APPLICATIONS OF SOME SMART MATERIALS BASED RELEASE DEVICES FOR HEALTH AND SAFETY PURPOSE

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ABSTRACT. In the present article, the authors have highlighted the applications of some natural backbone based smart materials for the controlled release of drugs and their antibacterial properties. Different natural backbones including Gum ghatti, Gum tragacanth and Gum salai guggal were graft copolymerized with different monomers like acrylamide, acrylic acid, methacrylic acid, aniline etc. Poly(methacrylic acid-aniline) conducting IPN was found to show non-Fickian diffusion mechanism at pH 2.2 and pH 7.0 for the controlled release of amoxicillin trihydrate. Fickian mechanism operated for the conducting hydrogel at pH 9.2. Gum ghatti-g-poly(acrylic acid-aniline) was evaluated for the release of amoxicillin trihydrate and paracetamol. The hydrogel exhibited Fickian diffusion mechanism for both the drugs at pH 2.4, pH 7.0 and pH 9.2 and can be applied for colon-specific drug delivery. Gum Salai guggal based smart material Sg-cl-polyAAm-IA-Ag^0 was found to possess antibacterial activity against both gram (+ve) and gram (-ve) bacteria. All the synthesized smart materials were found to be effective for targeted drug delivery and antibacterial applications. Thus, the synthesized smart materials can be of great importance in health and safety sector.

Keywords: Smart materials, Antibacterial activity, Electrostatic interactions

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INTRODUCTION

Recently, smart materials based release device have become most popular for the targeted drug delivery applications as these overcome the limitations of usual administration methods [1-2]. Functional cavities of the smart materials are capable of holding the drug molecules through different type of interactions including dipole-dipole interactions, electrostatic interactions and hydrogen bonding. The interactive forces make them suitable for carrying the drug molecules to the targeted site [3]. Due to the stimuli responsive swelling behavior of smart materials, the drug molecules can be loaded over the functional cavities and can be released at the desired target site under the impact of various stimulus like pH, temperature and electric pulse [4].

The 3-D network structure of the hydrogel can be macro-porous, microporous and nanoporous depending upon the pore size of the matrix. The pore size of macro-porous hydrogels ranges from 0.1 to 1μm. The drug release mechanism of these hydrogels depends upon drug diffusion coefficient, tortuosity and porosity of the hydrogel matrix [5-7]. Microporous hydrogels are having small pores (100-1000 Å) and the drug releases with molecular diffusion and convection mechanism. Nanoporus hydrogels have mess-like structure and have small pores of dimension 10-100 Å and the drug releases only via diffusion mechanism [8,9].

For drug delivery applications, hydrogel-drug complex can be formed by using a large number of crosslinking strategies including chemical-crosslinking method and UV photo polymerization technique [10]. Prior to implantation, it is necessary to remove all toxic reagents which may otherwise cause toxic impact on the targeted site. The defined dimensionality of bulk hydrogels limits their use for implantation. This problem can be solved by designing the performed hydrogel into micro or nanoparticles. Sometimes, the hydrogels can be formed *in vivo* after considering the risks of UV exposure initiation and crosslinking chemicals [11].

In this review, we highlighted the recent developments addressing the clinically relevant issues related with the use of hydrogels for drug delivery applications.

BIOMEDICAL IMPORTANCE OF SMART MATERIALS

Smart materials are biologically important materials which are designed to provide controlled drug delivery into the system of targeted site. Using smart materials as delivery vehicle, the drugs can be administered inside the body through parenteral, rectal, ocular, dermal, vaginal and nasal routes [12,13].

TYPES OF STIMULI RESPONSIVE SMART MATERIALS

pH responsive smart materials

Such type of materials responds to the change in pH of the external environment. These materials has some kind of ionisable functional groups which respond to the change in pH of external biological environment causing change in swelling/deswelling properties of the smart material.

Polyacrylic acid (PAA), polyacrylamide (PAAm), polymethylmethacrylate (PMMA) and polyethyleneglycol are the examples of some pH responsive smart materials [14]. pH sensitive smart materials are used for the delivery of insulin and drugs. The anionic copolymer of polyhydroxyethyl methyl acrylate (PHEMA) and polymethylmethacrylate showed higher swelling in basic medium and shrinkage of crosslinked matrix in acidic medium. pH and ionic strengths are the two major factors which determine the kinetics of swelling/deswelling process [15].

Temperature responsive smart materials

Temperature responsive smart materials show temperature variability of network structure in order to modulate the drug release. Most of the temperature responsive smart materials are composed of hydrophobic polymeric chains. Upon Heating, the gel matrix of negative thermo-sensitive hydrogel contract whereas positive thermos-sensitive hydrogel expands [16]. Biodegradable and biocompatible temperature responsive smart materials are used for the delivery of anticancer, antidiabetic and antibiotic drugs.

Glucose responsive smart materials

Glucose sensitive smart materials sense the presence of sugar molecules and accordingly respond for swelling / deswelling [17]. These glucose sensitive smart materials are used for implantable sensing applications to detect the sugar level inside the body and they are used for insulin delivery. Marek *et. al.,* has derived Poly(diethylaminoethyl methacrylate) Hydrogel Systems for the release of insulin and this therapeutic system controls the insulin release by change in pH or glucose concentration [18]. Some important stimuli responsive hydrogels for the release of therapeutically important drug are described in Table 1.

