



Polymeric Hydrogels: Recent Advances in Toxic Metal Ion Removal and Anticancer Drug Delivery Applications

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ABSTRACT

In recent years, many research groups paying attention in removal of heavy metal ions from polluted areas and also controlled drug delivery applications with the hydrogels based on both biomaterials and synthetic grade. Contamination with these heavy metal ions has also increased public concerns because of their toxicity even at lower concentrations, besides non-biodegradability and tendency of bioaccumulation. The increasing demand for the recovery of these metals from industrial effluents has elevated the development and the testing of new sorbing materials. Cancer is a class of disease which is characterized by abnormal cell growth in an uncontrolled manner in all over the body. Surgical intervention, radiation, and chemotherapeutic drug are major current cancer treatments. The use of chemotherapeutic treatment is often restricted by solubility of drugs, adverse systemic toxicity, and the appearance of drug resistance. Owing to these difficulties, there is a great demand to innovative drug delivery systems for better controlled and site specific delivery of antitumor drugs and that can overcome solubility and resistance problems. This review covers the recent developments of hydrogels in separation science and drug delivery applications. Synthetic methodologies for the fabrication of hydrogels and their responsiveness (pH and thermoresponsive) were discussed. In addition to this, we are focused on an overview of potential polymeric hydrogels for metal ion removal and anticancer drug release, paying attention to their efficacy in metal removal, and controlled release of 5-fluorouracil.

Key words: *Hydrogels, Drug delivery, Biomaterials, Toxic metal ion removal, 5-fluorouracil.*

1. INTRODUCTION

Now-a-day, polymers are very common in our daily life as well as in science, medicine, and engineering. Biopolymers, such as DNA, proteins, and polysaccharides, are fundamental to biological structure and function. Synthetic polymers, such as synthetic rubber, polystyrene, Bakelite, polyethylene, polypropylene, are using in many ways in daily life. Both natural and synthetic polymers are created via polymerization of many small molecules, known as monomers. The attractiveness of polymers in their applications such as environmental remediation, biomedical field is closely related to their properties. Polymeric material sorbents are effective and economic adsorbents for toxic heavy metals in wastewater treatment, and it is due to their hydrophilicity, cross-linking nature, and the presence of proper functional groups that are capable for interaction with heavy metal ions. The biocompatibility and biodegradability of hydrogels are very important in biomedical applications. The biocompatibility of polymeric

materials has been increased using specific polymers, particularly that exhibits similar properties to the extracellular matrix.

In recent years, hydrogels with chelating ligands have attracted attention for industrial applications, such as the removal of toxic heavy metal ions from aqueous media, along with biomedical applications such as delivery of drugs, proteins, and genes. In addition to this, there is growing interest in metal-containing polymer systems as they belong to peculiar class of polymeric materials with unique and valuable properties, along with easy processing methods. For the treatment of heavy metal bearing effluent streams, several techniques were developed and used to remove the heavy metal ions from different aqueous solutions. However, most of the methods do not achieve adequate removal ratio. Moreover, the implementation of these technologies is expensive, and so, their applications are limited in real applications. In addition to this, the responsive or “intelligent” hydrogels with integrated functionalities

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can perform controlled actions in biomedical applications such as pulsatile or controlled release, signaling to the sensor (sensing) device, recognize specific cells, and monitoring the concentration level in a biological and living system. Responsive hydrogels can control properties by changing the gel structure in response to the environmental stimuli. Therefore, the development of a new, cheap, flexible, responsive, and environmentally friendly process for treatment of industrial effluents and biomedical applications are a major challenge. The present thesis emphasized on highly effective hydrogels for environmental remediation of toxic metal ions and stimuli-responsive hydrogels for controlled drug delivery applications.

1.1. Hydrogels

Hydrogels are three-dimensional polymer networks made of hydrophilic polymer chains that are chemically or physically cross-linked. The cross-linked assembly of hydrogels is pronounced by junctions or tie points, which may be entangled using strong chemical linkages such as permanent entanglements such as covalent, ionic bonds, and/or weak interactions such as hydrogen bonds and hydrophilic or hydrophobic interactions. As a result of this cross-linking, hydrogels do not dissolve in water or physiological solutions, but they readily swell and bear large volume changes. Environmentally sensitive hydrogels can also be produced from hydrophilic, stimuli-responsive polymer networks that change volume in response to an external signal such as a change in temperature/electrical or chemical environment [1].

The hydrogels are attractive candidates for various biomedical, environmental applications due to their unique biocompatibility, chelating nature, desirable physical and physiological characteristics. They can serve as carriers for drug, protein, and genes and deliver the physiologically important entities in a controlled manner. The tissues scaffolds, which provide structural integrity in tissue engineering applications and environmental remediation of heavy metals and organic dyes [2-5].

1.2. Hydrogel Synthesis

Hydrogels may be synthesized in a number of classical polymerization methods. These include one-step procedures such as polymerization and parallel cross-linking of multifunctional monomers, as well as multiple step procedures involving preparation of polymer molecules having reactive groups and their subsequent cross-linking, and also by reacting polymers with suitable cross-linking agents.

1.3. Classification of Hydrogels

Hydrogels can be classified in different ways based on polymeric composition, physical appearance, and type of cross-linking. Schematic representation of this classification is shown in Figure 1 [6].

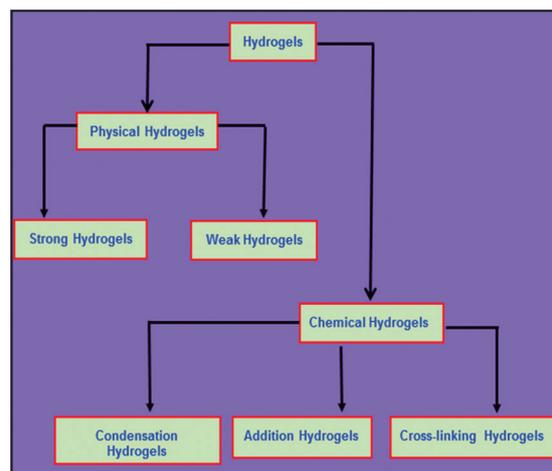


Figure 1: Classification of hydrogels based on the nature of cross-linking.

The number of monomers or polymers used for the preparation of hydrogels may lead to formations of some important classes of hydrogels, and they are homopolymeric hydrogels, copolymeric hydrogels, and multipolymer based interpenetrating network hydrogels.

- Homopolymeric hydrogels are resulting from a single species of monomer, which is a basic structural unit. The nature of monomer and type of polymerization are key points for the cross-linked skeletal structure of homopolymers.
- The copolymeric hydrogels are comprised 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 based interpenetrating network hydrogels are made from two different polymer chains that may be natural or synthetic, and cross-linked to form a network. Whereas in case semi-IPN hydrogels, one component is a cross-linked polymer and another component is a non-cross-linked polymer.

Based on physical appearance, the hydrogels are classified as matrix, film, microsphere, and beads and depend on the technique of polymerization involved in the preparation process.

Based on the nature of cross-linking, hydrogels are basically classified into two categories such as chemical gel and physical gel. Chemical hydrogels are formed by covalently cross-linked networks. These are permanent hydrogels and never dissociated without complete degradation. Whereas physical gels are formed when the networks are held together by molecular entanglements that are formed by secondary forces such as ionic, hydrogen bonding, or hydrophobic interactions. All of these physical interactions are reversible and can be disrupted by

alterations in physical conditions or application of stress.

Hydrogels, which are responsive to changes in temperature, pH, pressure, irradiation, electric fields, and chemical stimuli, are called responsive hydrogels. They undergo fast, reversible changes in microstructure from a hydrophilic to a hydrophobic or ionic to a non-ionic state [7]. These changes are apparent at the macroscopic physical and chemical properties such as size of swollen network and conductivity though the response (network property) is small change, it can trigger complete collapse and total transposal of their properties. The responsive polymers can be used for variety of applications in biomedical and engineering applications. Schematic representation of responsive nature is shown in Figure 2 [7-9].

