

# Hydrogel Formulation a Suitable Alternative for Drug Delivery of 'NSAID's For Treatment of Inflammation

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**Abstract:** Hydrogel or aquagel is a cross-linked polymer chain network, it is water insoluble and may occur as colloidal gel, in which dispersion medium is water. NSAID's are non-steroidal drugs anti-inflammatory and analgesic agent used for treatment inflammation they also produce GIT irritation, liver and kidney damage when oral administered. Topical delivery of this drugs can be achieved by incorporating into the gel matrix for effective delivery of drugs, avoiding first pass metabolism and then increased local action in pain management and inflammation without gastric irritation.

**Keywords:** Hydrogel, NSAID's, COX-I/COX-II.

## Introduction of NSAID's:

The nonsteroidal anti-inflammatory drugs (NSAIDs) and antipyretic analgesics are a class of drugs which possess analgesic, antipyretic and anti-inflammatory actions. They act primarily on peripheral pain mechanisms. The NSAID's may be used for relieving mild to moderate associated with dysmenorrhoea, post extraction dental pain, episiotomy pain and soft tissue athletics injuries, in addition to their use as anti-inflammatory drugs. Their action in inflammatory state is to reduce joint swelling, pain, stiffness and increase the functional capacity of the joint. Important to note that aspirin should not take combined with NSAID's, because of it can decrease the blood level and activity of this non-aspirin drugs.

## Classification of NSAIDs

### A. Non selective COX inhibitors (traditional NSAIDs)

1. Salicylates: Aspirin
2. Propionic acid derivatives: Ibuprofen
3. Anthranilic acid derivatives: Mephenamic acid
4. Aryl-acetic acid derivatives: Diclofenac, Aceclofenac
5. Oxicam derivatives: Piroxicam, Tenoxicam
6. Pyrrole-pyrrole derivatives: Ketorolac
7. Indole derivatives: Indomethacin
8. Pyrazalone derivatives: Phenyl butazone, Oxyphenbutazone

### B. preferential COX-2 inhibitors

1. Nimesulid, Meloxicam, Nabumetone

### C. Selective Cox-2 inhibitors

1. Celecoxib, Etoricoxib, Parecoxib

### D. Analgesic Antipyretic with poor inflammatory action

1. Para aminophenol derivatives: paracetamol
2. Pyrazalone derivatives: Metamizole, propyphenazone
3. Benzoazocine derivatives: Nefopam

