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# MODIFIED RELEASE HYDROGELS OF IBUPROFEN FOR ORAL DRUG DELIVERY: AN OVERVIEW

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**Abstract:**

*The Present study for hydrogels are specifically on the pH sensitive hydrogels for oral drug delivery system. Hydrogels are able to improve oral delivery of several therapeutic agents established by various in-vitro methodologies.*

*Hydrogels are basically cross-linked polymers with hydrophilic nature & consist of acidic, basic, or neutral monomers which are able to swallow large amounts of water. Due to hydrophilic nature of polymer chains, hydrogels will engross water to swell in the presence of abundant water. The swelling properties of hydrogels are due to elasticity of the network, presence of hydrophilic functional groups (such as -COOH,-OH, -SO3H,-CONH2) in the polymer chains. The physiochemical properties, swelling studies and gelling capacity significantly govern the selection of hydrogel component.*

*The development of hydrogels has received substantial consideration over past few years. This interest has been flickered by the advantages these advanced delivery system possess, which include modified, sustained and prolonged action, reduced dose, less side-effects, better drug utilization, better patient compliance, site specific drug targeting, protection of mucosa from irritation, prevention from general first pass metabolism .Non-steroidal anti-inflammatory drugs are mostly prescribed for the patients suffering from rheumatoid arthritis, osteoarthritis, soft tissue injuries, traumatic arthritis and other inflammatory disorders etc.*

*Ibuprofen is non-steroidal anti-inflammatory drug (NSAID) which is anti-inflammatory, antipyretic and analgesic properties. It is chemically "2-(4-iso-butylphenyl) - propanoic acid" and is poorly soluble in water. It is mostly administered through oral route and is rapidly absorbed to reach its maximal plasma concentration within 2 hrs. It has a short biological half-life period of 2 hours, which means that numerous doses are required to maintain the therapeutic efficacy level over extended period of time. Frequent administrations of drug cause GIT side effects such as gastric ulceration, perforation and bleeding.*

*pH sensitive hydrogel of ibuprofen attain a more modified & sustain release of the drug for long periods of time interval. Hence we can minimize the required dose and toxicity of the drug.*

**Keywords:** *Hydrogels, Polymer, NSAID, Ibuprofen & pH sensitive.*

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## INTRODUCTION:

Drugs which are easily absorbed from gastrointestinal tract and have short half-lives are eliminated rapidly from systemic circulation. So frequent dosing of these drugs after some time is required to achieve suitable therapeutic activity. In order to avoid this limitation, the development of oral sustained-controlled release or modified release formulations is a challenge to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time of interval. After oral administration, such a modified release drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be delivered continuously to its absorption sites in the gastrointestinal tract. [1]

So to formulate an orally administered sustained or modified release dosage form, it is desirable to achieve prolong gastric residence time by the drug delivery system. Extended gastric retention improves bioavailability of drug, increases the duration of drug release, reduces drug waste, and improves the solubility of drug that are less soluble in a high pH environment [2]. For this prolong gastric residence time few drug delivery approaches are being designed and developed, which comprises:

- High density (sinking) systems that is retained in the bottom of the stomach [3].
- Low density (floating) systems that causes resistance in gastric fluid [4,5,6]
- Mucoadhesive systems that causes bio adhesion to mucosa of stomach [7].
- Magnetic systems [8]
- Superporous hydrogel systems [9]

**Stimuli reactive polymers:**

Polymers which can reversibly swell or shrink in response to external conditions, such as pH, temperature, composition of solvent and electrical field are of great interest, especially in bio-medical and pharmaceutical technology. PH-sensitive hydrogels that change their properties by depend upon changes in pH have been extensively investigated for the development of novel drug delivery systems [10]. These kind of polymers can be prepared by the integration of one or more weakly acidic or basic monomers such as carboxylic acids (acrylic acid, methacrylic acid) and primary or substituted amines (N, N-dimethylaminoethyl methacrylate). Acidic gels are measured as good applicants for oral colon specific delivery of drugs that are susceptible to enzymatic degradation in the upper part of gastrointestinal tract. Although these systems have slow equilibrium degree of swelling in acidic medium of stomach & their swelling degree increases as it passes down to the GIT due to an increase in pH. Therefore pH-sensitive drug delivery protects the drug substances from acid of stomach and releases the whole drug in the colon [11].