Functional hydrogels consist of one or more polymer segments that can permit polymer affiliated reactions. The possible routes that utilize anhydrides, epoxides, click chemistry, etc., and for most of these transformations, both reaction partners are polymerizable or can be provided by functionalization of a precursor polymer [10,11]. The reactive sites of functional hydrogels are authorized for the modification with a variety of reagents and/or biomolecules. The combination of functionality and responsive behavior allows development of advanced materials for environmental remediation

of toxic ions, delivery of drugs and drug conjugates, biosensor applications, and affinity chromatography.

1.4. Separation of Toxic Metal Ions from Aqueous Environment

Recent revolution in industry and technology attains the urbanization of the world. The technological advancement in several areas, during the past 30 years, has been tremendous. However, the progress in industrial and technology always has been accompanied by a growing negative impact on the environment in terms of its pollution. The activities of industrial, mining, urban, and agriculture and also consumption of natural resources enhance the stress on the environmental system by the accumulation of wastes. Untreated or improperly treated waste which causes environmental pollution. Environmental degradation often tends to become irreversible and causes detrimental effect on living beings and their ecosystem.

1.4.1. Heavy metals and their pollution

Any metal or metalloid species may be considered a “contaminant” if it occurs where it is in unwanted form or concentration that causes negative impact on living beings or environment. These metals or metalloids include lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As), chromium (Cr), copper (Cu), selenium (Se), nickel (Ni), silver (Ag), and zinc (Zn). Other less common metallic contaminants include aluminum (Al), cesium (Cs), cobalt (Co),

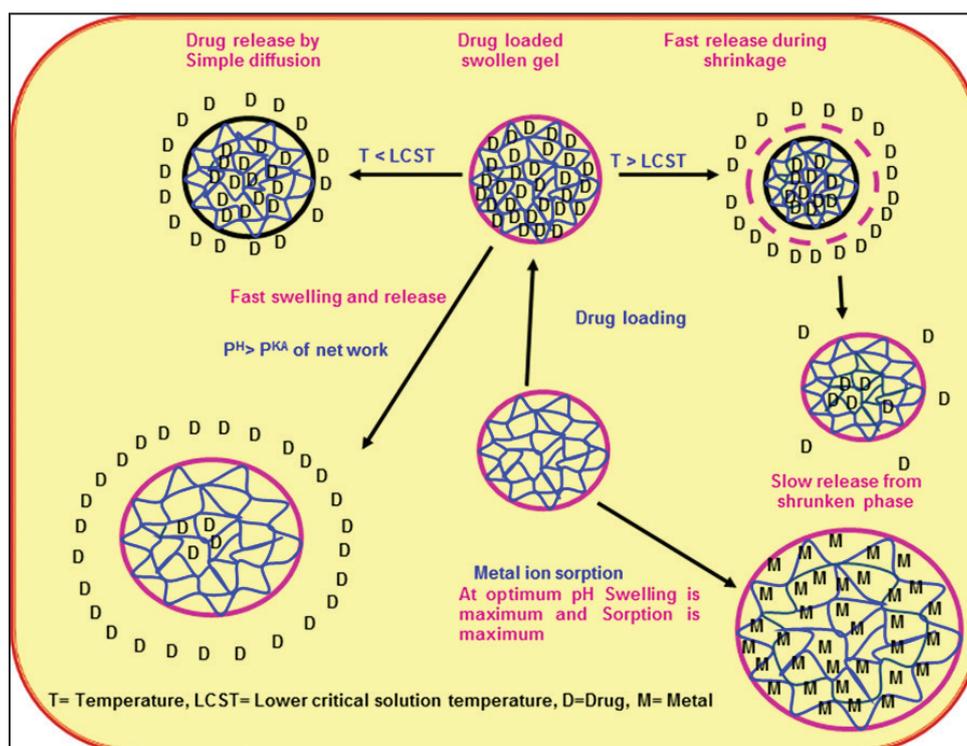


Figure 2: Schematic representation of stimuli responsive nature and their applications in both biomedical and environmental remediation applications.

manganese (Mn), molybdenum (Mo), strontium (Sr), and uranium (U).

Any metal that is toxic to living beings is called heavy metal, irrespective of their atomic mass or density. Heavy metals are highly toxic and non-degradable pollutants, which are an ill-defined group of elements that exhibit metallic properties. These include the transition metals, some metalloids, lanthanides, and actinides. These metals are often encountered in mining operations, industrial effluents from metal plating industries, electronic device manufactures, battery manufactures, and alloy industries, burning of leaded petrol and leaching of metal ions from the soil into lakes and rivers by acid rain.

Living organisms require varying amounts of heavy metals such as iron, cobalt, copper, manganese, molybdenum, and zinc as they provide essential cofactors for metalloproteins and enzymes. However, all metals are toxic at higher concentrations as the excessive concentrations lead to damage of living organisms by blocking essential functional groups, displacing other essential metal ions, or modifying the active conformation of biological molecules. Some heavy metals such as mercury, lead, cadmium, and arsenic are toxic to living organisms even at very low concentrations, as they affect directly various biochemical and physiological processes. Because of the accumulation of these heavy metals over a long time in the bodies of animals can cause serious illness. Certain metals such as vanadium, selenium, and tungsten are generally toxic but are beneficial at certain conditions. Permissible limits of some of the toxic metal ions and their hazardous effects are given in Table 1.

1.4.2. Food cycle

The heavy metals from the activities of industrial, mining, urban, and consumption of natural resources introduced into the soil and aquatic system through

various processes, prominently by irrigation. These contaminated bodies affect the quality of atmosphere and water bodies, and finally, threatens the health and life of animals and human beings by way of the food chain [12].

Food chain is one of the ways to transfer persistent chemical pollutants from the first link soil and water to the final link human via plants and animals. The deposition of many heavy metals mainly achieved by the food chain. The deposition and concentration of heavy metals in the food materials predominantly depend on the circumstances under which they are cultivated.

The accumulation of heavy metals is always in a cyclic order: Industry, atmosphere, soil, water, foods, and animals and humans. In developing countries, the industrial consumed and non-consumed wastewater, heavy metal containing insecticides and fertilizers are generally used for the agricultural purpose. The longtime usage of insecticides and fertilizers in the results accumulation of heavy metals into the soil thereby into the plants. From there, the toxic metals translocate to flora and fruits. Sometimes, the plants take up the metals when they exposed to contaminated air. Thus, these accumulated vegetables and food crops are the major origins for the contaminated food chain. When animals and human consumes such type of plant sources (leaves, fruits, and seeds), the toxic metals are expected to accumulate in their bodies. Some of the metals (Hg, Se) also accumulate in aquatic life. When human consuming sea water and seafood over a long period, it causes increase in the concentration of heavy metals which, therefore, results several health problems. Irrespective of the origin of the heavy metal pollution in the soil, excessive levels of heavy metals can result in degradation of soil quality, which can lead reduction of yield and the quality of agricultural products. Finally, it leads to detrimental effect on living beings and their ecosystem. Therefore,

Table 1: Permissible limits of heavy metals in drinking water and their hazardous effect [13].

Metal ion	Guideline value (mg/L)	Remarks
Arsenic	0.010	Skin manifestations, visceral cancers, vascular disease.
Manganese	0.400	Symptoms of manganese poisoning are hallucinations, forgetfulness and nerve damage
Uranium	0.015	Nephrotoxicity, genotoxicity, and developmental defects
Cadmium	0.003	Kidney damage, renal disorder, human carcinogen
Mercury	0.006	Rheumatoid arthritis, and diseases of the kidneys, circulatory system, and nervous system
Copper	2.000	Liver damage, Wilson disease, insomnia
Lead	0.010	Damage the fetal brain, diseases of the kidneys, circulatory system, and nervous system
Nickel	0.070	Dermatitis, nausea, chronic asthma, coughing, human carcinogen
Chromium	0.050	Headache, diarrhea, nausea, vomiting, carcinogenic
Zinc	0.800	Depression, lethargy, neurological signs, and increased thirst

it becomes essential to remove the accumulated heavy metals.