## Mechanism of action of NSAIDs

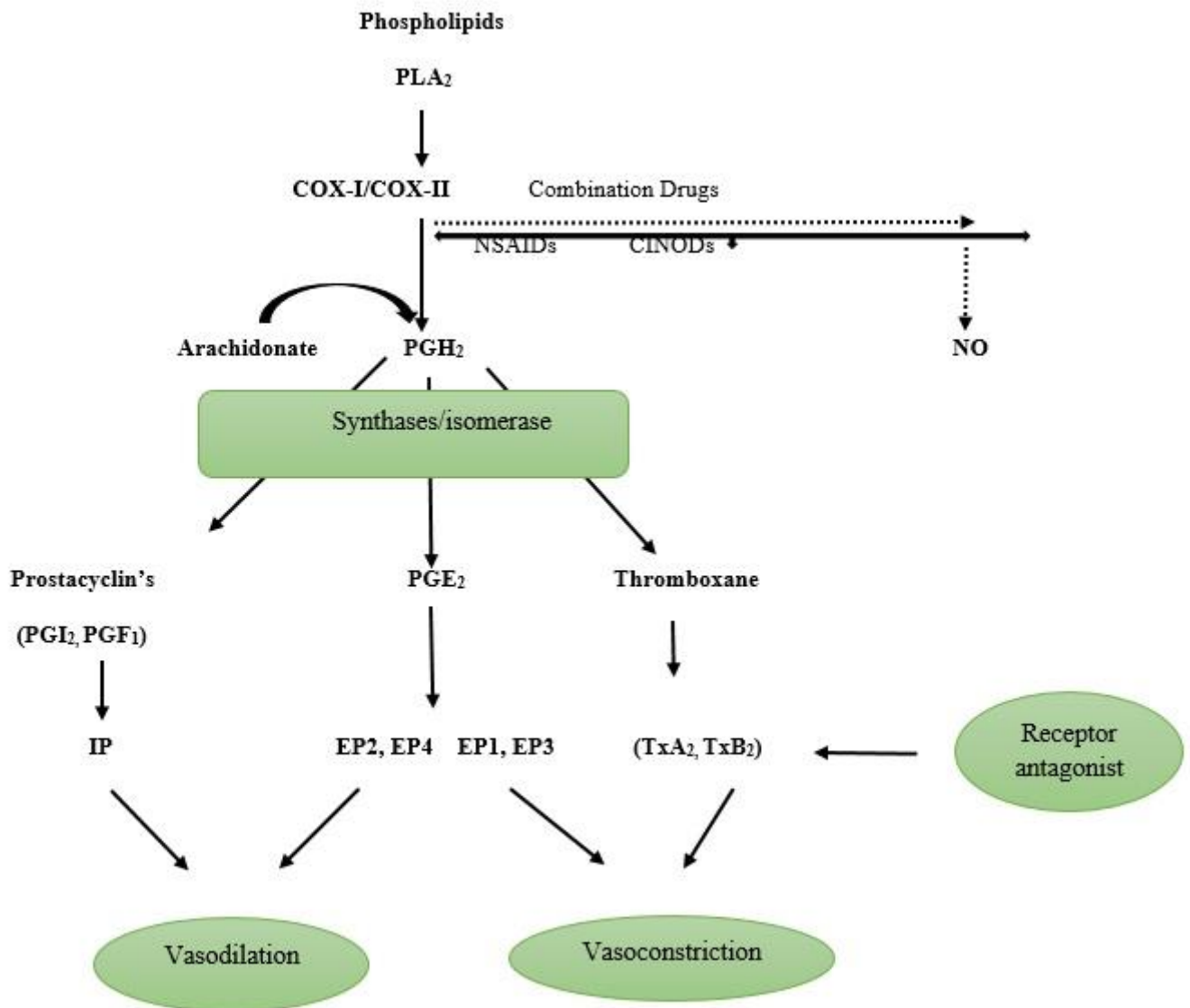
### Anti-inflammatory

- Inflammation is due to involvement of vasoactive, chemotactic and proliferative factors at different stage, and there are many targets for inflammatory action
- The most important mechanism of anti-inflammatory action of NSAIDs is considered to be inhibition of PG synthesis at the site of injury.
- The anti-inflammatory efficacy of many substances roughly correlates with their COX inhibitory potency. Nimesulide, on the other hand, is a strong anti-inflammatory but a poor COX inhibitor.
- PGs are only one of the mediators of inflammation; inhibition of COX does not depress the production of other mediators like LTs, PAF, cytokines etc.

**Mechanism of action COX -I Inhibitor:**

COXs come in a number of different isoforms. COX-I and COX-II have almost identical molecular structures, but their expression and function in time and space differ. COX-I is a physiologically important enzyme that is found in vascular endothelium, platelets, and epithelial cells of the renal tubules, among other cells. COX-I is responsible for the production of PG, which aids in the protection and preservation of the stomach mucosa.

COX enzymes are responsible for the production of PGs, which both prevent and cause vascular disease. Under physiological conditions, the COX and peroxidase activities of this enzyme are required for COX catalysis. The COX domain converts arachidonic acid (AA) to PGG<sub>2</sub>, while the peroxidase domain reduces PGG<sub>2</sub> to an unstable endoperoxide, PGH<sub>2</sub>. PGH<sub>2</sub> is transformed to thromboxane A<sub>2</sub> (TxA<sub>2</sub>), PGE<sub>2</sub>, and prostacyclin by the activity of particular downstream synthases (PGI<sub>2</sub>). TxA<sub>2</sub> is a platelet activator and vasoconstrictor produced from platelets, whereas PGE<sub>2</sub> is a proinflammatory chemical linked to atherosclerotic plaque instability. PGI<sub>2</sub> is a potent vasodilator and platelet activation and adhesion inhibitor produced by vascular endothelial cells. The efficacy of low-dose aspirin in decreasing cardiovascular disease is due to selective acetylation of COX-1 and platelet inhibition of TxA<sub>2</sub> generation while endothelial PGI<sub>2</sub> production is preserved. Endothelial COX-I from normal vessels more readily inhibited by NSAIDs than platelet COX-I, preventing endothelial PGI<sub>2</sub> formation but not platelet-derived TxA<sub>2</sub>. It may be that the apparent selectivity of a given COX inhibitor is determined by a target cell's peroxide content and arachidonate availability, rather than selectivity for a particular isoform.



