AN UPDATE ON NANOGEL AND FLURBIPROFEN

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ABSTRACT

Commonly available anti-inflammatory drugs have the disadvantage of hydrophobicity which leads to poor permeability and unpredictable bioavailability. Nanogel is the novel drug delivery systems that meant to enhance the permeability as well as solubility of drugs across the cell membrane. The nanogel helps to enhance the permeation of the drug formulation, along with polymer and co- polymer or permeation enhancers that can further improve permeability. The hydrogel component helps to increase the viscosity and spreadability of the formulation, making it ideal for topical application. The nanogel leads to creation of formulations that possess enhanced pharmacokinetic and pharmacodynamic properties, and simultaneously avoid systemic side effects in individuals with external inflammatory disorders e.g. ulceration in stomach. The nanogel possessed efficient spreadable, easily applicable, non-invasive administrable and subsequent ability to attain patient compliance make it more suitable for topical application in the combat of many inflammatory disorders, such as muscular pain, eye pain, rheumatoid arthritis, osteoarthritis and so on. Considering the potential advantages and long-term benefits of nanogels, this review compiled that elaborates the potential significance of utilizing nanogels in a topical delivery system for anti-inflammatory drug flurbiprofen.

KEYWORDS: Nanogel, flurbiprofen, anti-inflammatory, hydrogel, ulceration

INTRODUCTION

1. Nanotechnology

Nanotechnology, a unique technique, opens up a plethora of opportunities for drug production and delivery (nanomedicine) approaches that include the characterization, synthesis and design of molecules or materials, as well as devices, with effective function at the nano meter scale. The primary goal of this technique is to improve current therapeutic and diagnostic procedures[1].

According to studies conducted in academic labs and pharmaceutical companies around the world, the introduction of new nano-sized particulate drug delivery systems (DDS) has had a significant impact on disease diagnosis, prevention and treatment. This technique has overcome the challenges by improving drug absorption, lowering drug toxicity, controlling dose release, and reducing biodegradation. It also reduces the likelihood of immune cell activation following drug administration inside the body. The use of nanotechnology in medicine has resulted in the creation of functionalized nano-particles that may be loaded with pharmaceutical drugs or genetic material and delivered to specific areas of the body through a controlled mechanism.

As an advanced DDS, various nano-technological techniques such as protein-based nanoparticles, lipid-based nanoparticles, nanoemulsions, nanocrystals, nanodiamonds, carbon nanotubes, nanosuspensions, and Nanogels have been introduced, with Nanogels being the most advantageous over other DDS techniques[2].

2. Nanogel

The term "Nanogel" refers to a hydrogel nanoparticle with a cross-linked hydrophilic polymer network. Nanogels (nanosized hydrogels) are small, swollen particles made up of flexible hydrophilic or amphiphilic polymer networks that are physically or chemically cross-linked. These polymer networks may be anionic or ionic in nature. They act as drug carriers and are designed in such a way that they can easily absorb biologically active compounds through the formation of biomolecular interactions such as salt bonds, hydrophobic or hydrogen bonding. They are designed in such a way that these Nanogels can easily encapsulate a wide range of biomolecules by optimizing molecular composition, size, and morphology to ensure controlled drug release *in-vivo*[3].

When Nanogels are dispersed in aqueous media, their swollen networks soften and are able to encapsulate the required volume of water. By allowing the formation of spontaneous interactions between the polymer matrix and the agents, desired biological or drug molecules can be loaded into the Nanogels, resulting in the formation of highly dispersed hydrophilic particles. This resulting structure is capable of protecting the desired loaded biomolecule from degradation.

As a result, Nanogels are a versatile structure for drug encapsulation as well as drug controlled release at the target site. Nanogels were demonstrated to be a promising structure for systemic drug release, the design of multifunctional nanocarriers such as controlled drug release at the target site during the first decade of their development[4].