2. SEPARATION TECHNOLOGY

Various methods have been developed to remove heavy metal ions from contaminated water, such as chemical precipitation, ion-exchange, membrane filtration, solvent extraction, and adsorption techniques [14-44]. The heavy metals ions of industrial wastewaters can also be effectively removed to acceptable levels by precipitating the metal ions in an insoluble form; these are precipitated as hydroxides, carbonates, sulfides, or sulfates. The main disadvantage of this method is co-precipitation of other metals such as iron or aluminum, and also it requires special pre-treatments before heavy metal ions precipitation [14-16].

Ion exchange resins are widely used in analytical chemistry, water treatment, and pollution control. Ion exchange technique can remove traces of ion impurities from water [17-22]. This method is having some disadvantages such as relatively expensive, no selectivity toward heavy metal ions and alkali and alkaline earth metals.

Filtration of metal ion solution by semi-permeable membrane under pressures is called membrane filtration. There are different types of membrane filtration such as ultrafiltration, nanofiltration, and reverse osmosis. Membrane filtration is used for the treatment of influents from waste water [23-26]. In general, these techniques are having disadvantages such as high operational cost and prone to membrane fouling. Electro-treatments such as electro-dialysis [27], membrane electrolysis [28], and electrochemical precipitation [16,29] are also belongs to membrane filtration technology applicable to heavy metal ions. However, these techniques have been investigated less extensively due to the high operational cost.

Solvent extraction is also one of the separation techniques which separates metal ions in the form of liquid complexes based on solubility differences between two immiscible liquid phases, usually an aqueous and an organic phase, in contact with each other. Because of simple operation, a large number of extractants have been developed with various organic ligands such as phosphonic acid, N,N-dialkyl amides, crown ethers, β -diketones, picolinamide, and calixarenes [30-37]. Even though solvent extraction technique is the widely adopted process over the years, it suffers from limitations such as the third phase formation, requirement of large volumes of organic solvents, loss of material through phase disengagement, and disposal of large amount of extractant.

Adsorption by activated carbons is widely used for the variety pollutants such as heavy metals, organic

molecules, dyes, and dissolved gases [38-40]. Activated carbons are prepared by carbon based biomaterials from both plants and animals. However, this is having major disadvantages such as relatively high capital cost and spent adsorbent may be considered as a hazardous waste. Along with activated carbons adsorption by biosorbents also used heavy metals from aqueous streams, but use of biosorbents limited because of less selectivity and production of biosorbents may arise agricultural problems [41-44].

2.1. Polymeric Matrices for Separation Technology

In the contest of removal and/or recovery of heavy metal ions from industrial wastewater, most of the above said separation techniques are having one or more drawbacks such as economically expensive, low adsorption capacity, non-selectivity toward heavy metal ions, and other metal ions or production hazardous waste. The use of polymeric matrices for the separation technology is most advisable because of advantages in both economically and technically [45-50]. There are different types of polymeric matrices such as homo/copolymers, polymer blends; cross-linked polymeric matrices in the form of beads, microspheres, resins, membranes, and hydrogels.

The shortcomings in other separation technologies for the removal of metal ions from dilute aqueous solution led the researchers to explore alternative techniques such as sorption by polymeric hydrogel networks over a long period. The use of hydrogels for the removal of the heavy metal ions from dilute solutions was initiated a decade back. Afterward, various new dimensions have been explored and reported in the field of metal extraction by polymeric networks, beads, and hydrogels [51-58]. As hydrogels possess different functional groups, it is comparable with other technologies such as solvent extraction and ion exchange and also provides benefits with the simplicity of operating condition with solid phase ion exchange process. The advantages of the use of hydrogels over the other processes extend due to high adsorption capacity, degradability of end products, and minimal use of organic solvents [59-63].

2.2. Advantage of Hydrogels in Adsorption

In recent years, many researchers have worked on the treatment of heavy metal ions using different hydrogels having different functional groups. Hydrogels are hydrophilic water insoluble polymeric networks. Hydrogels can absorb large amounts of water based on intrinsic properties such as polarity, degree of cross-linking between the network chains, chain flexibility, and free volume. The water imbibing capacity of hydrogels also depends on the external stimuli such as pH, temperature, and ionic strength [1,64-68].

As the polymeric hydrogels having sequestered functional groups along the network, they can

have high adsorption capacities for metal ion uptake [69-72]. The heavy metal uptake mechanism of the hydrogels has been related to their high water permeability and to the presence of other small metal ions. Specifically, hydrogels composed of acrylic, vinylic, and other functional monomers, such as acrylic acid (AA), acrylamide (AM), 2-acrylamido-2-methyl-1-propane sulfonic acid (AMPS), hydroxyl ethyl methacrylamide (HEMA), N-vinyl imidazole (NI), and 4-vinyl pyridine (NVP), have demonstrated to be good adsorbents toward heavy metals and some other multiple applications [73-78]. Furthermore, work has been done on polymeric materials, such as chitosan, pectin, sodium alginate, guar gum, cellulose, poly(vinyl alcohol) (PVA), and poly(vinyl pyrrolidone), for the removal of toxic heavy metal ions. It is well documented that these polymeric materials utilize both an access and a recognition mechanism to selectively react with the metal ions, using their chelating and ionic groups present in these polymers and which are called functional polymers. The functional polymers were proved as potential candidates for the removal and recovery of heavy metal ions. Among these, polymeric sorbents investigated for toxic heavy metal removal, hydrogels has become one of the most promising sorbents [79]. Because of the hydrophilicity, cross-linking nature, high sorption capacity due of the presence of proper functional groups that are capable for interaction with heavy metal ions, and finally, these hydrogels have a great ability to control diffusion of these ions from solution using stimuli-responsive nature. Therefore, many various homo and copolymer hydrogels were investigated for heavy metal ions removal.

2.3. Recent Developments of Polymeric Matrices in Toxic Metal Ion Removal

Hydrogels based matrices were developed by various polymers for the adsorption of toxic metal ions from aqueous environment and maximum adsorption capacity of hydrogels are presented in Table 2. Khotimchenkoa *et al.* used pectin compounds for different metals such as zinc, lead, and cerium. Langmuir model indicating the number of active binding sites of molecules for Zn(II) is 131.6 mg.g⁻¹ and for Pb(II) 680 mg.g⁻¹ for Ce(III) 200 mg.g⁻¹ [80-82]. Gongga *et al.* [83] developed pectin-iron oxide magnetic nanocomposite adsorbent for the removal of Cu(II) in aqueous solutions. They achieved maximum adsorption capacity of 48.99 mg.g⁻¹ at pH 5.73. Cavus *et al.* [84] synthesized poly(2-acrylamido-2-methyl-1-propane sulfonic acid-co-itaconic acid) polymers for the removal of Cu(II) and Cd(II) from aqueous solutions. These polymers were shown maximum adsorption capacities 1.685 and 1.722 mmol.g⁻¹ for copper and cadmium, respectively. Liu *et al.* [85] prepared U(VI) (uranyl ion) imprinted hydrogels based on cross-linked chitosan/PVA blend polymers. The maximum adsorption capacity was

observed in the pH range of 5.0-6.0, and the maximum adsorption capacity according to Langmuir equation was 156 mg.g⁻¹.

Ozay *et al.* [86] developed poly(2-acrylamido-2-methyl-1-propansulfonic acid-co-vinyl imidazole) based magnetic hydrogels for heavy metal ion removal. The maximum uptake capacities obtained were 59.5, 65.8, 83.3, and 88.5 mg.g⁻¹ for Fe(II), Cu(II), Cd(II), and Pb(II), respectively. Recently, Luis *et al.* [87] synthesized super absorbing poly(acrylic acid-co-acrylamide) hydrogels by redox initiator and used for removal of Cu(II) ions from aqueous solutions. These hydrogels achieved maximum uptake capacity of 211.7 mg.g⁻¹. Milosavljevic *et al.* [88] developed poly(acrylamide-co-sodium methacrylate) hydrogels by free radical copolymerization method using poly(ethylene glycol) diacrylate as a cross-linker. They achieved maximum adsorption of 24.05 mg.g⁻¹ for Cu(II) ions and 32.99 mg.g⁻¹ for Cd(II) ions had been obtained at pH 5.0.

