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Swellable hydrogels for controlled drug delivery: An updated review

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Abstract

Hydrogel products are comprised of group of polymeric materials and the hydrophilic structure of these products make them capable of holding large amounts of water in their three-dimensional networks. Extensive employment of these products in a number of industrial and environmental areas of application is considered to be of prime importance. As expected, natural hydrogels were gradually replaced by synthetic types due to their higher water absorption capacity, long service life, and wide varieties of raw chemical resources. Literature on this subject was found to be expanding, especially in the scientific areas of research. However, a number of publications and technical reports dealing with hydrogel products from the engineering points of view were examined to overview technological aspects covering this growing multidisciplinary field of research. The primary objective of this article is to review the literature concerning classification of hydrogels on different bases, physical and chemical characteristics of these products, and technical feasibility of their utilization. It also involved technologies adopted for hydrogel production together with process design implications, block diagrams, and optimized conditions of the preparation process. An innovated category of recent generations of hydrogel materials was also presented in some details.

Keywords: Hydrogels; hydrophilic and hydrophobic monomers; metabolites; polymer networks.

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1. Introduction

The materials of interest in this brief review are primarily hydrogels, which are polymer networks extensively swollen with water. Hydrophilic gels that are usually referred to as hydrogels are networks of polymer chains that are sometimes found as colloidal gels in which water is the dispersion medium [1]. Researchers, over the years, have defined hydrogels in many different ways. The most common of these is that hydrogel is a water-swollen, and cross-linked polymeric network produced by the simple reaction of one or more monomers. Another definition is that it is a polymeric material that exhibits the ability to swell and retain a significant fraction of water within its structure, but will not dissolve in water. Hydrogels have received considerable attention in the past 50 years, due to their exceptional promise in wide range of applications [2–4]. Also, it is stable in the conditions of sharp and strong fluctuations of temperatures [5]. They possess also a degree of flexibility very similar to natural tissue due to their large water content. Hydrogels may be synthesized in a number of "classical" chemical ways. The polymer engineer can design and synthesize polymer networks with molecular-scale control over structure such as cross-linking density and with tailored properties, such as biodegradation, mechanical strength, and chemical and biological response to stimuli [6].

2. Classification of Hydrogel Products:

The hydrogel products can be classified on different bases as detailed below:

- Classification based on source: Hydrogels can be classified into two groups based on their natural or synthetic origins [7].
- Classification according to polymeric composition:

a. Homopolymeric hydrogels are referred to polymer network derived from a single species of monomer, which is a basic structural unit comprising of any polymer network [8].

b. 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 [9].
c. 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 semiIPN hydrogel, one component is a cross-linked polymer and other component is a non-cross-linked polymer [10,11].

Classification based on configuration:

The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows:

a. Amorphous (non-crystalline).
b. Semicrystalline: A complex mixture of amorphous and crystalline phases.
c. Crystalline.

Classification based on type of cross-linking: Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-link junctions. Chemically cross-linked networks have permanent junctions, while physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions [11].

Classification based on physical appearance:

Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process.

3. Effect of Environmental Conditions on Hydrogels:

As mentioned above, hydrogels as three-dimensional crosslinked hydrophilic polymer networks are capable of swelling or de-swelling reversibly in water and retaining large volume of liquid in swollen state. Hydrogels can be designed with controllable responses as to shrink or expand with changes in external environmental conditions. They may perform dramatic volume transition in response to a variety of physical and chemical stimuli, where the physical stimuli include temperature, electric or magnetic field, light, pressure, and sound, while the chemical stimuli include pH, solvent composition, ionic strength, and molecular species (Fig. 1).

The extent of swelling or de-swelling in response to the changes in the external environment of the hydrogel could be so drastic that the phenomenon is referred to as volume collapse or phase transition [12].

4. Utilization of Hydrogel Products:

With the establishment of the first synthetic hydrogels by Wichterle and Lim in 1954 [13], the hydrogel technologies may be applied to hygienic products [14], agriculture [15], drug delivery systems [14,16], sealing [14], coal dewatering [17], artificial snow [14], food additives [18], pharmaceuticals [19], biomedical applications [20,21] tissue engineering and regenerative medicines [22,23], diagnostics [24], wound dressing [25], separation of biomolecules or cells [26] and barrier materials to regulate biological adhesions [27], and Biosensor [28]. Acrylamide is a main component employed for preparation of agricultural hydrogel products [14].