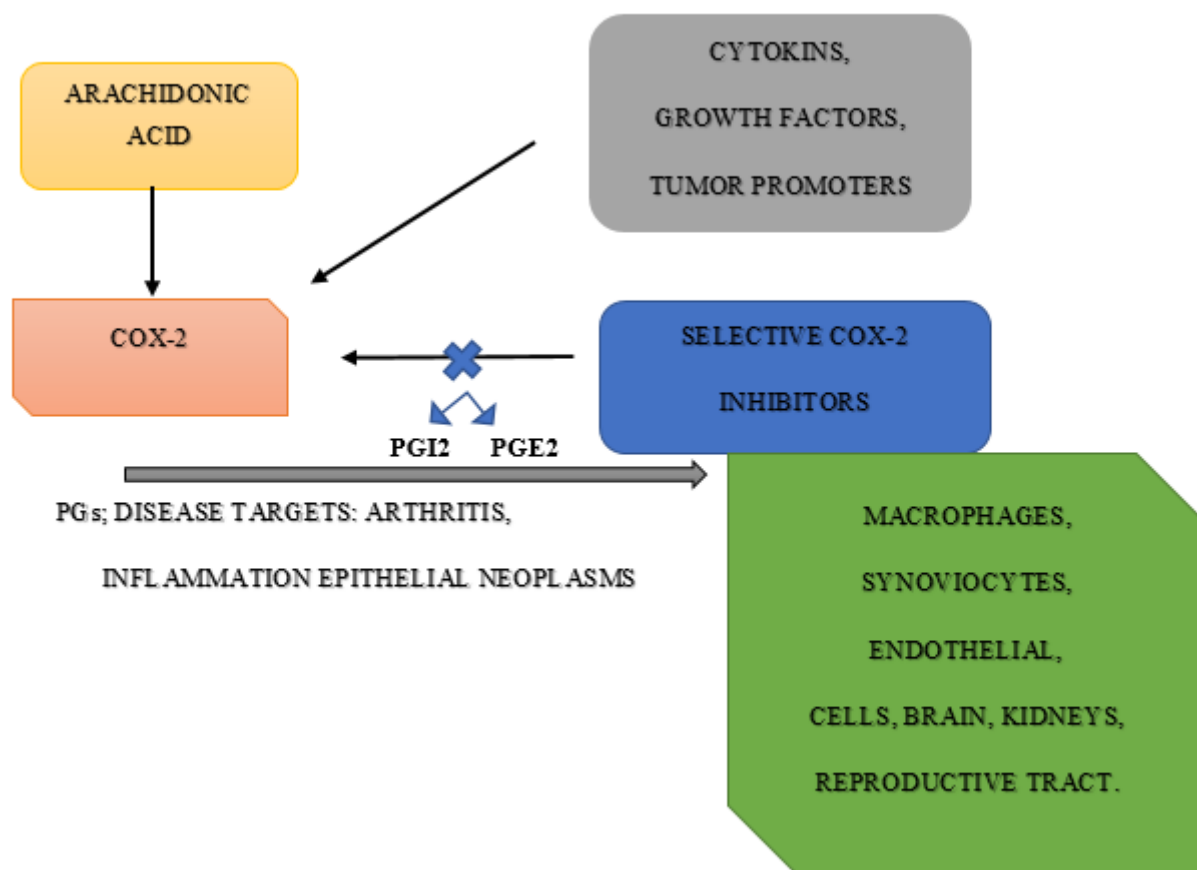
**Abbreviation:** PLA<sub>2</sub>-Phospholipid A<sub>2</sub>, PGH<sub>2</sub>- Prostaglandin -H<sub>2</sub>, TxA<sub>2</sub>-Thromboxane A<sub>2</sub>, TxB<sub>2</sub>-Thromboxane B<sub>2</sub>, PGI<sub>2</sub>- Prostacyclin I<sub>2</sub>, PGF<sub>2</sub>- Prostacyclin F<sub>2</sub>

**Adverse effect COX-I inhibitor:**

All NSAIDs produce stomach discomfort, mucosa (erosion/ulceration), and blood loss to some extent gastric irritation and inflammation is important factor to be considered during Inhibition of COX-I-mediated synthesis of gastroprotective PGs (PGE<sub>2</sub>, PGI<sub>2</sub>) is definitely involved, however local action causing H<sup>+</sup> ion back diffusion in the stomach mucosa also plays a role. Due to deficiency of PG reduction of mucus and bicarbonate ion reduction, acid secretion to increase, and mucosal ischaemia to occur. As

a result, NSAIDs increase while suppressing defence factors in the stomach mucosa, making them ulcerogenic. Paracetamol, a very weak COX inhibitor, has less stomach effects, whereas selective COX-II drugs are much safer.