Shamsipur *et al.* [89] prepared polymer coated silica gel sorbents using "grafting from" radical polymerization method. These coated silica gels used for U(VI) uptake studies, they achieved 52.9 μmol.g⁻¹ of uranyl uptake at pH=3. Liu *et al.* [90] synthesized polyaniline mesoporous silica composites for U(VI) uranyl removal and recovery studies, the maximum uranyl ion uptake capacity of PANI-CMK-3 achieved was 118.3 mg.g⁻¹ at pH=6. Abbaszadeh *et al.* [91] synthesized PVA/titanium oxide nanofibers, which were modified with mercapto groups. The maximum metal ion uptake capacity of nanofibers was 196.1 and 238.1 mg.g⁻¹ for U(VI) and Th(IV) at pH of 4.5 and 5.0, respectively. Ortabay *et al.* [92] synthesized terpolymer/montmorillonite nanocomposite hydrogels for U(VI) removal from aqueous solutions by acrylic monomers and montmorillonite suspension polymerization method. The adsorption efficiency of the nanocomposite hydrogels was 0.723 mmol.g⁻¹ at pH 5.5.

Anirudhan *et al.* [93] developed carboxylate grafted cellulose densified with TiO₂ for uranium(VI) from aqueous solutions. Titanium dioxide densified cellulose was grafted with poly(methacrylic acid) using N,N-methylenebisacrylamide as cross-linker and Mn(IV)-citric acid as initiator. This system achieved 99.4 mg.g⁻¹ of U(VI) at pH=6. Donia *et al.* [94] synthesized magnetic glycidyl methacrylate chelating resins treated with tetraethylenepentamine and applied for removal of uranium ions from aqueous solutions. The maximum uptake capacities obtained was 1.68 mmol.g⁻¹. Milja *et al.* [95] developed imprinted polymer nanospheres by quinoline-8-ol functionalized 3-aminopropyltrimethoxysilane modified silica nanoparticles followed by surface imprinting with the functional monomers such as NVP, 2-hydroxy

Table 2: The adsorption capacities of different types of hydrogels with various polymers.

S. No	Adsorbent	pH	Metal ion	Maximum metal ion uptake (mg.g ⁻¹)	Reference
1	Pectin compounds		Zn(II)	131.6	[80]
			Pb(II)	680.0	[81]
			Ce(III)	200.0	[82]
2	Pectin-iron oxide magnetic nanocomposite	5.73		48.99	[83]
3	Poly(2-acrylamido-2-methyl-1-propane sulfonic acid-co-itaconic acid) polymers		Cu(II)	1.69 mmol.g ⁻¹	[84]
			Cd(II)	1.72 mmol.g ⁻¹	
4	Chitosan/PVA blend polymers	5.0-6.0	U(VI)	156	[85]
5	Poly(2-acrylamido-2-methyl-1-propansulfonic acid-co-vinyl imidazole) based magnetic hydrogels		Fe(II)	59.5	[86]
			Cu(II)	65.8	
			Cd(II)	83.3	
			Pb(II)	88.5	
6	Poly(acrylic acid-co-acrylamide) hydrogels		Cu(II)	211.7	[87]
7	Poly(acrylamide-co-sodium methacrylate) hydrogels	5.0	Cu(II)	24.05	[88]
			Cd(II)	32.99	
8	Polymer coated silica gel sorbents	3.0	U(VI)	52.9 μmol.g ⁻¹	[89]
9	Pani-cmk-3	6.0	U(VI)	118.3	[90]
10	Polyvinyl alcohol/titanium oxide nanofibers	6.0	U(VI)	196.1	[91]
			Th(IV)	238.1	
11	Terpolymer/montmorillonite nanocomposite hydrogels	5.5	U(VI)	0.723 mol.g ⁻¹	[92]
12	Carboxylate grafted cellulose densified with TiO ₂		U(VI)	99.4	[93]
13	Glycidylmethacrylate chelating resins		U(VI)	1.68 mmol.g ⁻¹	[94]
14	Uranyl Imprinted quinoline-8-ol Functionalized 3-aminopropyl trimethoxysilane modified silica nanoparticles		U(VI)	97.1 μmol.g ⁻¹	[96]
15	Acrylamide and acrylic acid hydrogels	13	U(VI)	236.6	[96]
16	Polystyrene based microspheres modified with dithiocarbamate.	7.0	Hg(II)	33.2	[97]
17	Surface modified chitosan hydrogel beads by chloroacetic acid	5.0	Cu(II)	130	[98]
18	Poly(hydroxyethyl methacrylate-co-methacrylamidohistidine) beads		Cu(II)	122.7	[99]
19	Aam-ampsna/clay nanocomposite hydrogels	3 to 4.5	Cu(II)	1.07 mmol.g ⁻¹	[100]
			Cd(II)	1.28 mmol.g ⁻¹	
			Pb(II)	1.03 mmol.g ⁻¹	
20	Surface modified magnetic Fe ₃ O ₄ nanoparticles		U(VI)	12.33	[101]
21	Ion-imprinted magnetic chitosan resins	5.0	U(VI)	187.26	[102]
22	Diethylenetriamine functionalized glycidyl methacrylate and trimethylolpropane trimethacrylate beads	1-5	Cu(II)	1.16 mmol.g ⁻¹	[104]
			Pb(II)	1.32 mmol.g ⁻¹	
23	Chitosan-g-poly(acrylic acid) hydrogels	3-7	Ni(II)	161.8	[105]
24	Poly(2-acrylamido-2-methyl-1-propane sulfonic acid-co-itaconic acid). Hydrogels		Cu(II)	2.1 mmol.g ⁻¹	[106]
			Pb(II)	0.6 mmol.g ⁻¹	
25	Hexa functional hydrogels with poly(propylene glycol) with 1,3-propanediamine and 1,2-ethanedithiol		Fe(III)	329	[107]
			Co(II)	108	
			Ni(II)	143	
			Cu(II)	190	
			Zn(II)	241	
			Cd(II)	272	
			Hg(II)	82	
Pb(II)	294				

(Contd....)

Table 2: (Continued)

S. No	Adsorbent	pH	Metal ion	Maximum metal ion uptake (mg.g ⁻¹)	Reference
26	Guanidine modified 2-acrylamido-2-methylpropan sulfonic acid based hydrogels	5	Pb(II) Cd(II)	22.73 27.78	[108]
27	Poly(N-(hydroxymethyl) methacrylamide-1-allyl-2-thiourea) hydrogels	0.5	Pt(II) Pd(II)	477 407	[109]
28	Modified polyacrylamide hydrogels	6-8	Cd(II) Pb(II) Zn(II)	5.3 mmol.g ⁻¹ 0.63 mmol.g ⁻¹ 1.27 mmol.g ⁻¹	[110]

ethyl methacrylate, and cross-linker ethylene glycol dimethacrylate. The material offers high retention capacity of 97.1 $\mu\text{mol.g}^{-1}$. Raj and Chauhan [96] synthesized AM and AA hydrogels by free radical initiation using N,N-methylenebisacrylamide as cross-linker. The hydrogel was hydrolyzed to partially convert some of the amide groups into carboxylate groups. The partially hydrolyzed hydrogel exhibited the maximum U(VI) ion uptake of 236.6 mg.g^{-1} at pH=13.

Denizli *et al.* [97] developed polystyrene based microspheres modified with dithiocarbamate. These microspheres show the maximum Hg(II) adsorption capacity about 33.2 mg.g^{-1} of dry polymer, which was observed at pH 7.0. Yan *et al.* [98] developed surface modified chitosan hydrogel beads by chloroacetic acid. These surface modified carboxymethylated chitosan beads (CMC) provide not only boosted the adsorption but also improved selectivity for Cu(II) ions from lead (Pb(II)) and magnesium (Mg(II)) ions in aqueous solutions. These beads show maximal Cu(II) uptakes at pH 5.0 about 130 mg.g^{-1} . Say *et al.* [99] synthesized poly(hydroxyethyl methacrylate-co-methacrylamidohistidine) beads by the radical suspension polymerization of methacrylamidohistidine and 2-HEMA conducted in an aqueous dispersion medium. The maximum adsorption achieved beads were 122.7 mg.g^{-1} of Cu(II).