5. HYDROGEL PREPARATION TECHNOLOGIES:

Hydrogels are usually prepared from polar monomers. According to their starting materials, they can be divided into natural polymer hydrogels, synthetic polymer hydrogels, and combinations of the two classes. These include nonreacted monomer, initiators, cross-linkers, and unwanted products produced via side reactions (Fig. 2). From a preparative point of view, they can be obtained by graft polymerization, cross-linking polymerization, networks formation of water-soluble polymer, and radiation cross-linking, etc. There are many types of hydrogels; mostly, they are lightly cross-linked copolymers of acrylate and acrylic acid, and grafted starch-acrylic acid polymers prepared by inversesuspension, emulsion polymerization, and solution polymerization. The polymerization techniques have been described below.

Bulk polymerization:

The choice of a suitable initiator depends upon the type of monomers and solvents being used. The polymerized hydrogel may be produced in a wide variety of forms including films and membranes, rods, particles and emulsions.

However, the viscosity of reaction increases markedly with the conversion which generates the heat during polymerization. These problems can be avoided by controlling the reaction at low conversions [33].

Solution polymerization/cross-linking:

In solution copolymerization/cross-linking reactions, the ionic or neutral monomers are mixed with the multifunctional crosslinking agent. The polymerization is initiated thermally by UV-irradiation or by a redox initiator system. The presence of solvent serving as a heat sink is the major advantage of the solution polymerization over the bulk polymerization. The prepared hydrogels need to be washed with distilled water to remove the monomers, oligomers, cross-linking agent, the initiator, the soluble and extractable polymer, and other impurities. Phase separation occurs and the heterogeneous hydrogel is formed when the amount of water during polymerization is more than the water content corresponding to the equilibrium swelling. Typical solvents used for solution polymerization of hydrogels include water, ethanol, water–ethanol mixtures, and benzyl alcohol. The

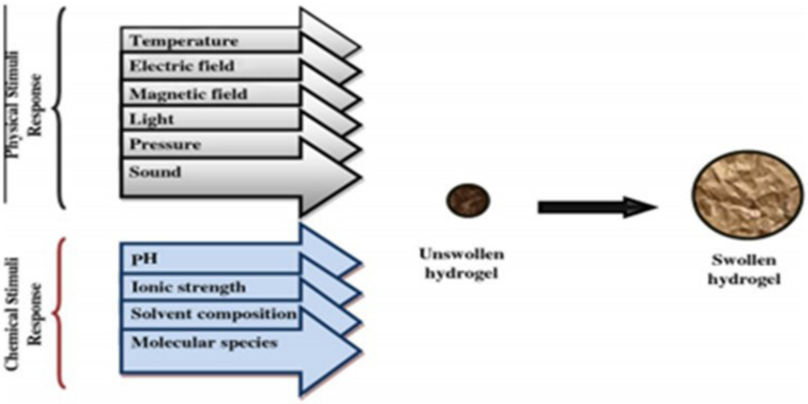

Fig 1. Stimuli response swelling hydrogel

synthesis solvent may then be removed after formation of the gel by swelling the hydrogels in water.

Suspension polymerization or inverse-suspension polymerization:

Dispersion polymerization is an advantageous method since the products are obtained as powder or microspheres (beads), and thus, grinding is not required. Since water-in-oil (W/O) process is chosen instead of the more common oil-in-water (O/W), the polymerization is referred to as ''Inverse Suspension''. In this technique, the monomers and initiator are dispersed in the hydrocarbon phase as a homogenous mixture. The viscosity of the monomer solution, agitation speed, rotor design, and dispersant type mainly governs the resin particle size and shape [22]. Some detailed discussions on hetero-phase polymerizations have already been published [23,24]. The dispersion is thermodynamically unstable and requires both continuous agitation and addition of a low hydrophilic–lipophilic-balance (HLB) suspending agent (fig.4).

