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Hydrogels of Meloxicam: A Review on It's Novel Approaches to Enhance The Solubility

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ABSTRACT

Hydrogels have gained considerable attention in the pharmaceutical field due to their unique properties and versatile applications. This review article focuses on the formulation and characterization of hydrogels containing meloxicam, a nonsteroidal anti-inflammatory drug (NSAID) with poor water solubility. The aim of this review is to explore the various novel approaches employed to enhance the solubility of meloxicam within hydrogel systems. The article encompasses an overview of hydrogels, the challenges associated with meloxicam solubility, and the advancements made to overcome these limitations. The review also discusses the methods of preparation, characterization techniques, and potential applications of meloxicam-loaded hydrogels.

Keywords: Meloxicam, Hydrogel, Rheumatoid Arthritis

INTRODUCTION

Hydrogels

Hydrogels are threedimensional (3D) networks of hydrophilic polymers that can absorb large a mounts of liquid or water. Hydrogels are formed by physical and chemical crosslinking. Physical ly crosslinked hydrogels are formed by molecu lar entanglement, ions, hydrogen bonds or hydro phobic forces. These hydrogels are not strong an d their gelation is reversible. Hydrogels undergo covalent crosslinking by redox reactions, photo polymerization, Michael reactions, enzymatic re actions or disulfide bonds to form chemical reac tions that are strong and irreversible bonds. Hyd rogels can be divided into natural hydrogels and synthetic hydrogels according to the surface. N atural and synthetic polymers each have advanta ges and disadvantages, and many materials can be used together to enhance physical and biologi cal properties.

hydrogels are one of the important biomaterials used and can act as natural ECM due to their uni que properties, high water content, porosity and flexibility. In addition, the hydrogel does not aff ect the body's metabolic processes, and metaboli tes easily pass through the hydrogel. [1].

Meloxicam

Meloxicam has been shown to be effective in th e treatment of rheumatoid arthritis, osteoarthritis , and many other joint diseases.

Despite good gastrointestinal benefits compared to other NSAIDs, stomach upset and dyspepsia are common side effects. Side effects on the hea rt are also suspected. Therefore, meloxicam is n ot suitable for the treatment of patients with rhe umatic disease who also have stomach ulcers.

A topical formulation of meloxicam has been de veloped to avoid gastrointestinal infections and reduce toxicity. [2].

However, oral NSAIDs can affect the digestive system and even shorten the lifespan of patients with rheumatoid arthritis. [3].

Meloxicam Solubility Enhancement Techniques

The separation of the drug and its release from t he dosage form is related to its bioavailability. Addressing the solubility problem is a major cha llenge for the pharmaceutical industry as new ph armaceutical products are developed, as about h alf of the active substances are detected by new analysis methods. Check if it is insoluble or slig htly soluble in water. [4]

Solid dispersion and inclusion complex formation

Solid dispersion (SD) was proposed in the 1970 s and is a good way to improve the amount of p oorly soluble drugs and thus improve their bioav ailability. Chiou and Riegelman define the term SD as a solid dispersion of one or more active in gredients in an inert carrier or matrix prepared b y fusion, solvent or molten heavy duty. When S D is exposed to an aqueous environment, the car rier dissolves and the drug is released as fine col loidal particles. The resulting surface area can in crease the dissolution rate and bioavailability of poorly soluble drugs. Additionally, in SD, some of the drug dissolves immediately to saturate the GI fluid, and excess drug precipitates as fine su bmicron-
sized colloidal particles or fat globules.[5]

Inclusion complex technique

Methods to prepare inclusion complexes

The process used to prepare inclusion complexes is crucial since it affects the product's functionality and morphometric properties. There are many different ways to make cyclodextrins-guest complexes, but several of them stand out:

A few examples include co-precipitation, kneading, supercritical carbon dioxide, grinding, microwave irradiation, and spray-drying. The first technique to be discussed is co-precipitation. The co-precipitation approach is appropriate for compounds that are not water soluble.

According to Jiang, Yang, Wang, Ren, and Zhou, the guest-containing ethanol solution is added to CDs dissolved in water while being stirred, in order to create the inclusion complex. According to other writers, the compound guest can dissolve in a variety of organic solvents, including benzene and diethyl ether.

The compound can also be precipitated by utilizing an antisolvent in a similar manner. Co-precipitation is one of the most popular techniques, according to Jiang et al. (2019), and it stands out for being straightforward and effective.