Kasgo *et al.* [100] synthesized nanocomposite hydrogels based on AAm-AMPSNa/clay for heavy metal ion removal. The maximum uptake was observed at pH 3-4.5, and its values were 1.07, 1.28, and 1.03 mmol.g^{-1} for Cu (II), Cd (II), and Pb (II) ion, respectively. Sadeghi *et al.* [101] synthesized surface modified magnetic Fe₃O₄ nanoparticles with quercetin. These quercetin modified nanoparticles used for the removal of uranyl ions from aqueous solutions. The monolayer adsorption capacity achieved according to Langmuir isotherm was found to be 12.33 mg.g^{-1} . Zhou *et al.* [102] developed U(VI) ion-imprinted magnetic chitosan resins. The maximum capacity values obtained at pH 5.0, the monolayer adsorption capacity achieved according to Langmuir isotherm was found to be 187.26 mg.g^{-1} for imprinted resins

and 160.77 mg.g^{-1} for non-imprinted resins. Luoa *et al.* [103] successfully synthesized magnetic ion-imprinted polymer by surface imprinting technique combined with a sol-gel process. These surface ions imprinting polymer possessed both higher adsorption capacity and selectivity coefficient.

Liu *et al.* [104] synthesized microbeads by copolymerization of glycidyl methacrylate and trimethylolpropane trimethacrylate. Finally, these microbeads are functionalized with diethylenetriamine. These microbeads are used for the removal of copper and lead. They studied adsorption in the pH range 1-5 and achieved the maximum adsorption capacity of 1.16 mmol.g^{-1} for Cu(II) and 1.32 mmol.g^{-1} for Pb(II). Zheng *et al.* [105] developed chitosan-g-poly(acrylic acid) hydrogels were prepared from an aqueous dispersion polymerization method and used for removal recovery of Ni(II). They studied adsorption in the pH range 3-7 and achieved the maximum adsorption capacity of 161.80 mg.g^{-1} . Evren *et al.* [106] were synthesized hydrogels from poly(2-acrylamido-2-methyl-1-propane sulfonic acid-co-itaconic acid). Hydrogels were prepared by free radical polymerization monomers in aqueous solution. The metal ion adsorption capacities achieved were 2.1 and 0.6 mmol.g^{-1} for Cu²⁺ and Pb²⁺ ions, respectively. Zheng *et al.* [107] developed hydrogels using hexafunctional poly(propylene glycol) with 1,3-propanediamine and 1,2-ethanedithiol for the removal of heavy metal ions. Maximum adsorption capacities achieved by this hydrogels were 329, 108, 143, 190, 241, 272, 82, and 294 mg.g^{-1} for Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), and Pb(II), respectively.

Yetimoglua *et al.* [108] developed hydrogels by poly(guanidine modified 2-acrylamido-2-methylpropan sulfonic acid/acrylic acid/N-vinylpyrrolidone/2-Hydroxyethyl methacrylate). These hydrogels showed maximum adsorption capacity at pH 5. The maximum uptake capacity of these hydrogels by Langmuir equation was 22.73 mg.g^{-1} and 27.78 mg.g^{-1} for Pb²⁺ and Cd²⁺, respectively. Doker *et al.* [109] synthesized poly(N-(hydroxymethyl) methacrylamide-1-allyl-2-thiourea)

hydrogels by radiation-induced polymerization for the removal and pre-concentration of Pt(II) and Pd(II). The hydrogels shown maximum adsorption in acidic media around pH 0.5, maximum adsorption capacity was found to be about 477 and 407 mg g⁻¹ for Pt(II) and Pd(II), respectively. Sharaf *et al.* [110] developed hydrogels by the transamidation and dithiocarbamylation of cross-linked polyacrylamide. The developed hydrogels were used for heavy metal ions such as Cd(II), Pb(II), and Zn(II) ions. pH for the removal of Cd(II), Pb(II), and Zn(II) ions was ranged from 6 to 8. At the optimum pH for each metal ion, the maximum sorption capacities of hydrogel toward Cd(II), Pb(II), and Zn(II) ions, estimated from the Langmuir model were 5.3, 0.63, and 1.27 mmol.g⁻¹, respectively.

3. ROLE OF POLYMERIC MATRICES IN CONTROLLED RELEASE APPLICATIONS

As the most of the drugs have low levels of lethal toxicity, it is necessary to develop controlled drug release systems (CDRSs). CDRSs are designed to deliver the drugs at programmed rates for predefined periods. CDRSs may be classified into two general ideas: One is targeting and another is controlled release. Systems delivering active agent to the desired tissues and organs are called as “targeted or site specific CDRSs” and systems controlling the release rate of active agent are called as “CDRSs” [111].

CDRSs were first developed, in the 1950s, and were originally used to administer non-medical agents such as antifouling substances and pesticides. They were first used in medical research in the 1960s, and in the 1970s, the systems for slow release of large molecules were developed. The earliest drug delivery systems,

first introduced in the 1970s, were based on polymers formed from lactic acid. In the 1980s, several polymer drug conjugate systems became available in clinical use [112]. Today, polymeric materials still provide the most important parameters for drug delivery research, primarily because of their ease of handling and the ability to readily control their chemical and physical properties via molecular synthesis [113].

The CDRSs are combined name for different release systems, which differ slightly from each other such as delayed release, prolonged release, sustained release, and repeat action dosage forms. In delayed release products, release of active substance is delayed for a finite “lag time,” after which release is unhindered. In prolonged release products, the rate of release of active substance from the formulation after administration has been reduced, to maintain therapeutic activity, to reduce toxic effects, or for some other therapeutic purposes [114]. Sustained-release products are designed to release loaded dose to produce an immediate response, followed by a constant dose (maintenance dose) required to maintain a therapeutically effective level for some desirable period. In general, sustained release systems can discharge drugs in less than a day, and physiological conditions may influence the release rates, which leads to the patient to patient variations. A repeat action dosage form is designed to release initially the equivalent of a usual single dose of drug. Moreover, then after a definite period another single dose of the drug is released [115].

3.1. Conventional Versus Controlled Drug Release

The primary aim of CDRSs is to achieve a drug delivery profile that would yield optimum drug levels

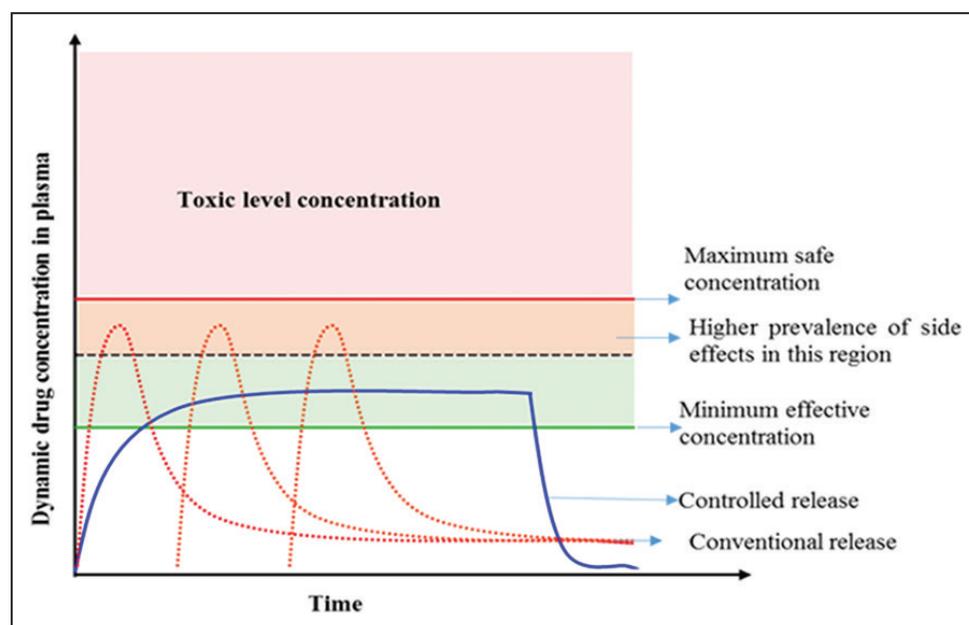


Figure 3: Drug levels in the blood plasma (a) conventional drug dosing and (b) controlled-delivery dosing.

of the blood serum over a predefined period. In case of conventional formulations, the level of drug in the blood follows the profile shown in Figure 3, in which the drug level rises after each administration of the drug and then decreases until the next administration. When the drug administered in the traditional way, the blood level of the drug exceeds toxic level immediately, and after sometimes, drug concentration falls below an effective level. CDRDs are designed for sustained as well as long-term administration of drug where the drug level in the blood follows the profile shown in Figure 3 [116], remaining constant, between the desired toxic level and effective level of drug, for an extended period.