pH sensitive swelling is accredited to ionic hydrogels having some charge carrying pendant groups and which is controlled by factors like ionic charge, pKa or pKb values of ionizable groups, degree of ionization, hydrophilicity, concentration of polymer and pH of the swelling medium.

pH and nature of pendant groups are the key factors for controlling the properties of pH sensitive hydrogels between all these factors . Cationic hydrogels swell at low pH (acidic medium) like chitosan and polyethylene imine due to protonation of amino/imine groups. Due to protonation charged moieties on the polymer chains cause repulsion among groups and hence are responsible for swelling [12].

**Modified or sustained-release drug delivery systems:**

Modified or Sustained release dosage forms are prepared to release a drug content at a predetermined rate. These formulations maintain a constant level of drug for a specific period of time with less side effects. In recent era, we are focus on the development of modified or sustained-release drug delivery systems. Basis of modified or sustained-release drug delivery systems. Optimization of biopharmaceutical, pharmacokinetic, and pharmacodynamic properties of a drug in such a way that its efficacy is maximized, side-effects are reduced, in the minimum possible time by using smallest quantity of drug administered by the most suitable route. Modified or sustained-release products are designed to pass the blood level of a drug immediately to therapeutic concentrations by means of a preliminary dose portion and then sustain this level for a certain predetermined time interval with the maintenance portion. Modified or sustained-release of drugs in GIT following oral administration is not affected by the absorption process. Main goal of modified or sustained-release dosage forms is the improvement of drug therapy evaluated by the relationship between advantages and disadvantages of the use of modified or sustained-release systems [13].

**A) Advantages**

- Patient Compliance
- **Reduced 'see- saw' fluctuation**
    - Reduced total dose
    - Improved efficiency in treatment

**B) Challenges [13]**

- Dose dumping
- **Limited choice of selecting desired dose in the unit:**
- **Poor In Vitro – In Vivo correlation**
- Patient variation

**C) Criteria to be met by drug proposed to be formulated in Modified or Sustained release dosage forms [13]:**

**a) Desirable half-life of drug:**

The half-life of a drug means by index of its residence time in the body. If any drug has a short half-life (less than 2 hours), dosage form may contain a excessively huge quantity of the drug. Also drug with elimination half-life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from and Modified or Sustained release dosage forms is generally not necessary in such cases. Drug should have half-life of three to four hours ideally.eg. Ibuprofen.

**b) High therapeutic index of drug:**

Drugs which has low therapeutic index are not suitable for incorporation in Modified or Sustained release formulations. If this system fails inside the body, dose dumping may occur, which leading to mortalities eg. Digitoxin.

**c) Small dose:**

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for SR is seriously undetermined. This is chiefly because the size of a unit dose Modified or Sustained release formulations would become too big to administer without difficulty.

**d) Desirable absorption and solubility characteristics of drug**:

Absorption of poorly water soluble drug is often depends upon the dissolution. Incorporating such compounds into Modified or Sustained release formulations is therefore impractical and may reduce overall absorption efficiency.

**e) Desirable absorption window of drug:**

Some drugs when administered through oral route are absorbed only from a specific part of gastrointestinal tract. This part is called as the *'absorption window'*. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as Modified or Sustained release formulations dosage form are inappropriate.