Preparation and process optimization of hydrogel by solution polymerization technique:

Free-radical initiated polymerization of acrylic acid (AA) and its salts, with a cross-linker, is frequently used for hydrogel preparation. The carboxylic acid groups of the product arepartially neutralized before or after the polymerization step. Initiation is most often carried out chemically with free-radical azo or peroxide thermal dissociative species or by reaction of a reducing agent with an oxidizing agent (redox system) [31]. The solution polymerization of AA and/or its salts with a water-soluble cross-linker, e.g., methylene bis-acrylamide (MBA) in an aqueous solution is a straight forward process. The reactants are dissolved in water at desired concentrations, usually about 10–70%.

The AA monomer is inhibited by methoxyhydroquinone (MHC) to prevent spontaneous polymerization during storage. In industrial production, the inhibitor is not usually removed due to some technical reasons [15]. Meanwhile, AA is converted to an undesired dimer that must be removed or minimized. The minimization of acrylic acid dimer (DAA) in the monomer is important due to its indirect adverse effects on the final product specifications, typically soluble fraction and the residual monomer. As soon as AA is produced, diacrylic acid is formed spontaneously in the bulk of AA reaction. Since temperature, water content, and pH have impact on the rate of DAA formation, the rate can be minimized by controlling the temperature of stored monomer and excluding the moisture [22].

Preparation and process optimization of hydrogel beads using a suspension polymerization technique:

The inverse-suspension is a highly flexible and versatile technique to produce hydrogels with high swelling ability and fast absorption kinetics [19]. A water-soluble initiator shows a better efficiency than the oil-soluble type. When the initiator dissolves in the dispersed (aqueous) phase, each particle contains all the reactive species. The resulting microspherical particles are easily removed by filtration or centrifugation from the continuous organic phase.

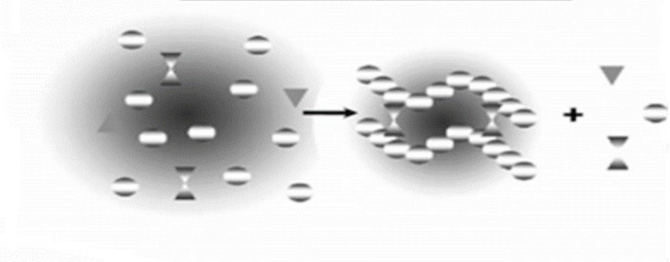

Fig 2. Schematic diagram of hydrogel preparation.

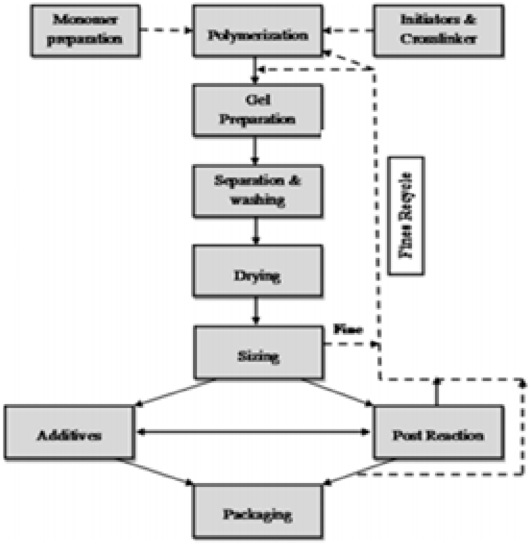

Fig. 3. Hydrogel preparation block diagram (solution polymerization/cross-linking procedure).

Upon drying, these particles or beads will directly provide a free flowing powder.

In addition to the unique flowing properties of these beads, the inverse-suspension process displays additional advantages compared to the solution method. This method is employed to prepare spherical hydrogels microparticles with size range of 1 µm to 1 mm. In suspension polymerization, the monomer solution is dispersed in the nonsolvent forming fine monomer droplets, which are stabilized by the addition of stabilizer. The polymerization is initiated by radicals from thermal decomposition of an initiator. The newly formed microparticles are then washed to remove monomers, cross-linking agent, and initiator. Fig. 5 represented the block diagram of suspension polymerization process for hydrogel production.

Preparation and process optimization of hydrogel based on grafted starch:

Hydrogels may be based on natural polymers, including macromolecules extracted from animal collagen, plants, and sea weed. These natural macromolecules are typically polysaccharides and proteins comprised of glycosidic and amino acid repeating units, respectively.