**Mechanism of action COX -II Inhibitor:** COX-I and COX-II are two isoforms of cyclooxygenase that have been identified. While both isoforms catalyse the same processes, COX- I is essential enzyme in most cells. Once the cell is fully matured, the level of COX- I activity does not fluctuate substantially. COX-II, on the other hand, is inducible by cytokines, growth factors, and other stimuli during the inflammatory response, even though it is ordinarily present in little levels. COX-I eicosanoids are thought to have a role in physiological (housekeeping) processes such mucus secretion for gastric mucosa protection, haemostasis, and renal function maintenance, whereas COX-II eicosanoids cause inflammatory and other pathological alterations. However, specific areas of the kidney and brain constitutively express COX-II which may play physiological role.



COX-II, like COX-I, creates prostaglandins, however it is only found in parts of the body that are usually implicated in inflammation, not in the stomach. Inflammation is reduced when the COX-II enzyme is stopped; however, because the COX-II enzyme does not play a function in protecting the stomach or intestine, COX-II specific NSAIDs do not possess the same risk have stomach or intestine irritation. NSAIDs such as (aspirin, ibuprofen, naproxen,) all work by inhibiting both COX-I and COX-II enzymes. COX-II inhibitors selectively block the COX-II enzyme, which means they're less likely to cause stomach or intestine ulcers.

#### Adverse effect COX-II inhibitor:

NSAIDs, including COX-II inhibitors, may increase the risk of heart attacks, stroke, and related conditions. This risk may increase in patients with risk factors for heart disease and related conditions and with longer duration of use hence COX-II inhibitors even though found to have selective action rarely used for treatment.

#### Introduction of Hydrogel:

Hydrogels are the polymeric material which not dissolve in water but has the ability to swell and trap a large fraction of water in the network structure. The drug is mixed with an appropriate hydrophilic polymer and solvent the polymer slowly degrade and release the drug from the core. One of the most common and important pharmacological dose forms is topical gel formulation. This result in achievement of with minimum or no systemic side effects are utilised for long term treatment of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have long been used to treat rheumatoid arthritis and other inflammatory diseases. As most inflammatory disorders manifest themselves locally and near the body's surface, topical application of an NSAID to the inflamed area would have the benefit of delivering a drug directly to the affected site and producing its local effect. Along with prevention of gastrointestinal discomfort and reduce negative systemic effects. The majority of NSAIDs act by inhibition prostaglandin

production. They are powerful inhibitor of the enzyme cyclooxygenase COX-I and COX-II, which are involved in the biosynthesis NSAID's have of prostaglandins and has analgesic and anti-inflammatory properties. And are commonly used to treat rheumatoid arthritis, osteoarthritis, and other joint diseases.

#### Advantages of Hydrogel:

1. Degree of flexibility very similar to natural tissue.
2. Release of medicines or nutrients timely.
3. Biocompatible and biodegradable.
4. They have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as a result of such a change.
5. They possess good transport properties and easy to modification.

#### Preparation of Hydrogels

The three integral parts of hydrogel preparation are monomer, initiator, and cross-linker.

In general, hydrogels can be prepared from either synthetic polymers or natural polymers. These polymers can be cross-linked to form hydrogels in a number of ways: Linking polymer chains through chemical reaction; using ionizing radiation to generate main-chain free radicals which can recombine as cross-link junctions; and physical interactions such as entanglements, electrostatics, and crystallite formation.

Based on the methods of preparation, hydrogels may be classified as homopolymer, copolymer, semi-interpenetrating network (semi-IPN) and interpenetrating network (IPN).

#### Methods Of Preparation, Hydrogels Are Classified As:

- **Homo-polymer:** Homo-polymeric hydrogels are referred to polymer network derived from a single species of monomer, which is a basic structural unit comprising of any polymer network. Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique.
- **Copolymer:** Copolymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network.
- **Multipolymer Interpenetrating network:** Multipolymer Interpenetrating polymeric hydrogel (IPN), an important class of hydrogels, is made of two independent cross-linked synthetic and/or natural polymer component, contained in a network form. In semi-IPN hydrogel, one component is a cross-linked polymer and other component is a non-cross-linked polymer.

#### Classification:

Hydrogels can be classified considering different parameters like:

**Chemical Stimuli:** An increased interest in chemically crosslinked hydrogels relate to their favourable mechanical strength. Hydrogels of this type are initiated by covalent crosslinking of polymer units via a crosslinker agent by applying various strategies:

- (1) reaction of a low molecular weight crosslinker agent (e.g., diacid chlorides, isocyanates, glutaraldehyde, etc.
- (2) use of a crosslinked hybrid (polymer-polymer) network (HPN)
- (3) photopolymerization using a photosensitive crosslinker agent.
- (4) enzyme-catalyzed crosslinking processes.