**f) First pass clearance:**

As discussed earlier in disadvantages of Modified or Sustained release delivery system, delivery of the drug to the body in desired concentrations is seriously destitute in case of drugs undergoing extensive first pass metabolism, when administered in Modified or Sustained release forms

**Rheumatoid arthritis:**

Rheumatoid Arthritis is a disease which is chronic in nature. Inflammation of synovial membrane of multiple joints is its main manifestation [14]. Mainly Cartilage damage, bone erosions and subsequent changes in joint integrity are characteristics of the disease mainly caused by the synovial inflammation [15]. This disease is 1% of world's population. It is commonly in women than in men, with women to men ratio of 3 to 1. Rheumatoid Arthritis may be in any age, but the highest onset for the women is from fourth to fifth decades and for men is at sixth to eighth decades [14]. Reason of Rheumatoid Arthritis is still unknown but autoimmunity, genetic susceptibility and environment have very important roles in development, progression and chronicity of this disease [13]. Rheumatoid Arthritis which is untreated cause joint destruction which is followed by disability and shortened life of joints. The joint pathologic conclusions include chronic synovitis with formation of pannus, which is an inflammatory pathologic formation surrounding articular cartilage. Pannus also erodes bone, cartilage, tendons and ligaments near to joints [14].

**a) Diagnosis:**

For treatment of Rheumatoid Arthritis no test is specified. However two-thirds of adults who have Rheumatoid Arthritis, autoantibodies are found which are reactive with the Fc portion of IgG. Therefore, these rheumatoid factors are used to evaluate patients. [15].

**b) Treatment:**

For the treatment of Rheumatoid Arthritis, the therapies aim decreasing pain and inflammation, preservation of function and prevention of further irregularity. Since the main cause of Rheumatoid Arthritis is still unknown therapy remains somewhat experimental. Therapeutic applications are not remedial; they are comforting, namely focused on relieving the symptoms of Rheumatoid Arthritis [15].Non-steroidal anti-inflammatory drugs (NSAIDs) help to relieve symptoms in Rheumatoid

Arthritis. However, NSAIDs do neither protect from erosions neither change progression. Although, using NSAIDs may cause side effects such as gastric ulceration, perforation and gastrointestinal hemorrhage. NSAIDs may also cause renal toxicity. Some NSAIDs interact with function of platelet and delay bleeding time. Most commonly used NSAID is Ibuprofen. Low dose corticosteroids produce a rapid anti-inflammatory effect in Rheumatoid Arthritis [14]. Progression of bone erosions can be delayed by low dose glucocorticoid therapy. In some patients monthly pulses with high-dose glucocorticoids may be useful and may fasten the response when therapy with a disease modifying anti rheumatoid drug (DMARD) is initiated [15]. Until the slower acting disease modifying anti rheumatoid drug effect, low dose corticosteroids are often used in order to decrease disease activity or they are used as adjunctive therapy for active disease which persists despite treatment with disease modifying anti rheumatoid drug. Also patients who use corticosteroids for long term should take measures to prevent osteoporosis, which is a bone disease [14].

**Research envisioned:**

Ibuprofen is most widely prescribed NSAID for relieving symptoms of Rheumatoid Arthritis. It is a non-steroidal anti-inflammatory drug (NSAID) with well-known anti-inflammatory, antipyretic and analgesic properties. It is chemically 2-(4-iso-butylphenyl) - propanoic acid and which is poorly soluble in water. Most commonly it is administered through oral route and is rapidly absorbed to reach its maximal plasma concentration within 2 hrs. It has a short biological half-life of 2 hrs. That means that frequent doses are required to maintain the concentration of drug over extended time periods. Regular administration cause gastrointestinal side effects such as gastric ulceration, bleeding and perforation.

These problems may be solved by the preparation of pH sensitive hydrogel. These pH sensitive Hydrogels, in which drugs content are delivered by chemically or biologically induced cleavage of the covalent bonds, allows one to achieve a more constant release of the drug for long periods of time interval. pH sensitive Hydrogel of Ibuprofen provide relief over a long period of time by single dose administration as well as preventing the dose related side effects as frequency of drug administration is reduced. By designing the pH sensitive hydrogel, drug can be delivered in a controlled pattern. Ibuprofen hydrogel can increase the effective drug duration & reduce the side effects of Ibuprofen making its solubility and therapeutic efficiency better compared to conventional delivery system. Production of pH sensitive hydrogel is cheaper, thus lowering investment and manufacturing costs.

