pyrrolidone, with differences in composition and/or crosslinking method. Pecogels are suitable for cosmetic purposes, such as sunscreen cream or mascara .Furthermore, in some of the commercially available compounds such as Hydro Gel Face Masks by Fruit & Passion Boutiques Inc;. The moisturizing action of these organic polymeric gels is coupled with more complex drug-delivery systems

developed to release of biomolecules like vitamin C or B_3 [19].

Dental applications

Pulp regeneration therapy is important to overcome the limitations of conventional therapy to induce reparative dentinogenesis. Fibroblast growth factor-2 (FGF-2), which is normally stored in the extracellular matrix and released by enzymatic degradation of extracellular matrix molecules, plays a role in physiologic conditions such as enamel and dentin formation of the tooth germ , as well as pathologic conditions . It was previously demonstrated that a gradual and continual release of biologically active FGF-2 was achieved by *in-vivo* biodegradation of gelatin hydrogels that incorporated FGF-2. Furthermore, a controlled release of FGF-2 from gelatin hydrogels induced neovascularization and regeneration of several tissues, including bone, periodontal tissues [19].

Wound healing applications

Wound healing is the promise of a new way to heal damaged skin tissue with high biocompatible and bioactive materials. Skin burned, diabetic ulcer, are problems that at the state of the art are very expensive to treat. Prosthetic-tissue engineered skin are been made, unfortunately they are not ready-to-use; they are expensive and have many needs that are not always matched by patients. Theoretically, in wound healing applications a crucial parameter to assess is the wound contraction that can be evaluated in this way, remembering that A_0 is the original burn wound area, and At is the burn wound area at the time of biopsy:

Wound Contraction % $A_0 - A_t / A_0 * 100$

Many systems has been studied, with or without chemicals to aid the skin regeneration. Hyaluronic-acid and gelatin are both two promising materials for the aim because of their natural presence inside human ECM of the skin tissues. Moreover, in literature can be found healing systems made from cellulose, alginate chitosan copolymers, chitosan-gelatin-honey copolymers and new biphasic gelatin-silk . Most of the products already on the market use a combination of selected materials and proper seeding of cells from various origins (allogenic or autogenic), for instance we cite to applications of HYAFFTM esterified hyaluronic acid both produced by FIDIA Ltd.:Laserskin Autograft®, made of a HA-membrane with keratinocytes, and Hyalo-graft 3D®, made with HA, but with fibroblasts added [20].

Hydrogel Implants

Histrelin acetate (Supprelin LA®, Vantas) subcutaneous implant is a long term delivery platform for the nonapeptide histrelin acetate. The drug is used to treat the symptoms of advanced prostate cancer and is released from this synthetic nonbiodegradable platform over a 12-month period. The hydrogel platform is composed of 2-hydroxyethyl methacrylate,2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, and other nonpolymeric additives.

Hydrogel Inserts

The vaginal insert Cervidil® is composed of a cross-linked polyethylene oxide/urethane polymer (rectangle shape, 29 mm _ 9.5 mm _ 0.8 mm) and has been designed to release dinoprostone at about 0.3 mg/h in vivo. Once placed in a moist environment, the platform swells and releases the drug.

Contact Lenses

A contact lens material should have a combination of properties such as ease of manufacturing, FDA acceptability, wet ability, and permeability. There are generally three types of contact lenses, i.e., hard, soft, and gas permeable. Hard lenses are originally based on poly (methyl methacrylate) and their service temperature is below the polymer glass transition temperature. To make the lens material, methyl methacrylate monomer is polymerized in bulk in the presence of crosslinker and initiator via a radiation technique (ultraviolet or infrared). Hard lenses prepared in this way are then cut with a precision lathe. Hard lenses are now obsolete and have been replaced by soft and gas permeable lenses. Soft contact lenses are typically formed via a simultaneous polymerization and castmolding or spin casting. These are generally based on 2-hydroxyethyl methacrylate with either N-vinyl pyrrolidone or methacrylic acid monomer, crosslinked with ethylene glycol dimethacrylate. Alternatively, soft lenses are manufactured based on polydimethyl siloxane, so calledsiloxane lenses. Focus Night and Day® (Ciba Vision), Acuvue Oasys® (Vistakon)and Pure Vision® (Bausch and Lomb) are silicon based hydrogel lenses. Some recently approved gas permeable contact lenses are Pahrifocon A® (a crosslinked copolymer of acrylate, silicone acrylate, and fluorosilicone acrylate monomers, dimers and oligomers), Hexafocon A®, Enflufocon B®, and EnflufoconA® (aliphatic fluoroitaconate siloxanyl methacrylate copolymer available with or without UV blocker) [21].