The rigorously weighed cyclodextrins are thoroughly mixed with a tiny amount of purified water (in a mortar) to create a paste for the kneading process, also known as the paste method. The guest is then well mixed into the paste.[6].

Nanoparticles and nanosuspensions

Pharmaceutical uses for nanoparticle engineering have been explored and described over the past ten years. Sub-micron colloidal dispersions of solid medication particles in a liquid phase are known as nanosuspensions. The various techniques used to create nanosuspensions can be categorized into two main groups: "top-down" approaches, in which the raw material is first broken down using milling techniques to create nanosized particles; and "bottom-up" approaches, in which nanosuspensions are constructed from dissolved drug molecules. Precipitation, pearl milling, and high-pressure homogenization are the three nanosuspension engineering techniques that are currently used, either in water, water-miscible liquid mixes, or nonaqueous media. Additionally, the creation of nanosuspensions might result in particles that are entirely amorphous or even increase the amorphous proportion present in them.[7]

Cyclodextrin inclusion

Transdermal absorption of CDs has not received much research, and it is still unclear how CDs work. Although it is clear that the solubilizing abilities of CDs can enhance drug release, absorption, and bioavailability, the question of whether they might also enhance drug percutaneous absorption by changing skin permeability has generated some debate. On the one hand, interactions with some SC components, the inclusion of phospholipids and cholesterol, protein extraction, removal and disorganization of the lipid matrix as a result of complexation, and interactions with keratin that increase order in the lipid lamella are some ways that CDs may affect the permeation of drugs. However, it would seem that such

massive, relatively hydrophilic molecules as CDs would not quickly penetrate the skin. In fact, it has been found that CDs only slowly and with great effort pass through lipophilic biological membranes. Because gel-based (hydrogel) formulations are discovered to be better absorbed through the skin than cream and ointment bases, gels have become increasingly important.[8]

Supercritical fluid technology

Supercritical fluids (SCF), and supercritical carbon dioxide in particular, are playing a bigger role in the processes used to prepare medicinal powders. After fast decompression, pharmaceuticals are precipitated using the supercritical solution procedure, which involves dissolving a solute drug in supercritical carbon dioxide at high pressure and injecting the resultant liquid as a spray into an atmospheric chamber. Reduced particle size, improved drug solubility and dissolution rate for poor solubility medicines, and increased medication bioavailability are the outcomes. [9]

Preparation of Meloxicam-loaded Hydrogels

Physically cross linked hydrogels

Due to the lack of cross-linkers employed in synthesis, there is currently more interest in physically cross-linked hydrogels. Examples of physically cross-linked hydrogels are shown in Table 1 (each case includes the polymer, technique type, and loaded drug). The many techniques for creating physically cross-linked hydrogels are listed below.

By hydrogen bonds

Polyethylene glycol forms compounds with polyacrylic acid and polymethacrylic acid. The carboxylic group of polyacrylic acid/polymethacrylic acid and the oxygen of polyethylene glycol form hydrogen bonds in these complexes. Poly (methacrylic acid-g-ethylene glycol) contains hydrogen bonds as well as polymethacrylic acid and polyethylene glycol. Only until the protonation of carboxylic acid groups takes place, which results in the pH-dependent expansion of the gels, can hydrogen bonds actually develop.

From amphiphilic graft and block polymers

In aqueous conditions, amphiphilic graft and block polymers have the capacity to self-assemble to produce hydrogels and polymeric micelles, in which the hydrophobic components of the polymer are assembled. Lamellar phases, micelles, etc. are produced by hydrophilic deblock polymers. Hydrophobic chains with hydrophilic grafts may be found in multi-block polymers, as well as segments linked to a water-soluble polymer backbone.

Cross-linking by ionic interactions

Calcium ions may be used to cross-link alginate. Cross-linking takes place at ambient temperature and physiological pH. Alginate gels can be utilized as a matrix for the release of proteins and the encapsulation of living cells.

Cross-linking by protein interaction

Genetically engineered proteins use

In materials chemistry, Tirrell and Cappello established the discipline of protein engineering. The benefit of protein engineering is that the genetic code in artificial DNA sequences may be rationally designed to regulate the peptide sequence, and as a result, its physical and chemical properties. Synthetic amino acids can also be employed in place of natural amino acids.

Through genetic engineering, Cappello and colleagues created polymers with sequential blocks comprising repeats of elastin- and silk-like segments that are associated with the geometry of aligned hydrogen bound beta sheets.