**Novel drug delivery systems for oral route:**

Oral route of administration is the most common route due to flexibility in dosage form, design and patient compliance. But we know that various pHs inside the body which encounter drug during its transit, gastrointestinal motility, the enzyme system and its influence the drug and the dosage form.

The idea of Hydrogels began with the need to prevent degradation during absorption to achieve the therapeutic blood levels over a prolonged period. Therefore, a primary objective of using oral hydrogels would be achieved by obtaining a substantial increase in residence time of the drug for drug effect and to permit twice daily dose [16].

**Hydrogels:**

Hydrogels are basically cross-linked polymers with a network structure consisting of acidic, basic, or neutral monomers which are able to swallow large amounts of water. Due to hydrophilic nature of polymer chains, hydrogels will absorb water to swell in the presence of abundant water. Swelling properties of hydrogels are basically related to the elasticity of the network, presence of hydrophilic functional groups (like -OH, -COOH, -CONH2, -SO3H), the extent of cross-linking, and porosity of the polymer [17].

These kind of unique physical properties of hydrogels have motivated particular interest in their use in drug delivery applications. Due to their highly porous structure they 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 [18].

In fact such slow swelling is beneficial for many applications, there are many situations where a fast swelling of the polymer is more necessary. Therefore hydrogels of new generation, which swell and absorb water very rapidly, has been developed. Examples of such hydrogels are super porous hydrogels and super porous hydrogels composites which swell to equilibrium size in a small period of time [19].

Super porous hydrogel is a three-dimensional network of a hydrophilic polymer that absorbs a large amount of water in a very small period of time due to the occurrence of interconnected microscopic pores. Super porous hydrogels and super porous hydrogels composite can be used in order to make formulation appropriate for intestinal delivery of drugs. When

that formulation will be delivered into the intestine, it will swell in the environmental pH before finally releasing the drug. After releasing the drug in controlled manner, the polymers become super hydrated and are easily broken down by the peristaltic force of the gut and afterwards excreted as fine particles. pH sensitive systems are basically controlled drug delivery systems, which are intended to deliver drugs at predetermined rates and have been used to overcome the inadequacies of conventional drug formulations.[20]

**Mechanism of drug release in ph sensitive hydrogels:**

Many release mechanisms of entrapped/encapsulated drug in hydrogels such as diffusion controlled, swelling controlled, and chemically controlled mechanisms. The Porosity of the hydrogels is linked to the diffusion coefficient of the hydrogels if the molecular dimensions of the drug molecules are much smaller than the pore size of porous hydrogels. When pore size in the hydrogels and the size of the drug molecules are similar, the release of the drug molecules is delayed by the cross-linked polymer chains. So in results the diffusion coefficient is decreased. In other case, if the rate of drug release exceeds the rate of swelling then drug release follows a swelling controlled mechanism and absorption of water molecules followed by desorption of the drug. Resistance of a dry polymer hydrogels to undergo a polymers change in shape and increase in volume during the hydration process controls the rate of drug release which in turn can be controlled by the composition of the hydrogels and the cross-linking density. Free spaces between intermolecular chains allow the solvent to penetrate the surface of the hydrogels when they are in contact with water or certain physiological solutions. This swelling process is convoyed by desorption of the drug and its controlled release. So the drug release is due to the reactions of hydrogels (hydrolytic or enzymatic degradation of polymer chains) is said to follow a chemically controlled mechanism. The general mechanism of pH dependent s welling as well as drug release is shown in Figure 1