Wound healing properties

Smart materials are usually tissue sensitive, therefore instead of ordinary lotions, they have been designed for better patient compliance. Due to the moisturising properties of the smart materials, dryness and scaling is not happening with the drug delivery of such type of systems [30], [31].
Hydrogels possess wound healing properties due to their biocompatibility with the natural tissues. Gum *Salai guggal* based semi-IPN nanocomposites possessed antibacterial activity due to the presence of nanosilver present inside the crosslinked semi-IPN matrix. The nanosilver was found to possess an average particle size of 5±1 nm. Gum *Salai guggal* based nanocomposites can be used as a scaffolds against bacterial infection caused by gram (+ve) and gram (-ve) bacterial strains [32]. Ggum-poly(Itaconic Acid) based superabsorbents possess wound healing properties due to their antibacterial activity against gram positive bacteria *S. aureus* [33]. Gum xanthan is a high molecular weight polysaccharide which is obtained from the fermentation of glucose, sucrose or similar complex substrate obtained from sugarcane, corn or similar complex. The crosslinking of acrylic acid onto the gum xanthan results into crosslinked hydrogel Gx-cl-poly(AA)-MW. The synthesised hydrogel possessed antibacterial activity against *Bacillus*

subtilis and *Salmonella enteritis* [34]. The inhibited bacterial zone of test samples against different bacterial strains is summarized in Table 2.

Table 1: Some therapeutically important smart materials for the release of drugs

Stimulus	Smart Materials	Therapeutic moieties	Reference(s)
pH	Tri polymer of N-vinyl 2- pyrrolidone methacrylamide and itaconic acid.	Insulin	[19]
pH	Copolymer of polymethacrylic acid and polyethylene glycol	Calcitonin	[20], [21]
pH	Copolymer of cationic guar gum and acrylic acid monomer	Ketoprofen	[22]
pH	Polyethyleneglycol.	Camptothecin	[23]
pH	poly(ethylene glycol) monomethyl ether monomethacrylate (PEGME)	N-(4-hydroxyphenyl)-2-(4-methoxyphenyl) acetamide	[24]
Temperatue	Co-polymer of poly-PNIPA and poly-PNIPA-Co-AA	5-Flurouracil	[25]
Temperatue	NIPAAm-Co-AAm	Vaginal Microbicide	[26]
Temperatue	Copolymer of gelatin and PVA	Adrenochrome	[27]
Temperatue	NIPAAm-Co.AAm	Insulin	[28]
Glucose	poly(hydroxyethyl methacrylate) (PHEMA)	protein	[29]

Target oriented drug delivery devices

The selective delivery of drug to the desired target site can be done through multifunctional smart polymeric materials. Smart materials based drug delivery is more target specific compared to ordinary drug delivery systems. Gamma radiation induced synthesis of semi-IPN matrices based on agar and gelatin was found to be effective for colon and intestine specific drug delivery of diethyl carbamazine citrate and amoxicillin. The drug release was found to be non-Fickian in pH 7.0, 9.2 and Fickian in pH 2.2 for carbamazine citrate drug diffusion. The drug amoxicillin showed case II diffusion in pH 9.2. Non-Fickian type of diffusion mechanism was followed for the release of drug amoxicillin in pH 9.2 and 7.0 [35]. An interpenetrating network of Gum ghatti-graft-poly(methacrylic acid-aniline) can also be used as controlled release device for the delivery of amoxicillin trihydrate. The release of drug was found to be higher in basic medium

i.e. pH 9.2 as compare to pH 7.0 and 2.2. The device was target oriented for colon specific drug delivery of amoxicillin in the lower gastrointestinal tract [36]. Gum tragacanth and acrylic acid based hydrogels Gt-cl-poly(AA) were found to be suitable for the delivery of antiulcerative drug pantoprazole sodium.

Table 2: Zone of inhibition of synthesized samples against different bacterial strains

Sample code	Bacteria	Zone of inhibition (mm)	Reference(s)
Sg-cl-polyAAm-IA-Ag^0	*P. aeruginosa*	25 ± 1	[32]
Sg-cl-polyAAm-IA-Ag^0	*B. cereus*	22 ± 1	[32]
Sg-cl-polyAAm-IA-Ag^0	*S. aureus*	13 ± 0.5	[32]
Sg-cl-polyAAm-IA-Ag^0	*E. coli*	14 ± 1	[32]
Ggum-cl-poly(IA)	*S. aureus*	22.5	[33]
Ggum-cl-poly(IA-ipn-ANI)-neutral	*S. aureus*	18.2	[33]
Ggum-cl-poly(IA-ipn-ANI)-acidic	*S. aureus*	16	[33]
Gx-cl-poly(AA)-MW	*Bacillus subtilis*	14.17 ± 0.12	[34]
Gx-cl-poly(AA)-MW	*Salmonella enteritis*	13.66 ± 0.54	[34]

The pH sensitive hydrogel Gt-cl-poly(AA) was found to be suitable for colon-specific drug delivery. Since, the final drug release was achieved after 30 hrs, therefore the device was found to be effective for prolonged drug delivery [37]. Gum tragacanth based binary graft copolymer poly[(acrylic acid)-co-acrylamide] was found to be suitable for the controlled release of antihypertensive drug losartan potassium. This device showed final release of the drug after 34 hrs indicating its applicability for the prolonged release of the drug losartan potassium [38].

CONCLUSION

Smart materials based release devices derived from natural backbones have sufficient potential against different gram (+ve) and gram (-ve) bacterial strains and can be used as scaffolds for the treatment of infected wounds. These device can also be used for the controlled and sustained release of different drugs and thus can be used for health and safety purpose.

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