Table : 1 Examples of Cross Linked Hydrogels

Polymer	Cross Link Method	Drug
PEG and PBT	Melt Polycondensation	Lysozyme
Pullulan	Hydrogel Nanoparticles	Adriamycin
Polyacrylamide	Antigen-Antibody Intraction	IgG

Table : 2 Examples of Chemical Cross-link Hydrogels

Polymer	Cross-link Method	API
Chitosan -PVA	Cross linking with Aldehyde	Nano-insulin
Gelatin	Cross linking with Aldehyde	TGF-β1
Albumin	Cross linking with Aldehyde	Adriamycin
Chitosan	Cross linking with Aldehyde	Mitoxantrone
Dextran	Addition Reaction	Hydrocortisone
PVA	Condensation Reaction	Diltiazem Hcl
Gelatin	Condensation Reaction	Lysozyme

By antigen–antibody interactions

Rabbit IgG was grafted to chemically cross-linked polyacrylamide in the presence of an additional cross-linking agent, such as an antibody. The hydrogel displayed a little swelling in the presence of free antigen because the polymer-bound antigen was replaced, causing the antibodies to release and the cross-linking density to decrease.

Chemically cross linked hydrogels

The good mechanical strength of chemically cross-linked hydrogels has led to an increase in interest in them in the modern period. Examples of chemically cross-linked hydrogels are shown in Table 2 (each case includes the polymer, technique type, and loaded drug). The many techniques for creating chemically cross-linked hydrogels are listed below.

Cross-linking by high energy radiation

Unsaturated materials may be polymerized using high energy radiation, such as gamma rays and electron beams.

Cross-linking by free radical polymerization

In addition to the free radical polymerization of vinyl monomer mixtures, hydrophilic polymers with derivatized polymerizable groups can also be used to create chemically cross-linked hydrogels. Natural, synthetic, and semi-synthetic hydrophilic polymers were used to

create gels in this way. Methacrylic groups have been added to mono- and disaccharides, which can be utilized to create hydrogels, using enzymes as a catalyst. Additionally, UVpolymerization allows for the production of hydrogels, designed structures, and photo-reversible systems, which allow for the release of drugs when prepared hydrogels are exposed to UV light.

Cross-linking using enzymes

Sperinde et al. came up with a clever way to make PEG-based gels by employing an enzyme. With the help of tetrahydroxy PEG (PEG-Qa), glutaminyl groups were functionalized. Transglutaminase was added to aqueous solutions of poly (lysine-co-phenylalanine) and PEG-Qa, and this caused PEG networks to develop. An amide bond was created as a result of a transglutaminase-catalyzed interaction between the c-carboxamide group of the PEG-Qa and the e-amine group of lysine.[10]

Characterization Techniques for Meloxicam-loaded Hydrogels

Rheological analysis

When the ambient temperature was lower than the gelation temperature, G″ was higher than G′, showing the stable viscous liquid. Near the gelation temperature, the difference between G″ and G′ became small; when the temperature was equal or higher than the gel temperature, G′ was increased and the gel formation occurred. The phase difference between strain and stress is denoted by δ, where G″ is divided to G′ or viscosity to elasticity. It is a gel behavior criterion calculated using Eq. (1):

If tan δ is more than 1, the gel will have a viscous behavior; if tan δ is lower than 1, the gel will have an elastic behavior. Tan δ, as shown in Table 1, was b1 for all samples, which referred to the elastic hydrogel Also, G′ was higher than G″ in all frequencies for all samples; it was almost a straight line depicting a strong gel. Particles dispersion is an important factor influencing the mechanical hydrogel support; if nanoparticles are agglomerated, they cannot perform as the mechanical reinforcement. G′ and G″ for N1, N2 and N3 were higher than those for S1, S2 and S3, because nanoparticles addition could lead to the reinforced gel structure. G′ was 87 pa for N1; with the increase of nanoparticles, it was enhanced, reaching to 227 pa for N2 and 125 pa for N3. So, the N2 sample was the best for reinforcing the hydrogel elastic characteristics. Santos et al. also showed that 3% PLGA nanoparticles on the chitosan hydrogels could increase G′, as compared with both the pure hydrogel and also, 5 and 10% nanoparticles. Nanoparticles N3% caused the weakening of the hydrogel by the restriction of the cross-linking points. Also, Kim et al. reported that the mechanical properties of the polyacrylic hydrogel were increased by polystyrene nanoparticles, which could be attributed to the nanoparticles amount, particle size and dispersion. For the hydrogels containing the solution, G′ was decreased to 57 pa for S1, 18 pa for S2, and 16 pa for S3.