The main processes of this procedure are mixing of starch and water, grafting with acrylonitrile, separation and drying followed by saponification with alkali at 950C for an hour, precipitation with methanol, washing with water free ethanol, and drying under vacuum at 600C for 3 h. A redox system (Fe^{2+}/H_2O_2) has been employed as a source of [OH -] free radicals (Table-1)

Fig. 5 represents a block diagram of the design process for hydrogel preparation via grafting onto a polysaccharide (starch). The main process parameters concluded in this study may be outlined as follows [19]: AN/starch, 1.4; H_2O_2 dose, 1.2; and 1.5 g/g corn and potato starches, respectively, $H_2O_2/FeSO_4\text{-}7H_2O$ = 6 (w/w);

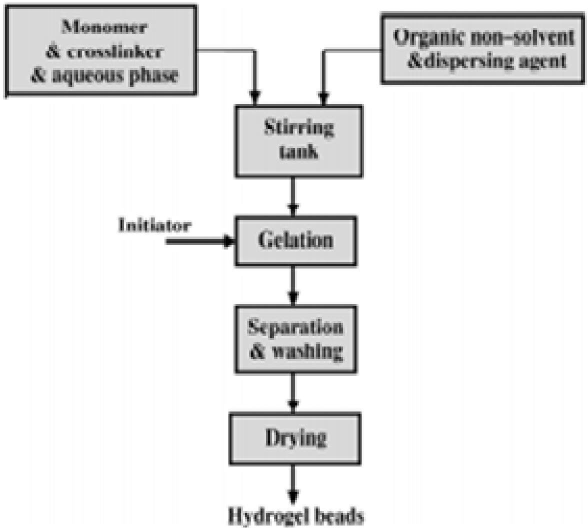

Fig.4. Block diagram of suspension polymerization process

Table 1: The optimized conditions for PHEMA hydrogel preparation

Parameter	Range
Suspending agent	0.85 – 1.7%
Dissolved salt	18 – 20%
Continuous phase/monomer ratio	3.5 – 5.25%
Initiator	0.2 – 0.4%
Stirring speed	80 – 120 rpm

6. CONCLUSION:

Recently, many hydrogel based networks have been designed and tailored to meet the needs of different applications. The favourable property of these hydrogels is either ability to swell when put in contact with an aqueous solution. The presented review demonstrates the literature concerning classification of hydrogels on different bases, physical and chemical characteristics of these products and technical feasibility of their utilization.

It also involved technologies adopted for hydrogel production together with process design implications, block diagrams and optimized conditions of the preparation process. An innovated category of recent generations of hydrogel materials was also presented in some details. Super-porous hydrogels are new materials that, regardless of their original size, rapidly swell to a large size. Based on the literature survey, it can be concluded that batch or semi-batch reactors are suitable reactors for polymerization processes. The variables for batch reactors include temperature, pressure, batch cycle time, the amount of reactants, and the feed addition strategy. Optimization variables such as batch cycle time and amount of reactant are continuous variables with fixed values for a certain batch reactor system depends mainly upon material and energy balance.

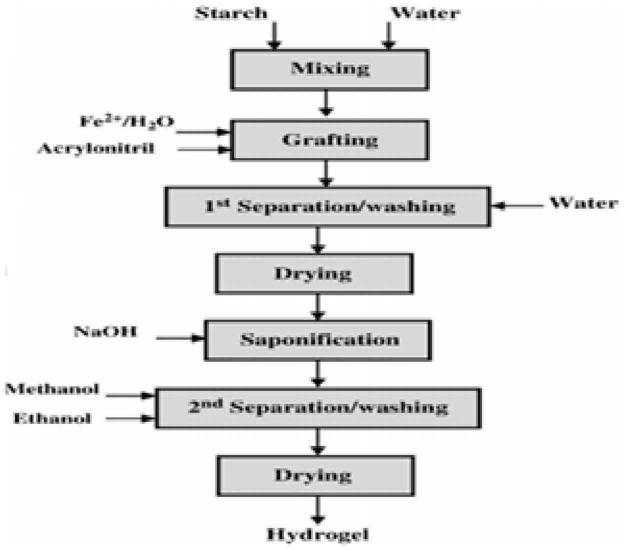

Fig.5. Block diagram for preparation of high swelling hydrogel

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