Rectal delivery

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. In this context, hydrogels may offer a valuable way to overcome the problem in conventional suppositories, provided that they are designed to exhibit a sufficient bio-adhesive property following their rectal administration. It offers better bioavailability without the occurrence of any irritation.

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. Certain dosage forms, such as suspensions 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.

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. Recent research trends in transdermal applications 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 transdermals ionophoresis assisted with an AC current, resulting in an enhanced permeation of insulin and vasopressin across human skin *in vitro.*

Subcutaneous delivery

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.
4. Unique possibilities (crosslinking density and swelling) to manipulate the release of incorporated drugs.
5. Some of these may offer an advantage for the delivery of certain delicate drugs, such as peptides and proteins. Giammona *et al*., developed new hydrogels originating from the chemical reticulation of a,b-polyasparthydrazide (PAHy) by glutaraldehyde. PAHy is a new water soluble macromolecule, synthesized from a polysuccinimide by reaction with hydrazine. Histological analysis revealed that this hydrogel was inert when implanted subcutaneously in to 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. 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(1-caprolactone)and PEG macromer 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* [22].

Table 1. Porous Structure of Hydrogel

Structure	Range	Release Mechanism
Macro porous	0.1-10μm	Depend on drug diffusion Coefficient
Micro porous	100-1000μm	Molecular diffusion and convection
Non-porous	10-100μm	Diffusion

Table 2. Diffusion control parameters

Hydrogels	Drug Diffusion Coefficients
Porous Hydrogels- pore size >>> molecular dimensions of drug.	Related to porosity
Non- porous Hydrogels Porous gels with pore sizes comparable to the drug molecular size34,35	Decreases due to stearic hindrance from polymer chains with in cross linked networks.

Fig 1. Anatomy of Human Skin

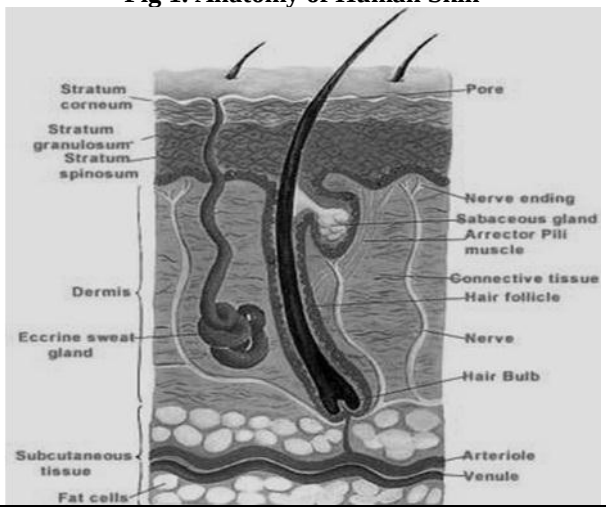
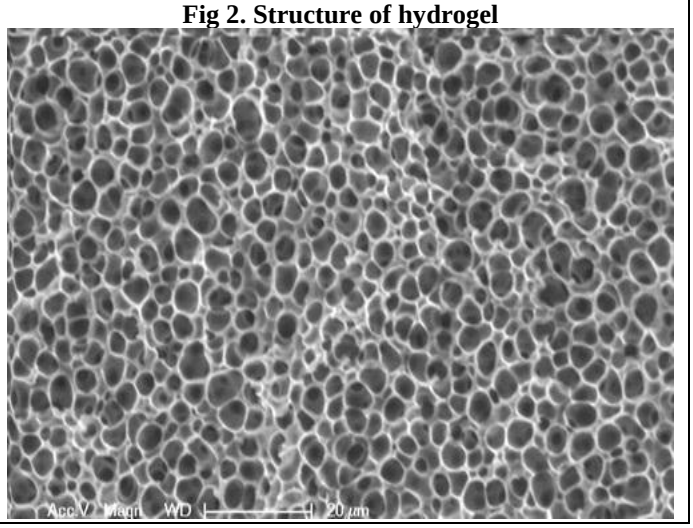


Fig 2. Structure of hydrogel



CONCLUSION

Hydrogels are polymeric matrixes that swell but don't dissolve in water. It resemble natural living tissue more than any other class of synthetic biomaterials. This is due to their high water content and soft consistency which is similar to natural tissue. Furthermore, the high water content of the materials contributes to their biocompatibility. Drug release mechanism of hydrogel is entirely different from conventional delivery devices because of its film forming nature and porous structure. Instead of conventional creams, the hydrogels have been formulated for better patient compliance. These hydrogels have moisturizing properties therefore scaling and dryness is not expected with this drug delivery system.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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