Swelling studies

Swelling was increased after 2 h in the aqueous medium, reaching its maximum; then, it was constant and did not alter considerably. Swelling was 718 ± 15% for the free hydrogels at the pH value of 7.4. It was reduced by the addition of nanoparticles, reaching to 576 ± 12%, 290 ± 10% and 418 ± 11% for N1, N2 and N3, respectively. So, swelling was almost reduced to half with the addition of nanoparticles from 3.5 to 4.5% (w/v). This was predictable because of the structure reinforcement by nanoparticles and creation of a compressed gel. In another study on the polyethylene glycol hydrogel, it was found that although the structure and size of the holes were not altered by silica nanoparticles, swelling was reduced, which could be due to the restriction of the polymeric chains motion by the nanoparticle's interaction; also, the mechanical properties and the stiffness of these hydrogels were remarkably increased.

Swelling was increased in the hydrogels containing the meloxicam solution because of the weakened hydrophilic polymeric interactions. Swelling was 731 ± 11%, 803 ± 9% and 976 ± 14% for S1, S2 and S3, respectively, at the pH value of 7.4. [11]

Structural characterization

Characterization of the structural properties however requires suitable analysis algorithms. Here, we developed custom analysis software to perform a network analysis of 3D fluorescence images. Our analysis approach can be broadly used to map out the architectural features of other fibrillar hydrogels. Furthermore, our results show that a decrease in the concentration of the polymer led to an increase in the diameter or the pores and a higher connectivity, in particular for low concentrations (c = 0.25 mg mL1). The polymer length, which contributes strongly to the gel stiffness has a negligible effect on the micrometer-scale fiber architecture of the hydrogel. This implies that PIC-based hydrogels with different polymers but the same polymer concentration will have different mechanical properties but similar structure.

Consequently, these hydrogels can be used to investigate the influence of mechanical properties, independently of structural features, and vice versa [12]

Applications and Future Perspectives

Drug delivery

Many patents and academic papers about possible applications of hydrogels in drug delivery have been published, however, only a few have resulted in commercial products. Hydrogels have attracted noticeable interest for their use in drug delivery due to their unique physical propertie

Topical drug delivery

The topical application of hydrogels can effectively be used to deliver drugs that can help to alleviate the symptoms of many pathological conditions. For instance, Nho et al. proposed a therapeutic hydrogel made of poly (- vinyl alcohol) or poly(vinylpyrrolidone) for the treatment of atopic dermatitis. This product contained an extract from medicinal plants such as Houttuynia cordata, elm, celandine and Canavalia gladiate, which could be used for the treatment of dermatitis. To prepare this hydrogel poly(vinylpyrrolidone) and poly(vinyl alcohol) were dissolved in the medicinal plant extract. Then, the solution was left to set to produce a gel. It is possible to freeze/thaw the cast and introduce physical cross-links into the gel. Finally, the physical gel must be treated with gamma, UV or electron beam-radiation to initiate chemical cross-linking and to sterilize the final product. The hydrogel was supported by a hydrophilic non-woven fabric sheet and an air-permeable polyethylene film.

Transdermal drug delivery

hydrogels are suitable for transdermal iontophoretic delivery of drugs, as was demonstrated in the European Patent Application EP 0 524 718 A1, where polyurethane hydrogel matrices were used as monolithic drug reservoirs. These hydrogels were synthesized from mixtures prepared by adding a prepolymer solution containing an isocyanate-capped oxyalkylene-based prepolymer in anhydrous aprotic organic solvent to water. When the organic solvent has evaporated completely, the hydrogel matrix can be loaded with a drug. Transdermal iontophoresis is defined as the transport of ionic drugs through the skin, driven by a very weak electric current. The applied current helps to transfer the ionized drugs through the stratum corneum into the dermis, in which the active ingredient can diffuse into capillaries and then into the systemic circulation. Alternatively, hydrogel compositions can be employed as passive transdermal reservoirs. The hydrogels used in the aforementioned work showed a high swelling ratio, good flexibility, strength and transparency.