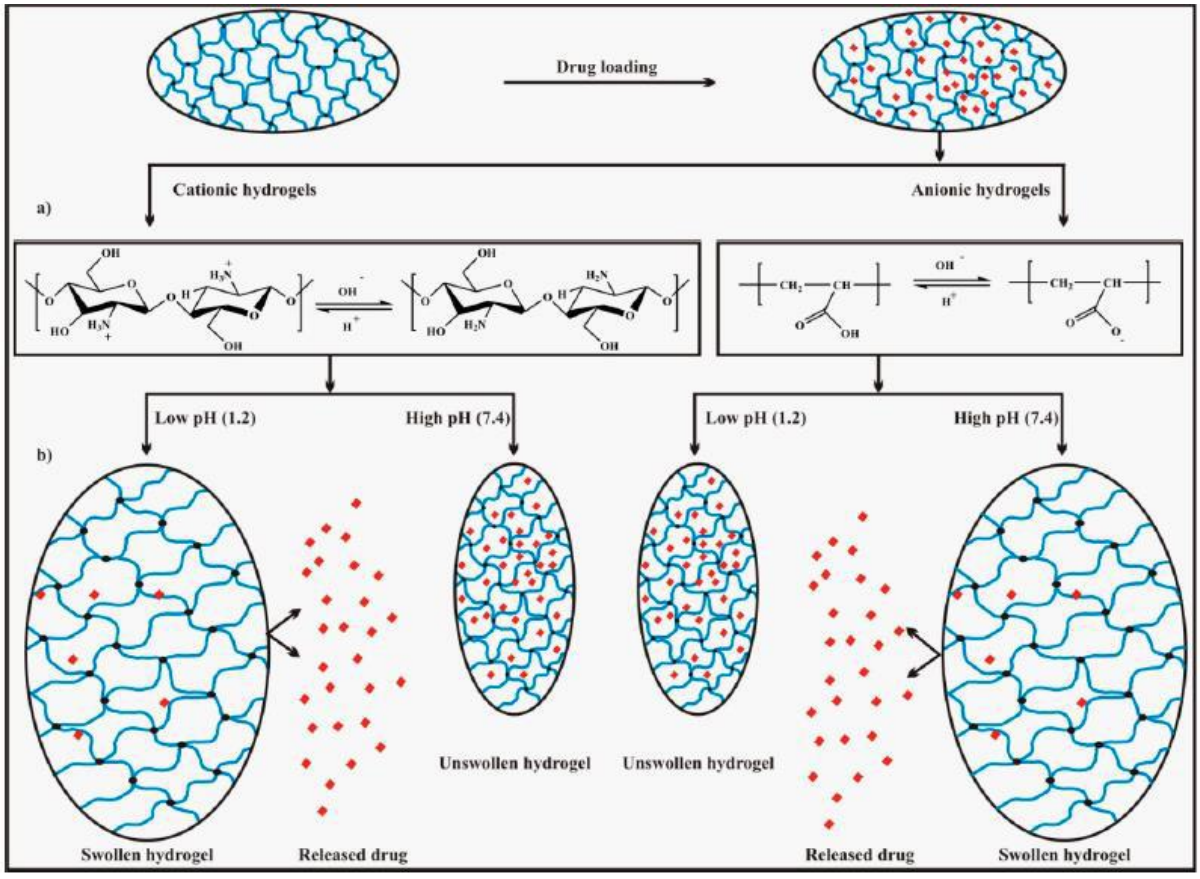


**Figure 1** (a) pH dependent ionization of specific acidic or basic functional groups on hydrogel chains responsible for the swelling of hydrogel, (b) pH dependent swelling and drug release mechanism of hydrogels [12].

**Classification of hydrogels [21]:**
In a general view, hydrogels can be classified based on a variety of characteristics, including:
**Nature of side groups:**

- Neutra
- Ionic
- Mechanical and structural features:
- Affine
- Phantom

**Method of preparation**:

- Homo- polymer
- Co-polymer
- Physical structure
- Amorphous
- Semicrystalline
- Hydrogen bonded
- Supermolecular
- Hydrocollodial

**Advantages of hydrogels:**
Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of swallowing large amounts of water or biological fluids may offer several advantages:
Sustained and prolonged action in comparison to conventional drug delivery systems

- Decreased dose to be administration.
- Less side-effects.
- Drug loss is prevented by extensive first pass metabolism.
- Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body functions or diseases.

