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AN OVERVIEW OF MICROPARTICLES LOADED HYDROGEL SYSTEM FOR TRANSDERMAL DELIVERY

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ABSTRACT

Transdermal delivery of drug through the skin is beneficial, because it overcomes the risks associated with intravenous therapy and thus the inconveniences associated with varying gastric pH, emptying time, and hepatic metabolism. Modern advancements in nanotechnology have improved the ability of molecules to pass through the skin by enhancing the pharmacokinetics of drugs; however, an appropriate vehicle remains to be developed to ensure drug delivery using non-invasive techniques. Hydrogels are 3-D, cross linked networks of water-soluble polymers. Polymeric microparticles DDS are widely discovered for controlled delivery of active pharmaceutical ingredients. Here, we have highlighted the loading and drug release patterns from hydrogel microparticles, various technologies employed, and components equipped in the preparations and applications in the pharmaceutical field. Transdermal delivery of hydrogel loaded microparticles can be aimed for various purposes such as solubility enhancement of hydrophobic drugs, and targeted drug delivery, magnetic carriers.

INTRODUCTION

The skin is the human body's largest organ. It covers the whole body and is a line of defence against the external invasion of microorganisms and other environmental stressors like heat, entry of chemicals and toxins, as well as dehydration.[1] Since the skin is the organ that is most exposed to the environment, the risk of damage of its integrity or the occurrence of a localized disease is very high. Transdermal delivery of drug through the skin is beneficial, as it overcomes the risks associated with intravenous therapy and thus the inconveniences associated with varying gastric pH, emptying time, and hepatic metabolism. Transdermal administration of drug isn't easy due to the impermeable nature of the skin. The stratum corneum of the skin is about ten to hundred microns thick. It forms the primary defence barrier for permeability. Thus, not allowing macromolecules to easily pass through the dermal layer.[2] The stratum corneum consists of layers of dead keratinocytes which are surrounded by a lipid matrix, similar to a ''brick and mortar system'', which makes it difficult for drug molecules to pass through the skin.[3, 4]Although modern advancements in nanotechnology have improved the ability of molecules to pass through the skin by

enhancing the pharmacokinetics of drugs; however, an appropriate vehicle remains to be developed to ensure drug delivery using non-invasive techniques. The gels are considered as a beneficial vehicle for topical delivery of drugs or for the localized and targeted drug action on skin such as in case of spasms, sprains or acute musculoskeletal disorders. A gel is a semisolid formulation, which possess external solvent phase, which is either hydrophobic or hydrophilic in nature, and is immobilized within the spaces available of a three-dimensional network structure. Gels are unique materials that are rigid and elastic in nature and have a broad range of applications in cosmetics, medicine, biomaterials and food technologies.[5-6] Typically, gels can be differentiated into two different types according to the nature of their liquid phase. For example, organogels (oleogels) hold an organic solvent and hydrogels contain water.[7] Compared to creams and ointments, gels, as a result of their high-water content, allow a greater dissolution of drugs and facilitate migration of the drug through the vesicle. In addition, gels will hydrate the skin by holding a significant amount of transepidermal water and facilitate drug transport.[8]

HYDROGELS:

Hydrogels are a part of novel drug delivery systems since the early 1960s. First of all, Wichterle and Lim introduced a kind of hydrophobic gel, cross-linked hydroxyethyl methacrylate (HEMA) hydrogels, developed for biological purpose.[9,10] Hydrophilic polymeric networks that are capable of imbibing huge volumes of water and undergoing swelling and shrinkage appropriately to facilitate controlled drug-release are referred as hydrogels. Hydrogels are 3-D, crosslinked networks of water-soluble polymers. It is often formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. Hydrogels have several advantages like their biocompatibility potential, hydrophilicity, controlled drug release and smart drug delivery, etc.[11, 12] so, there was an excellent interest among scientists of various fields to develop and progress these delivery systems. Hydrogels are made up of hydrophilic polymers which are cross-linked. They form a polymeric network that absorb water from 10-20 percent up to thousand times of their own weight. Depending on the type of bonds formed during the fabrication process hydrogels may be classified as physical or chemical hydrogels. Physical hydrogels are developed by weak forces involved in the formation of molecular entanglements and secondary forces, including ionic and H- bonding. They are reversible in nature due to the presence of free chain ends or chain loops as network defects.[15]On the other hand, chemical hydrogels are often termed as permanent hydrogels, where the bonds involved are covalent. The physical hydrogels have various advantages over chemical hydrogels, *e.g.* with low toxicity, stimuli responsiveness, high drug loading efficiency and an *in-situ* gel forming ability.[16] The physical hydrogels developed by Corrente *et al.*[17] using carboxymethyl-scleroglucan calcium ion were tested for their potential in topical formulations. These physical hydrogels were found to be competent in the loading of non-steroidal anti-inflammatory drugs *viz.*, ibuprofen, ketoprofen, and diclofenac. The use of naturally modified chemical hydrogels has also given rise to a new area of research. For example, the chemical hydrogels synthesized by Patenaude and co-workers[18] were based on *N*-isopropylacrylamide (NIPPAm) and carbohydrate polymers. The union of natural and synthetic polymers has opened up the door for rapid gelling hydrogels and unique engineering methods for developing injectable hydrogels.