3. Nanogel Drug Release Mechanism

There are number of drug release mechanisms including degradation of nanogel structure, simple diffusion, temperature, and pH changes, counter ion displacement or induced due to external energy source[5] some are described below:

(a) Thermosensitive & Volume Transition Mechanism: thermosensitive polymer gels mechanism depends on the reversible volume change from collapse to swell via irregular volume change with temperature. Three pattern observed as (1) Thermoswelling is shrunken-swollen of polymer with irregular volume change (2) Thermoshrinking is swollen- shrunken of polymer with irregular volume change (3) Convexo pattern is shrunken-swollen- shrunken with two irregular volume change. For intense N–isopropyl acrylamide is a polymer that efflux indomethacin drug by initially shrunken in gel volume with the temperature reaches above lower critical solution temperature (LST)[6] while N – isopropyl acrylamide – co – acrylamide polymer release 5 – fluorouracil drug at body temperature[7]. Superficially modified polyethylene used to formulate nanogels effectively applied for a gene delivery systems[8]. Poly alkylene oxides containing nanogel's thermally trigerred volume can be incease 1 μm in nanogel size[9]. Nanogels of poly (N–isopropyl acrylamide) and chitosan, the lower critical solution temperature could be altered by altering in ratio of polymers and used in the hyperthermic cancer treatments[10].

(b) Photochemical Internalization & photo isomerization: nanogels containing photosensitive polymer produces nascent oxygen during photochemical excitation by light is reactive oxygen species cause oxidation of cellular wall components which affects drug release in to cytoplasm

easily, or else inhibited by intracellular compartment[11]. In photo isomerization the polymer of nanogels converts their configuration in the presence of light e.g. Cis-trans isomerization, E-Z configuration etc. Nanogels having azo dextran as polymer E- configuration show better aspirin release profile than Z- configuration of azo group at 365 nm radiation[12].

(c) Diffusion Mechanism: in this type of mechanism drug travels high concentration to low concentration. Numerous nanomedicines have prepared already that pursues diffusion mechanism, is a simple procedure, e.g. polymeric micelles that have in clinical trail stage[13]. Stable hydrogel nanoparticles of Doxorubicin formulated using puronic block copolymer follows the diffusion mechanism for drug release.

(d) PH responsive Mechanism: nanogel containing platinum nanoparticles at the acidic skin pH the reactive oxygen species scavenging on & off catalytic activity and protonation of crosslinked poly (2 – (N, N – diethylamino) methacrylate) core and PEG[14] when lower the pH the polymers methacrylic acid ethyl acrylate are insoluble, again on increasing of pH, acidic groups ionizes because of polymeric chains repulsions begins and lead to drug release profile of procaine-HCl[15]. The pH sensitive polyacryrlic acid chains shows swelling provide control release kinetics mechanism of the drug temozolidine[16]. Glycol chitosan nanoparticles and grafting of diethylaminopropyl groups formulated nanogel notably increases the release of doxorubicin [17].

(e) Displacement by Ions present in the Environment: nanogels that release drug on the specific site of action due to the signal of environmental responses. POEOMA like water soluble polymers containing nanogels are biodegrade in the presence of glutathione tripeptide which is generally found in cells. Cationic nanogels when triggered with negatively charged drug in cell membrane from complelexes and explain cellular accumulation of drug delivered with nanogel[18].

4. Polymer Used in Nanogel Drug Delivery[19-21]

There are many polymers used to prepare nanogels e. g. Pullulan, folate-pheophorbide, poly(ethyleneimine), PEG, Poly(N-isopropylacrylamide), chitosan, Poly(acrylamide), Methylacrylic acid and N,N'-methylene-bis-(acrylamide), Acetylated hylauronic acid, and Pluronic poly(ethyleneimine)

5. Nanogel formulations prepared for flurbiprofen

Firdous Ahmad Burki, et al (2023) designed solid lipid nanoparticle (SLN) transdermal formulations of flurbiprofen. Chitosan-coated SLNs were prepared by the solvent emulsification method, and their properties and permeation profiles across the excised rat skin were characterized. The drug association efficiency was improved when a higher concentration of chitosan was employed over SLN droplets that endowed a higher affinity of flurbiprofen with chitosan. The drug release was significantly retarded as compared to the uncoated entities and followed non-Fickian anomalous diffusion. Also, the total permeation of chitosan coated SLNs (F7−F9) was significantly higher than that of the noncoated formulation (F5). Overall, this study has successfully designed a suitable carrier system of chitosan-coated SLNs that provide insight into the current conventional therapeutic approaches and suggest new directions for the advancements in transdermal drug delivery systems for improved permeation of flurbiprofen[22].