**A) Methods to produce hydrogels**
In hydrogels cross-linked networks of synthetic polymers such as polyethylene oxide (PEO), polyvinyl pyrollidone (PVP), polylactic acid (PLA), polyacrylic acid (PAA), polymethacrylate (PMA), polyethylene glycol (PEG), or natural biopolymers such as alginate, chitosan, carrageenan, hyaluronan, and carboxymethyl cellulose (CMC) have been testified. The various preparation techniques are:

- Physical crosslinking
- Chemical cross-linking
- Grafting polymerization
- Radiation cross-linking

Such modifications in hydrogels can improve the mechanical properties and viscoelasticity for applications in biomedical and pharmaceutical fields. In this review article only first two techniques are discussed in detail.

**Physical cross-linking:**
There has been an increased interest in physical or reversible gels due to relative simplicity of production and the advantage of not using cross-linking agents during preparation. Due to this, these agents affect the integrity of substances to be entrapped (e.g. cell, proteins, etc.) as well as the need for their removal before application. Mainly Careful selection of hydrocolloid type, concentration and pH can lead to the formation of a broad range of gel surfaces and is currently an area receiving considerable attention, particularly in the food industry. Various methods reported in literature to obtain physically cross-linked hydrogels are:

- Heating/cooling a polymer solution

- Ionic interaction
- Complex coacervation
- H-bonding
- Maturation (heat induced aggregation)

**a) Heating/cooling a polymer solution**
These physically cross-linked gels are designed when cooling hot solutions of gelatin or carrageenan. This gel formation is due to helix-formation, association of the helices and forming junction zones. The Carrageenan in hot solution above the melting transition temperature is present as random coil conformation. After cooling it transforms to rigid helical rods. Due to presence of salt (K+, Na+, etc.), screening of repulsion of sulphonic group (SO3–), double elices further aggregate to form stable gels. In few cases, hydrogel can also be formed by simply warming the polymer solutions that causes the block copolymerization. Examples are polyethylene oxide-polypropylene oxide, polyethylene glycol-polylactic acid hydrogel [17].

**b) Ionic interaction:**
These can be cross-linked by the addition of di- or tri-valent counterions. This method motivates the principle of gelling a polyelectrolyte solution (e.g. Na+ alginate-) with a multivalent ion of opposite charges (e.g. Ca2+ + 2Cl-). Examples are chitosan-polylysine [14], chitosan-glycerol phosphate salt [15], chitosan-dextran hydrogels [12].

**c) Complex coacervation:**

These gels can be designed by mixing of a polyanion with a polycation. Principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on the concentration and pH of the solutions. Example is coacervating polyanionic xanthan with polycationic chitosan [13].

**d) H-bonding:**

These hydrogel can be obtained by lowering the pH of aqueous solution of polymers carrying carboxyl groups. Example of such hydrogel is a hydrogen-bound CMC (carboxymethyl cellulose) network designed by dissolving CMC into 0.1M HCl [`18]. The mechanism involves replacing the sodium in CMC with hydrogen in the acid solution to promote hydrogen bonding. The hydrogen bonds induce a decrease of CMC solubility in water and result in the development of an elastic hydrogel. Carboxymethylated chitosan (CM-chitosan) hydrogels can also prepared by cross-linking in the presence of acids or polyfunctional monomers. Another example is polyacrylic acid and polyethylene oxide (PEO-PAAc) based hydrogel prepared by lowering the pH to form H-bonded gel in their aqueous solution [21].

**e) Maturation:**

Acacia gum is predominately carbohydrate but contain 2-3% protein as an integral part of its structure. There are Three major fractions with different molecular weights and protein content have been recognized following fractionation by hydrophobic interaction chromatography with different molecular weights and protein content.They are arabinogalactan protein (AGP), arabinogalactan (AG) and glycoprotein (GP). Due to Aggregation of the proteinaceous components, induced by heat treatment, increases the molecular weight and subsequently produces a hydrogel form with enhanced mechanical properties and water binding capability. Maturing of these gum leads to transmission of the protein associated with the lower molecular weight components to give larger concentrations of high molecular weight fraction

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