CLASSIFICATION OF HYDROGELS:

Based on the method of preparation, hydrogels are classified into:

- Homopolymer hydrogels
- Co-polymer hydrogels
- Multi polymer hydrogels

Based on the ionic charge hydrogels can be classified into:

- ❖ Neutral hydrogels
- ❖ Anionic hydrogels
- ❖ Cationic hydrogels
- ❖ Ampholytic hydrogels

Based on the structure hydrogels can be classified into:

- ❖ Amorphous hydrogels
- ❖ Semi-crystalline hydrogels
- ❖ Hydrogen bonded hydrogels

Based on the mechanism controlling the drug release they are classified into:

- ❖ Diffusion controlled release systems
- ❖ Swelling controlled release systems
- ❖ Chemically controlled release systems
- ❖ Environment responsive systems

HYDROGELS FOR SKIN: The tissue regeneration technology using hydrogels has emerged as a boon in skin regeneration. Hydrogels are constructed in such a manner that they promote the formation of new blood vessels and skin. Lot of literature is available depicting the use of hydrogels in wound healing applications.[19-20] Skin is the first line of defence for protecting the entire body against pathogens and major loss of water. Osti studied a transparent adhesive film possessing selective permeability, which included a hydrogel acting as a burn shield and showed that these films were effective to reduce skin macerations, pain and also the incidence of hypertrophic scars[20].

ADVANTAGES OF HYDROGEL

- They exhibit a degree of flexibility as like natural tissue, due to their significant water content.
- They are biocompatible, biodegradable and can be injected.
- Hydrogels possess significant transport properties and remains easy to modify.
- Hydrogels that are environmentally sensitive have the tendency to sense changes of pH, concentration of metabolite, temperature, and drug load release as result of such a change.

2.4 DISADVANTAGES OF HYDROGEL

1. They are non-adherent and may need to be secured by a secondary dressing and also cause sensation felt by movement of the maggots.
2. Hydrogels exhibit low mechanical strength. Thus, are difficult to handle and expensive.

2.5 PROPERTIES OF HYDROGEL

Hydrogels are hydrophilic gels that are appreciated for their use in the field of pharmaceutical and biomedical engineering.

Swelling properties: Even a small change in environment can trigger fast and reversible changes in hydrogel. The changes in environmental parameters like electric signal, pH, temperature, and presence of enzyme or other ionic species can cause changes in their physical texture[22].

Mechanical properties: The desired mechanical property of the hydrogel might be achieved by changing the degree of Crosslinking and by increasing the degree of crosslinking a stronger hydrogel could be achieved though the higher degree of crosslinking decreases the % elongation of the hydrogels creates a more brittle structure[23].

MICROPARTICLES: Polymeric microparticles DDS are widely discovered for controlled delivery of active pharmaceutical ingredients. Microparticles provide several advantages as drug delivery vehicles, such as protection of encapsulated drug from unfavourable environmental conditions and ability to regulate a drug release profile for a specified period of time. Especially, the potential to regulate the drug release profile for an extended period of time is one of the most attractive behaviors[24-25].

HYDROGEL MICROPARTICLE:

Hydrogel microparticles consist of a hydrophilic mixture, which has the characteristics of both solid and liquid.[26]The hydrogel structure consists of networks that are formed by random crosslinking of macromolecules. It contains the following three phases: Polymeric-network matrix solid phase, Interstitial fluid phase, and Ionic phase.