3.2. Cancer

Cancer is a class of disease which is characterized by abnormal cell growth in an uncontrolled manner in all over the body [117,118]. The cells having abnormal growth are usually termed as cancer cells or tumor cells. Similar to healthy cells, cancer cells cannot live without oxygen and nutrients. Hence, they secrete angiogenic factors that encourage new blood vessels to grow into the tumor; this is called angiogenesis [119]. Once tumor cells can stimulate blood vessel growth, it can grow more quickly. As tumor gets bigger, it takes up more volume in the body, and it starts to spread in the body by local invasion and/or by circulation through lymph and blood vessels. These phenomena are called metastasis.

There are different types of cancers, and the abnormal cells that compose the cancer tissue are further identified by the name of the tissue that the abnormal cells originated from (for example, breast cancer, lung cancer, and colon cancer). Cancer is not only confined to humans but also other living organisms such as animals. So that, any living organism can affect cancer, and it troubles the body when abnormal cells divide uncontrollably to form lumps or masses of tissue called tumors. In general, tumor cells frequently divides and get away from original cells, these tumor cells travel through the blood and lymph systems, and stay in other organs where they can again repeat the uncontrolled growth cycle. In this process, tumor cells leaving one area and growing in another body area is termed metastatic spread or metastasis.

As per the survey of the National Cancer Institute 200 types of the cancers are there [120], most of them are fit in to the following and starts form various organs in the body such as, carcinoma from skin, sarcoma from bone related organs, leukemia from blood, lymphoma and myeloma from cells of the immune system, central nervous system cancers from tissues of the brain and spinal cord and colon cancer from both rectum or colon, and it is known as the colorectal or colon cancer.

3.3. Treatment of Cancer

In general, the treatment of cancer depends on the stage of cancer (area it has spread) and the type of cancer, age, resistance of the human body, and some other extra personal characteristics. Usually, cancer treatment has categorized into 3 types: Surgery, radiation, and chemotherapy (immunotherapy, hormone therapy, or gene therapy) [121,122].

3.4. Chemotherapy

Chemotherapy is the treatment of cancer with chemical means (medication) in a systematic way and the drugs which are called chemotherapeutic agents. In general, these drugs are cytotoxic antineoplastic in nature. Based on the chemical structure, action, and relationship to another drug, the chemotherapeutic agents are classified into several categories such as, alkylating agents, antimetabolites, antitumor antibiotics, topoisomerase inhibitors, mitotic inhibitors, corticosteroids, and miscellaneous chemotherapy drugs [121,122].

3.5. 5-Fluorouracil (5-FU)

5-FU is one of the major drugs used in the treatment of cancer. It is a pyrimidine derivative that is intracellularly metabolized into its active metabolite 5-fluoro-2'-deoxyuridine phosphate. Even though 5-FU can act in several ways, it principally acts as an inhibitor for the enzyme thymidylate synthase (TS) and causing the collapse of thymidine in nucleotide synthesis (Figure 4). In general, TS catalyzes the reductive methylation of deoxyuridine monophosphate to give deoxythymidine monophosphate (dTMP). As a result, the administration of 5-FU led to a deficiency of dTMP and impaired DNA synthesis, finally the fast-dividing malignant cells undergo "thymine less cell death" [123,124]. The extensive clinical use of 5-FU and the clinical development have focused much attention on pyrimidine metabolism, particularly by the cytosolic enzyme dihydropyrimidine dehydrogenase, which catalyzes the initial step of the catabolic pathway, finally leading to the detoxification of 5-FU to 5-fluoro-5,6-dihydrouracil [125-127]. The treatment of cancer with 5-FU has several shortcomings poor absorption, short biological half-life of the drug (10-20 min in blood plasma) [128]. These limitations may result in suboptimal treatment efficacy or excessive toxicity.

As the dividing line between the levels of lethal toxicity and optimum therapeutic dosage is terrifyingly narrow. It is hence desirable to develop controlled release systems to give antineoplastic drugs a prolonged and site-specific effect, thereby preventing harmful secondary responses and increasing their bioavailability. Numerous studies have found that controlled release of 5FU in plasma can greatly increase desirable outcomes while minimizing negative side effects of 5FU therapy [129-133].

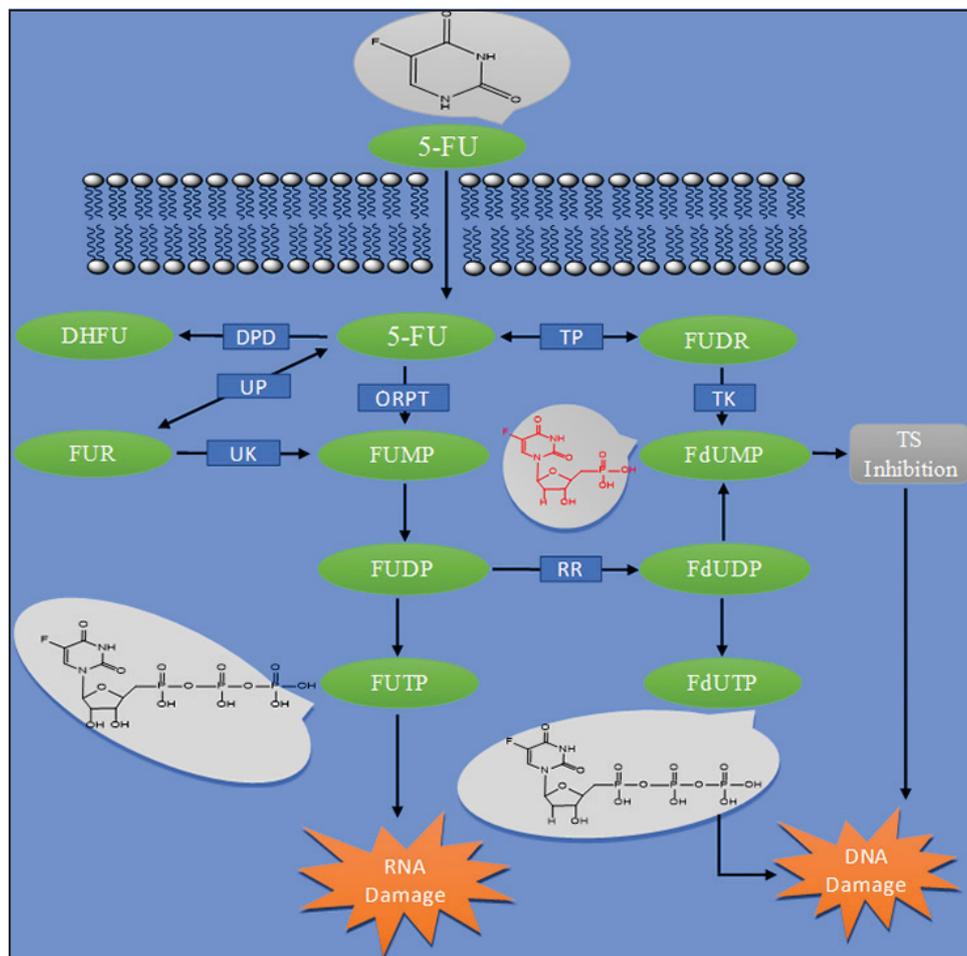


Figure 4: Mechanism of 5-Fluorouracil action (Adopted from reference [124] with courtesy). DHF: Dihydro fluorouracil, FUR: Fluorouridine, DPD: Dihydro pyrimidine dehydrogenase, UP: Uridine phosphorylase, UK: Uridine kinase, ORPT: Oratate phosphoribosyl transferase, FdUM: Fluoro deoxyuridine monophosphate, FdUD: Fluoro deoxyuridine diphosphate, FdUT: Fluoro deoxyuridine triphosphate, FUM: Fluoro uridine monophosphate, FUD: Fluoro uridine diphosphate, FUT: Fluoro uridine triphosphate, RR: Ribonucleotide Reductase, TP: Thymidine phosphorylase, TK: Thymidine kinase, TS: Thymidilate synthase.