Ayse Nur Oktay, et al (2023) developed and characterized flurbiprofen (FB)-loaded cyclodextrin (CD) based nanogel formulations for dermal application. Nanogels were produced via emulsification solvent evaporation and then incorporated into a hydroxypropyl methyl cellulose (HPMC) gel. The final nanogel formulation was physically and chemically stable over 12 months. Skin irritation test showed no skin irritation or cellular infiltration on the histological level. In vitro and ex vivo permeation showed that the nanogels could be effective and stable formulations, especially in the dermal application of a hydrophobic molecule[23].

Heera Battu, et al (2022) developed flurbiprofen microemulsion gel for transdermal delivery. To prepare a microemulsionoil, surfactant and co-surfactant selection is one of the important criteria. Selected to prepare different ratios of oil and surfactant mixture using ternary phase diagram. Based on results of physicochemical properties, we have optimized one formulation. The optimized microemulsion formulation incorporated into carbopol P 934 gel base. The In vitro diffusion of drug release shown maximum (98.6% in 12hrs) for prepared microemulsion gel than marketed gel (60.5% in 16hrs) [24].

Keerthana K,et al(2022) carry out the formulation design and evaluation of Solid Lipid Nanoparticles (SLNs) loaded topical gel of Flurbiprofen. Flurbiprofen solid lipid nanoparticles (SLNs) were formulated using Glyceryl monostearate (GMS) as lipid matrix by solvent

evaporation method followed by probe sonication. A 32 full factorial design was utilized to optimize the SLNs. Drug: lipid ratio and sonication time were chosen as independent variables. Particle size, entrapment efficiency (%) and PDI were dependent variables. In vivo skin irritation study on wister rats proved that formulation didn't had any signs of irritation[25].

Gangadhara R, et al (2021) analyzed is to see how effective a Nanosponge-loaded topical gel is at distributing flurbiprofen through the skin. Flurbiprofen was entrapped in Nanosponge and formulated into a gel for this purpose. Flurbiprofen Nanosponges were developed by solvent evaporation using pluronic F68 and ethyl cellulose. Using Guar gum, Carbopol, and HPMC K4M, a total of 6 formulations were produced to determine the sustained drug release and were tested for physiochemical tests, producing positive results. According to the findings of the above in vitro drug release trials, formulations containing carbopol release more drug at the end of 11 hours than other formulations and follow a zero-order with case II transport mechanism[26].

Maddiboyina, Balaji et al (2021) formulated and evaluated a thermosensitive *in-situ* nano gelling method to improve solubility and ocular residence time of flurbiprofen. This study was carried out in two phases. In the first phase, an insolubility drug has been formulated in the form of a nanoparticulate system and evaluated for its characteristics. In the second phase, nanoparticulate systems were dispersed in aqueous solutions of Pluronic F 127 (14%) and various concentrations of Carbopol 934 in combination to form an in situ nano gel. The prepared in situ gel was investigated for its physicochemical properties. Greater concentration of drug in aqueous humor was due to its improved saturation solubility of the drug, and amplified residence time was attributed to the formation of gel matrix-embedded nanoparticles[27].

Diksha S. Chodankar, et al (2020) formulated flurbiprofen (FLB) emulgel, evaluation of the formulations and the selection of an optimized formulation through in vitro drug release and drug content studies. The development of a dermal drug delivery system can overcome side effects e.g. systemic side effects like gastric irritation and GI bleeding. The emulgel formulations were produced using different combinations of oil and emulsifying agents. Carbopol 940 was used as a gelling agent. The study revolved aroundthe formulation of emulgel containing Flurbiprofen for dermal delivery of the drug. Emulgel was formulated with the purpose to enhance the permeation of poorly water-soluble drug FLB[28].

Mohammed Layth Hamzah (2020) developed and evaluated nanoemulsion-based gel (nanogel) for transdermal delivery of Flurbiprofen. Among the various excipients tested, oleic acid, tween 80 and ethanol were selected as oil, surfactant, and co-surfactant respectively. Nanoemulsions region was identified by constructing pseudo-ternary phase diagrams using aqueous phase titration. Then these Nanoemulsions were converted to nanogel using chitosan as a gelling agent. The nanogel showed a significant increase in the anti-inflammatory activity as compared to conventional gel[29].