The solid phase consists of a network of cross-linked polymeric chains. Polymeric chains result in a 3-Dmatrixwithinterstitialgapsoccupiedbywaterandusuallywith biological fluids. The cross-linked polymeric network is often made physiochemically, for instance, by Vander Waals interactions, hydrogen bonding, electrostatic interactions, and physical entanglements also as by covalent bonding. The fluid phase imbibes into polymeric network pores and provides wet and elastic properties to hydrogel microparticles. Owing to these properties, the structure of hydrogels resembles to a living tissue. The ionic phase consists of ionizable groups that are bounded to polymeric chains and mobile ions (counterions and co ions). This phase exists due to the presence of an electrolytic solvent. Hydrogel microparticles can be formed from both natural and artificial polymers[27-29].

4.1DRUG LOADING IN HYDROGEL MICROPARTICLES

In hydrogel microparticles, drug can be loaded by two methods[30].

- Post loading and
- In situ loading.

In post loading of drug, first the particles matrix is made then drug is absorbed. The method of diffusion pulls drug molecules inside the particles. Release of drugs from these particles is additionally administered by diffusion and swelling of hydrogel microparticles[31]. The polymer solution is mixed with drug and drug–polymer conjugates are formed in *in situ* loading of drug. During this method, matrix formation and encapsulation of drug molecules is carried out side by side. Release of drug is determined by diffusion, hydrogel swelling, reversible drug–polymer interactions, or degradation of labile covalent bonds[32].

4.2 DRUG RELEASE MECHANISMS

The drug release from matrix of hydrogel microparticles is predicted based upon composition of the formulation (type of polymer, drug, monomer, initiator, cross-linker, etc.), size and shape of the particles, method of preparation, and environmental conditions. Additionally, to those factors, the subsequent factors also affect the release of drug from swollen particles[33].

- Water penetration into the particles through pores,
- Wetting of the particle matrix with release media,
- Creation of pores by the entrapped water,
- Drug and polymer degradation,
- Alteration in pH of particles matrix due to degradation of polymers,
- Swelling ability of particles,
- Presence of acidic or alkaline environment due to degradation of products,
- Amount of drug in the matrix of hydrogel microparticles,
- Diffusion of the drug in the fluid,
- Absorption and desorption processes,
- Hydrostatic pressure evolved in drug delivery devices, and changes in pore sizes due to swelling of polymers.

By these mechanisms, drug release follows the following phenomenon[34]:

1. Exterior diffusion,
2. Interior diffusion,
3. Desorption, and
4. Chemical reactions.

5. METHODS OF PREPARATION HYDROGEL MICROPARTICLE: [24]

Ionic gelation method: In this method, a monomer–cross-linker solution is formed by dissolving during a suitable solvent and a polymer solution containing an initiator is formed separately. both the solutions are mixed, and thus the reaction is administered at a specific temperature for a prescribed period of time. Centrifugation is completed for few minutes, and then particle's solution is vacuum dried[35].

Spray drying: In spray drying, solid and liquid active constituents are encapsulated using a polymer solution through utilization of a crosslinking agent and hot air to achieve desired physiochemical changes within the encapsulated moiety[35].

Dispersion photopolymerization

It includes the mixing of monomers with the addition of crosslinker, uv-initiator, and dispersion stabilizer. Following irradiation with ultraviolet light for specified period of time, particles are then freeze dried and stored for further analysis[36].

Ionotropic gelation method

This technique is based on cross-linking ability of different polyelectrolytes in the presence of opposite ions to yield hydrogel microparticles. hydrogel microparticles are formed by way of pouring drug containing polymer solution to the aqueous solution containing polyvalent ions. cations diffuse into the drug-loaded polymeric drops, forming a three-dimensional lattice of ionically cross-linked moiety[37].

Suspension cross-linking technique

This process results in stable globules of polymeric solution suspended in immiscible solvent. subsequent hardening of globules results in proper cross-linking. when active drug that is miscible with dispersion medium is mixed, the microencapsulation process produces microparticles. this technique can be used to prepare water in an oil system with or without addition of stabilizer[38].

Free radical precipitation polymerization

It is a heterogeneous polymerization that includes a consistent system of a continuous phase in which monomer and initiators are completely dissolvable. But when the reaction begins, the yielded polymer remains insoluble and precipitated[39].