3.6. 5-FU Release from Hydrogels

Hydrogels-based matrices were developed by various polymers for 5-FU release, the nature of polymer; release environment, and release time of hydrogels are presented in Table 3. Mishra *et al.* [134] developed pH-responsive poly[2-(methacryloyloxyethyl) trimethylammonium chloride-co-methacrylic acid] hydrogel carriers for the delivery of 5-FU to amplify its antitumor activity while reducing its toxicity, for the treatment of colorectal cancer. Poly(vinyl alcohol)-co-poly(methacrylic acid) hydrogels (PVA-MA) developed for pH sensitive delivery of 5-FU [135]. As MA content increased in the PVA-MA hydrogel, increases the equilibrium swelling, drug loading, and drug release efficiency at pH 7.4 has been observed. Sodium alginate (NaAlg)-based hydrogels were developed by free radical polymerization of different monomers such as AM, methacrylamide (Mam), and *N*-isopropylacrylamide (NIPA) for controlled release of 5-FU [136].

These hydrogels showed more than 95% of cumulative release for three monomers (AM, MAM, NIPA) with NaAlg in 24 h. In a similar way, sodium alginate-g-poly(vinyl caprolactam) (NaAlg-g-PNVC) developed for *in vitro* release studies of 5-FU. This study showed that thermoresponsive graft copolymer beads had higher drug release behavior at 25°C than that at 37°C and followed a good Fickian diffusion mechanism for the 5-FU release [137]. Varaprasad *et al.* [138] developed dual responsive chitosan-based hydrogels from chitosan and poly(*N*-isopropylacrylamide-co-2-acrylamido-2-methyl-1-propanesulfonic acid) (Cs/P[NIPA-AMPS]) polymer for controlled release of 5-FU.

4. RECENT DEVELOPMENT OF POLYMER MATRICES FOR CONTROLLED RELEASE OF 5-FU

Mishra *et al.* [139] synthesized pH-sensitive poly(*N*-[3(dimethylamino)propyl] methacrylamide

Table 3: 5-FU release from different types of hydrogels at various conditions.

S. No	Polymer present in the hydrogel	Temp (°C)	Gel nature (pH/temp)	5-FU release time (h)	Release condition 1.2/7.4	References
1	PMTAM	37	pH	24	1.2 and 7.4	[134]
2	PVA-MA	37±0.5	pH	48	1.2 and 7.4	[135]
3	NaAlg/PAm, PMAm, PNIPA	37	pH	24	pH 7.4	[136]
4	NaAlg-g-PNVC	25 and 37	temp	12	pH 7.4	[137]
5	Cs/PNIPA-AMPS	25 and 40	temp	12	pH 7.4	[138]
6	PDMAPMA-co-HEMA	37	pH	12	1.2 and 7.4	[139]
7	Liposomes	37	temp	24	pH 7.4	[140]
8	PHEMA-AGA	37±0.5	pH	12	pH 7.4	[141]
9	Phe-peptide	-	-	7	7.4	[142]
10	PAsp	37±0.5	pH	7	1.2 and 7.4	[143]
11	ACS	37	temp	7 d	7.4	[144]
12	St/Ac-HEMA	37	pH	3 d (40%)	7.4	[145]
13	C-g-PAA/BT	37	pH	24	1.2 and 7.4	[146]
14	PSMA	37	-	6 d	2 and 7.4	[147]
15	CMCs-g-PEG	37	pH	10	2.1 and 7.4	[148]
16	PECE	37	temp	24	7.4	[149]
17	SPAHEMA gels	37	pH	-	7.4	[150]
18	PVA/AMAGA	37	pH	12	7.4	[151]
19	CBCS	37±0.5	pH	10	1.0 and 7.4	[152]
20	PALGYCS	37	pH and temp	24	2.1 and 7.4	[153]
21	NIPA-IA	37	pH and temp	28	Cold buffer	[154]
22	PEGDA	37±0.1	-	10	1.0 and 7.4	[155]
23	PHEA/GMA	37±0.1	-	2.5	1.0 and 7.4	[156]
24	PHEMAAM	37	-	9 d	7.0	[157]
25	TPT-PHEMA	37	-	6.6 d	7.4	[158]
26	Am-MPI	15, 25 and 37	-	48	7.0	[159]
27	PAIMMI	15, 25, 30 and 37	temp	-	7.0	[160]
28	PHEMA	15, 25, 30 and 37	-	-	7.0	[161]
29	HA/PLGA	37	-	35 d	7.4	[162]
30	Pn/PAV	37	pH	24	1.2 and 7.4	[163]
31	Es-CPNs	37	pH	-	7.0	[164]
32	Pn coated CS microgels	37	pH	48	0.65, 7.4	[165]
33	CTP 5-FU	-	-	-	-	[166]
34	HMCP-NVP	-	-	70	7.4, 2.0	[167]
35	POPZ	37	pH and temp	-	7.4	[168]

d=days. PMTAM=Poly[2-(methacryloyloxyethyl) trimethylammonium chloride-co-methacrylic acid], PVA-MA=Poly(vinyl alcohol)-co-poly(methacrylic acid), NaAlg=Sodium alginate, NaAlg-g-PNVC=Sodium alginate-g-poly(vinyl caprolactam), Cs/PNIPA-AMPS=Chitosan and poly(N-isopropylacrylamide-co-2-acrylamido-2-methyl-1-propanesulfonic acid), PDMAPMA-co-HEMA=Poly(N[-3(dimethylamino) propyl] methacrylamide and 2-hydroxyethyl methacrylate), PHEMA-AGA=Poly(hydroxyethyl methacrylate-co-acrylamido glycolic acid), PAsp=Poly(aspartic acid), C-g-PAA/BT=Poly(acrylic acid) grafted carrageenan based composite hydrogels with bentonite, PSMA=Poly(sodium methacrylate), CMCs-g-PEG=Poly(ethylene glycol) grafted carboxymethyl chitosan, SPAHEMA=Starch-g-poly(acrylic acid-co-2-hydroxy ethylmethacrylate), PVA/PAMAGA=PVA/poly(acrylamide-co-acrylamidoglycolic acid), CBCS=N-(2-carboxybenzyl) chitosan, PALGYCS=Poly(N-acryloylglycine-chitosan, PEGDA=Poly(ethylene glycol) dimethacrylate, PHEMAAM=Poly(HEMA-co-Am), PAIMMI=Poly(acrylamide-co-monomethyl itaconate), Pn/PAV=Pectin/poly(acrylamidoglycolic acid-co-vinylcaprolactam), Es-CPNs=Eudragit S100 coated citrus pectin nanoparticles, CTP 5-FU=Cyclotriphosphazene 5-fluorouracil, POPZ=Poly(organophosphazene)

and 2-hydroxyethyl methacrylate) (PDMAEMA-co-HEMA) hydrogels, and these gels released 88% of 5-FU within 12 h. Ankita *et al.* [140] developed thermoreversible hydrogels, containing liposomes for the controlled delivery of 5-FU. These hydrogels showed gelation temperature $36^{\circ}\text{C}\pm 1^{\circ}\text{C}$. The formulation is optimized by response surface methodology. The optimized formulation was achieved % encapsulation efficiency about 68.51% and *in vitro* drug release about 64.44% in 24 h. Rao *et al.* [141] synthesized pH sensitive poly(hydroxyethyl methacrylate-co-acrylamido glycolic acid) (PHEMA-AGA) hydrogels for controlled release of 5-FU. The cumulative release of 5-FU was observed 75% in pH 7.4 buffer within 12 h. The drug release studies indicated that release of 5-FU was controlled more than 12 h from hydrogels. A phenylalanine-containing self-assembling peptide nanofibrous (Phe-peptide) hydrogels were developed for the controlled release of 5-FU and leucovorin, and these nanofibers showed a kind of burst release during the initial 60 minutes, but later they follow the Peppas model release from the scaffold [142].