Ocular drug delivery

Hydrogels could be useful as ocular drug delivery carriers, not only in the form of lenses as previously discussed. The US Patent 8,409,606 B2 presented a system that provided the release of specific drugs through punctual plugs. In this work very soft biodegradable covalently crosslinked hydrogels with high-swelling capability were used, in order to be able to remain in situ (in the punctum or lacrimal canal) with greater comfort for the patient. The system could be designed to be ‘temporary’ or ‘permanent’ and the plugs could be accordingly made of collagen or silicone, respectively.

Ocular therapeutics™ produces ophthalmic drug delivery systems and medical devices using poly(ethylene glycol) hydrogels. For instance, dexamethasone punctum plug is designed for the controlled release of the corticosteroid in case of post-operative inflammation and pain and it has entered the Phase 3 trials. After a four-week treatment period, during which the plug releases the drug from the canaliculus to the ocular surface, it is naturally removed via the nasolacrimal system.

Vaginal drug delivery

One of the successful examples of hydrogels for drug delivery is the vaginal insert Cervidil for cervical ripening, which has been on the market since 1995. This controlled release formulation has been used to induce or bring on labor in patients who are at or near the time of delivery. Each insert contains 10 mg of dinoprostone (prostaglandin E2 or PGE2) in 271 mg of cross-linked polyethylene oxide/ urethane polymer and it releases the drug over a period of 12 h at approximately 0.3 mg/h. The drug release is triggered by the hydrogel swelling when placed in a moist vaginal environment.

Oral drug delivery

They can be used to protect drugs or proteins (e.g. insulin) susceptible to the proteolytic degradation that occurs in the stomach. In the US Patent application WO1998043615 A1 a hydrogel matrix made of poly (methacrylic acid-g-ethylene glycol) cross-linked with tetraethylene glycol dimethacrylate is presented. This hydrogel could be loaded with insulin simply by immersing it into its solution at pH 7.4. When administered orally, insulin will be protected from the acidic environment of the stomach by the formation of inter-chain complexes within the hydrogel network. Hydrogen bonding between the carboxyl and the ether groups on the grafted chains stabilized these complexes at acidic pH. These hydrogels exhibited pH-sensitive swelling behavior: once in the upper small intestine (at higher pH), the complexes dissociate increasing the pore size and allowing the insulin to be released from the matrix. Additionally, the ability of these hydrogels to strongly adhere to the intestinal mucosa significantly improves the release and absorption of the protein [13].

CONCLUSION

Summary of the reviewed approaches and their efficacy

Many attempts have been made to develop new products, which could not only swell, but also retain the fluids absorbed under external pressure or against an applied restraining force. An absorbent material composed of a porous matrix of fibers and superabsorbent hydrogel is described in the US Patent which has the capability to initially imbibe fluids and swell, while being exposed to a load.

Compared with other types of biomaterials, hydrogels have distinct properties such as high water content, controllable swelling behavior, ease of handing, as well as biocompatibility, which makes them attractive for biomedical applications. Based on their chemical structure and crosslink network, hydrogels can respond to different types of stimuli including thermal, pH, light, and chemical stimuli, which can meet various application requirements. Two different hydrogel swelling mechanisms were discussed to give a thorough understanding of how the bulky structure affects the properties of the swollen hydrogels under specific conditions. Hydrogels based on natural materials such as polysaccharides and polypeptides, along with synthetic hydrogels were exampled in detail.

Potential for future research and development

Hydrogels are widely present in everyday products though their potential has not been fully explored yet. These materials already have a well-established role in contact lenses, hygiene products and wound dressing markets but commercial hydrogel products in tissue engineering and drug delivery are still limited. Many hydrogel-based drug delivery devices and scaffolds have been designed, studied and in some cases even patented, however not many have reached the market. More progress is expected in these two areas. Limited commercial products with hydrogels in drug delivery and tissue engineering are related to some extent to their high production costs.

Development of successful hydrogel based delivery system is possible upon knowledge about physiochemical properties of the hydrogel forming polymers and understanding the influencing factors which control the swelling behaviors, hydrophilicity, biodegradability, biocompatibility and targetability of the selected

polymer. Hydrogels as drug delivery systems have many advantages including biocompatibility, low toxicity and good swelling behavior but depending on chemical moieties of the gel forming polymers and route of administration some limitations would appear in delivery of active pharmaceuticals such as slow responsiveness of stimuli-sensitive hydrogels, possibility of rapid burst drug release, possibility of drug reactivation, limited hydrophobic drug delivery, low mechanical strength, etc.

CONFLICT OF INTEREST

The authors declare that this article content has no conflict of interest.

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