Membrane emulsification technique

It is comparatively a new technique, during which the membrane is employed for permeation of liquid droplets of 0.1–8μm. resulting uniform size droplets are then dispersed into a continuous phase leading to oil in water, water in oil and multiple emulsions oil in water in oil. After the formation of emulsion, the cross-linking agent was incorporated. the final product was hardened after repeated washing[40].

Inverse emulsion polymerization

It involves the water in oil polymerization method during which water-soluble droplets were uniformly dispersed during an endless organic phase with the help of oil-soluble surfactants. mechanical stirring was performed on inverse emulsion to yield stable formulations. polymerization was initiated in aqueous droplets upon addition of a radical initiator resulting in the formation of colloidal particles[41].

Michael addition reaction

This reaction involves formation of thiol-acrylate networks for hydrogel microparticles due to chemical modification of functional groups of polymers. more particularly, it involves modification of the hydroxyl group of dextran with thiol groups. It consists of a two-step reaction; in the first step, activation of the hydroxyl groupofdextranoccursby4-nitrophenylchloroformate and within the second step this substituted moiety is reacted with cysteamine. after this thiol-dex is added to peg tetra-acrylate to make a hydrogel matrix[41].

Free radical polymerization

Free radical polymerization includes formation of polymers by means of repeated

addition of free radicals building blocks. It requires polymer, monomer, initiator, and cross-linker for generation of polymeric conjugates. In majority of preparation methods, a result of hydrogel microparticles is made by passing hydrogel through a sieve of desired size, utilization of antisolvent, or by blending at a high rate[42].

6. EVALUATION OF MICROPARTICLE LOADED HYDROGEL FOR TRANSDERMAL DRUG DELIVERY

Physical appearance: The physical appearance and homogeneity of the prepared gels were tested by visual observations. the marketed formulation was considered as reference.

Spread ability test: Spread ability can be determined by applying the gel over an even surface and observed for the gritty nature of the hydrogel if present.

pH determination: The pH of the gel formulation is determined using pH meter. for determination of pH, 1% of hydrogel formulation in deionized water is prepared determined.

Drug content: For assay of the drug in gels, drug is extracted from 1 g of each gel formulations with 20 ml of phosphate buffer pH 7.4 for 30 min. the resultant mixture is filtered through membrane filter (pore size 0.45 µm). the absorbance of the sample is determined spectrophotometrically at determined wavelength (elico sl150 uv-vis spectrophotometer) after appropriate dilution with phosphate buffer pH 7.4. the concentration of drug was estimated from the calibration curve.

Determination of viscosity: The viciousness of the gel formulations is determined using Brookfield viscometer with spindle no. 7 at 100 rpm at the temperature of 25^0c.

Accelerated stability studies: Stability studies are carried out on optimized formulation according to international conference on harmonization (ICH) guidelines.

7. APPLICATION OF MICROPARTICLE HYDROGELS

- Application of formulation on skin surface is generally meant for the topical use of dermatological drugs for pores and skin diseases. During this context, microparticle hydrogels are widely studied for topical transport of drug moieties.
- Several antifungal and anti-inflammatory agents are effectively formulated into hydrogel products using various polymers.[43]
- Another utilization of hydrogel is its usefulness in treating wounds due to burn.
- The hydrogels promote effective entrapment of drug and provide controlled release, which provoke rapid healing. Several hydrogel-based formulations are demonstrated for their potential in healing the skin wounds.
- The transdermal route is considered a promising path for transport of molecules into the systemic circulation. This avoids major limitations of oral therapy and provides steady state drug delivery.
- Hydrogels have assumed to be an integral role in the progress of transdermal drug delivery. This flexible hydrogel drug delivery system has been successfully utilized for the delivery of molecules into and through the skin.
- The use of hydrogels in transdermal delivery is essentially owing to their intrinsic properties such as controlled/ sustained drug release for transdermal transport, higher stability, greater percutaneous absorption, desired functionality, and nontoxic nature.
- Improved Vitamin E poor stability and increased its topical delivery.[44]
- Increased cellular uptake and transdermal delivery of curcuminoids.[45]

- Systems are meant for achieving effective plasma concentration for prolonged period.[46]
- Hydrogels provided more transcutaneous permeation of propranolol hydrochloride.[47]

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