Liu *et al.* [143] synthesized a pH responsive colon specific drug delivery system based on starch and poly(aspartic acid) for *in vitro* 5-FU release. Li *et al.* [144] developed N-carboxymethyl chitosan-based thermosensitive composite hydrogels to deliver an excellent 5-FU releasing effect in addition to the higher drug loading levels. Rejinold *et al.* developed thermo-responsive graft co-polymeric nanoparticles were prepared by ionic cross-linking method using sodium tri poly-phosphate as cross-linker. The *in vitro* drug release showed prominent release at 37°C . Cytotoxicity assay showed that the drug-loaded nanoparticles showed comparatively higher toxicity to cancer cells while they are less toxic to normal cells. [145]. The pH-sensitive poly(acrylic acid) grafted carrageenan based composite hydrogels with bentonite were prepared for colonic delivery of 5-FU. The cumulative release of 5-FU was observed 35% in pH 1.2 buffer within 24 h where as in pH 7.4 buffer it releases 88% within 2 h [146]. Kumar *et al.* [147] developed poly(sodium methacrylate) hydrogel for *in vitro* 5-FU release study. The release profiles were evaluated in pH 2 and 7.4, which showed that only 5% drug release was achieved at acidic pH due to the protonation of the network (poly(carboxylic acid)). Thus, the gel network is stabilized in acidic medium, hence the release of 5-FU is retarded. When the same hydrogel network was performed in pH 7.4, it showed 85% of drug release in 6 days in a controlled manner, due to its original ionic nature which may facilitate the free entrapment of drug molecules throughout the network.

Ibrahim *et al.* [148] prepared poly(ethylene glycol) grafted carboxymethyl chitosan (CMCs-g-PEG)

by photo-induced graft copolymerization method. These CMCs-g-PEG hydrogels shown the maximum cumulative release at 37°C within 2h at pH 2.1, whereas it shown maximum cumulative release in 10 h at pH 7.4. Wang *et al.* [149] developed a 5-FU based biodegradable triblock copolymer with PEG-PCL-PEG to alleviate its antitumor activity of carcinomatosis and tumor growth in mice. Sadeghi [150] designed pH-sensitive based on starch-g-poly(acrylic acid-co-2-hydroxy ethylmethacrylate) to facilitate the controlled release of 5-FU. pH is the main factor which affects the release behavior of the drug. The release experiments confirmed that maximum (90%) of the drug released at pH 7.4, due to high swelling nature of the hydrogel resulted by electrostatic repulsions between anionic groups of the hydrogel network and the buffer medium. It also confirmed that the porous network showed maximum % of drug release compared to dense network. Rao *et al.* [151] prepared PVA-based pH sensitive semi-IPN hydrogels with acrylamide and acrylamidoglycolic acid. These PVA/poly(acrylamide-co-acrylamidoglycolic acid) hydrogels were used for controlled release of 5-FU, and release was witnessed up to 12 h. pH-sensitive hydrogels were developed from N-(2-carboxybenzyl) chitosan, and release profiles of 5-FU were studied under both simulated gastric and intestinal conditions. These gels released almost 90% of the loaded drug within 10 h in pH 7.4 buffer, but pH 1.0 it released about 40% of the loaded drug in 12 h [152]. El-Sherbiny *et al.* [153] developed thermoresponsive IPN hydrogel form poly(N-acryloylglycine-chitosan) for controlled release of 5-FU at 37°C in buffer solutions at pH 2.1 and 7.4. The *in vitro* release profiles of 5-FU from the gels shown that release at pH 2.1 is greater when compare to pH 7.4. Tasdelen *et al.* [154] developed NIPA/itaconic acid based copolymeric hydrogels by radiation polymerization, and this study was suggested that the release profiles of 5-FU from hydrogels was the non-Fickian type.

Giammona *et al.* [155] developed UV curable copolymeric hydrogels from functionalized glycidyl methacrylate with α,β -Poly(N-2 hydroxyethyl)-DL-aspartamide (PHEA-GMA) and poly(ethylene glycol) dimethacrylate for controlled release application. These hydrogels released considerably more 5-FU in pH 1 than pH 7.4. Similarly, PHEA-GMA and PRGDA hydrogels are prepared by γ -irradiation for the same application [156]. Garcia *et al.* [157,158] developed poly(HEMA-co-Am) hydrogel discs, *in vivo* studies shows improved release time of 5-FU up to 6.6 days. Likewise, AM-based copolymeric hydrogels were prepared by AM, monopropyl itaconate, and monomethyl itaconate. The poly(acrylamide-co-monopropyl itaconate) (Am-MPI) hydrogels were shown 5-FU release up to 48 h [159]. Similarly, poly(acrylamide-co-monomethyl itaconate) hydrogels were prepared

for 5-FU release [160]. Garcia *et al.* [161] prepared PHEMA hydrogels with varying degree of cross-linking and that controls the release of 5-FU. Hence, the *in vivo* implants of PHEMA that would reduce the collateral effects like toxicity of 5-FU. Lin *et al.* [162] successfully entrapped 5-FU with in the composite microspheres of HA/PLGA via emulsification/solvent extraction technique. The drug release profiles were observed in pH 7.4 and was found that as the content of HA increases the initial burst release was decreased. Here, HA plays a potential role to avoid the over drug dose from the initial burst release and to encourage the sustained drug release of 5-FU up to 35 days.

Recently, pectin based hydrogels were developed from acrylamido glycolic acid and vinylcaprolactam [163]. The *in vitro* release of pectin/poly(acrylamidoglycolic acid-co-vinylcaprolactam) (Pn/PAV) hydrogels was 50% at pH 1.2, and 85% at pH 7.4 within 24 h. The release profile of Pn/PAV hydrogels revealed that the initial burst release was significantly reduced in both buffers with pH 1.2 and 7.4, followed by a continuous and controlled release phase; the drug release mechanism from polymer was due to Fickian diffusion. Biswaranjan *et al.* [164] Eudragit S100 coated Citrus Pectin Nanoparticles (Es-CPNs) were prepared for the colon targeting of 5-FU. The *in vitro* drug release studies revealed that the Es-CPNs were released 5-FU in the colonic region more than 70% in 24 h. Ana *et al.* [165] 5-FU-loaded chitosan microgels were prepared by super hydrophobic surface based encapsulation method. These microgels showed pH-dependent release profiles, and it released the 5-FU slower rate at acid pH than at pH 7.4. A pectin based magnetic nanocarriers for enhanced loading of 5-FU and these nanocarriers released 95% 5-FU in 48 h at pH 7.4. in the *in vitro* release study.

A thermosensitive macromolecular prodrug of 5-FU was synthesized using amino functionalized cyclotriphosphazene and carboxylic group-containing derivatives of 5-FU with glycine (CTP 5-FU) [166]. The *in vitro* antitumor activity of 5-FU-cyclotriphosphazene conjugates exhibit dose-dependent cytotoxicity against the tumor cell line, and all exhibited more prominent cytotoxicity than did 5-FU. A pH-sensitive maleic acid-substituted cyclotriphosphazene based network (HMCP-NVP) was synthesized by free radical copolymerization of phosphazene derivative with N-vinyl-2-pyrrolidone [167]. The drug release profile of the HMCP-NVP network depends on the pH of PBS, the percentage of cumulative release increased with an increase in pH of PBS, and these networks released 54.6% of 5-FU within 1 h at pH 7.4 but 13.9% at pH 2.0. A thermosensitive poly(organophosphazene) hydrogels were synthesized with both hydrophobic and hydrophilic moieties for a 5-FU delivery, and the *in vitro* drug release profiles from POPZ hydrogels

were established more than 95% cumulative release in phosphate-buffered saline at pH 7.4 at 37°C [168].

5. CONCLUSION

In conclusion, scientists need to focus on developing improved strategies for producing hydrogels with precise composition, strength, environmentally responsive, and biologically reproducible functionalization. For toxic metal ion removal, hydrogel network size as well as chelating functionalities should be specific and reusable. *In vivo* studies are more desirable than *in vitro* in this direction are needed, for potential *in vivo* biomedical applications, hydrogel reactivity, purity, and stability in physiological environments.

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