(5) the use of interpenetrating polymer networks (IPNs), where two or more polymers in the network are formed in such a way that one polymer is crosslinked in the presence of the other. The crosslink points between polymer chains promote 3D network formation that affect the various physicochemical properties of the polymer (e.g., elasticity, viscosity, solubility, and stability) in an step-by-step in accordance with the crosslink density and the crystalline nature of the formed hydrogel structure.

E.g. pH responsive, Ionic strength responsive, solvent composition responsive, molecule responsive.

**Physical Stimuli:** Physical hydrogels are obtained through physical crosslinks that include chain entanglement, hydrogen bonding, hydrophobic interactions, ionic interactions, and crystallite formation. These physical bonds may not be permanent in nature; however, they provide sufficient strength to render the materials insoluble in aqueous media with the propensity to ingress large amounts of water. Formation of hydrogel composites can be achieved by combining a natural and a synthetic polymer (hybrid), or a natural and/or synthetic polymer(s) that include additives such as inorganic nanoparticles where various synthetic methods such as physical blending, graft polymerization, host-guest inclusion, and freeze-thawing are applied.

E.g., Temperature responsive, Electric field responsive, Magnetic field responsive, Light responsive, Pressure responsive.

#### DRUG RELEASE MECHANISMS FROM HYDROGEL DEVICES:

**1. Diffusion controlled:** It is most widely applicable mechanism relating to drug release. Fick's law of diffusion is commonly used in modelling this release

##### Types of diffusion –

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

- ii. Matrix system: For matrix system (drug uniformly dispersed throughout the matrix), unsteady state drug diffusion in a one dimensional slab- shaped matrix may be described using Fick's second law of diffusion

**2. Swelling controlled:** It occurs when diffusion of drug is faster than hydrogel swelling. In this condition the modelling 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

**3. Chemically controlled:** It describes molecular release as a result of processes within a delivery matrix. The most typical reactions are:

- i. Polymer chain cleavage via hydrolytic or enzymatic degradation.
- ii. Interpolymer network reactions that are reversible or irreversible

#### APPLICATIONS OF HYDROGELS:

**Perfume delivery:** Hydrogels' role in the process is based on their swelling properties, which can be used in materials "wherein the release of a perfume fragrance is initiated by dynamic swelling force of the polymer when the polymer is wetted.

**Cosmetics:** Some of the commercially available compound such as Fruit & Passion Boutiques Inc. Hydro Gel Face Masks. These organic polymeric gels' moisturising properties are combined with more complicated drug-delivery systems designed to release biomolecules like vitamin C or B3.

**Dental applications :** To overcome the limits of conventional therapy in inducing reparative dentin genesis, pulp regeneration therapy is critical. In addition, a regulated release of FGF-2 from gelatin hydrogels resulted in neovascularization and regeneration of numerous tissues, including bone and periodontal tissues. [FGF-2] (fibroblast growth factor-2).

**Wound healing applications:** Cartilage present in the modified polysaccharide is used in hydrogel to treat cartilage defects. for example, combination of gelatin and poly vinyl alcohol (PVA) are used as blood coagulants.

**Hydrogel Implants:** Used to treat the symptoms of advanced prostate cancer, such as erectile dysfunction

1. Histrelin acetate is a non-peptide version of GnRH( Gonadotropin releasing hormone) that occurs naturally.
2. Retinoplastoma, the most common primary malignant intraocular tumour in children, is treated with hydrogel implants. Retinoplastoma arises from retinal stem cells.

#### Contact Lenses

E.g. Silicon hydrogel contact lenses: these are advance soft lenses that allows more oxygen to pass through the lens to cornea than regular soft contact lenses.

**Rectal delivery:** A problem 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, which frequently leads to a variation in the bioavailability of certain drugs. Hydrogels exhibit bio adhesive properties are used for rectal drug delivery. e. g Xyloglucan gel with a thermal gelling property as matrices for drug delivery.

**Transdermal drug delivery:** Transdermal drug delivery system have ability to deliver drugs for an extended period of time at a constant rate, it has advantage that drug delivery can interrupted if required ,it also bypass hepatic first-pass metabolism. Furthermore, because of their high water content, swollen hydrogels can provide a more comfortable feeling to the skin than conventional hydrogels.

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