Nafiu Aminu, et al (2019) developed a dual action, namely anti-inflammatory and antimicrobial, nanogels (NG) for the treatment of periodontitis using triclosan (TCS) and flurbiprofen (FLB). Triclosan, an antimicrobial drug, was prepared as nanoparticles (NPs) using poly-ε-caprolactone (PCL), while flurbiprofen, an anti-inflammatory drug, was directly loaded in a chitosan (CS) based hydrogel. The entwinement of both NPs and hydrogel loaded systems resulted in the Nanogel. The characterization data confirmed that the developed formulation consists of nanosized spherical structures and displays pH-dependent swelling/erosion and temperature-responsiveness. Besides, the NG exhibited adequate bioadhesiveness using the chicken pouch model and displayed antibacterial activity through the agar plate method. An in-vivo study of the NG on experimental periodontitis (EP) rats confirmed the dual antibacterial and anti-inflammatory effects which revealed an excellent therapeutic outcome. In conclusion, a dual action NG was successfully developed and proved to have superior therapeutic effects in comparison to physical mixtures of the individual drugs[30].

Aiswarya G, et al (2015) formulated topical gel loaded nanoemulsions containing flurbiprofen using volatile oil. The gel released the drug at a controlled rate to the targeted site. Flurbiprofen (logP = 4.09) in generally used for transdermal treatment of rheumatoid arthritis and osteoarthritis. Selection of the oil phase, surfactant, and cosurfactant was done by individual screening method with the aid of pseudo□ternary phase study. International Conference on Harmonisation Q8 guidelines was applied using 32 factorial designs coupled with response surface methodology. The formulations were prepared by using spontaneous emulsification method. The selected formulation from various statistical and other studies was investigated. It was found that selected formulation showed an optimum in□vitrodata. Later the optimized formulation obtained within the tentative design space was incorporated in the gel and compared

with the marketed formulation. The result suggested the optimized formulation with good potential for transdermal delivery of the drug than the marketed formulations[31].

Prajapati SK, et al (2012) design proniosomal gel drug delivery system of flurbiprofen in a trial to overcome the adverse effects associated with oral administration of the drug can be overcome by the use of vesicular drug delivery system. Encapsulation of a drug in vesicular structure can be predicted to prolong the existence of the drug in the systemic circulation and thus enhance penetration into target tissue and reduce toxicity. Due to the limited solvent system present, the proniosomes formed were the mixture of many phases of liquid crystal, viz. lamellar, hexagonal and cubic phase liquid crystals. The potential of proniosomes as a transdermal drug delivery system of flurbiprofen was investigated by encapsulating the drug in various formulations of proniosomal gel composed of various ratio s of sorbitan fatty acid esters, cholesterol, prepared by coacervation-phase separation method. It was concluded that proniosomes are a promising prolonged delivery system for flurbiprofen and have reasonably good stability characteristics[32].

CONCLUSIONS

Nanogels have achieved significant attention by the pharmaceutical technology society as drug targeting and delivery systems as well as therapeutic vehicles from a previous decade. Their biocompatibility, higher capacity of drug-loading, capacity to load both hydrophilic and hydrophobic drugs and the adjustable rheological properties makes it important drug delivery systems for different routes of administration. Dermal and transdermal drug delivery applications of nanogels have continuously increasing from last decade, due to the better mechanical and rheological properties compared to conventional semisolid dosage forms such as gels, pastes, creams and ointments, topical applications in dermatitis, wound healing, autoimmune diseases, ocular applications and treatment of systemic diseases. The use of dermal, transdermal nanogels of flurbiprofen can be elaborated with better modification, targeting moieties and biodegradable functionalized polymers. Finally, it is required to closely explore the fabrication methods of nanogels with biological molecules and/or in combination with active ingredients. In the conclusion, nanogels have all the desirable characteristics to act as potent carriers and offer an alternative solution for disease management.

CONFLICT OF INTERESTS

There are no Conflicts of interests.

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