

Hydrated Polymer System as Efficient Carrier for the Delivery of Drugs Against Viral Infections

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ABSTRACT

Hydrogels are crosslinked polymers which has the ability to absorb water in aqueous media. Hydrogels are being prepared by different methods such as suspension polymerization, chemical or physical crosslinking, solution polymerization, radiation polymerization etc., and using different types of polymers. Hydrogels exhibiting swelling mechanism have been extensively used as drug carriers in the controlled drug delivery systems. The wide application of these biomaterials is due to its characteristics such as swelling in the aqueous environment, specific response to the pH, temperature, ion, electric stimuli sensitivity etc., Hydrogels of biocompatible polymers have good loading capacity and so widely used for the encapsulation of drugs which can be targeted to the specific sites. Since the rate of drug diffusion from hydrogels can be controlled, these materials are potentially useful as drug delivery systems. Controlled release of many drugs including anticancer and antiviral agents has been efficiently done using hydrogels. Especially various anti-HIV drugs have been successfully formulated as hydrogel systems for the controlled release and prolonged action. Bilayer and multilayer hydrogels have grown importance in recent days, wherein a burst release followed by controlled release could be achieved for superior therapeutic action at reduced dose and side effects. Also the efficiency of incorporating more than one drug in different layers of hydrogels is being investigated to improve combination therapy for various disorders.

Keywords: Hydrogel, biocompatible, encapsulation, antiviral, anti-HIV.

INTRODUCTION

Hydrogels which are insoluble polymeric materials undergo crosslinking through different mechanisms like complexation, aggregation, hydrogen bonding, hydrophobic association etc., which comes under reversible physical cross linking process and covalent bond formation which is an irreversible chemical cross linking process^{1,2}. Hydrogels can be classified on different basis such as preparation methods, polymer used, biodegradability, porosity, swelling behavior and most importantly based on the sensitivity to the environmental changes where it resides. Environmental sensitive hydrogels are responsive to stimuli such as pH, temperature, electromagnetic radiation, electric field, external stress, light, solvent, salt type or combination of these³. Hydrogels have application in biomedical and pharmaceutical field which includes its use in contact lenses, artificial skin, artificial tendon materials, wound healing dressings and as excellent candidates for targetable devices for the efficient delivery of therapeutic agents for the controlled release of drugs^{4,7}.

Hydrogels are now being efficiently used for the delivery of antiviral drugs due to its controlled release and prolonged action. Antiviral drugs which are used to treat the viral infections deal with many viruses including Pox viruses, Herpes viruses, Human Papilloma Virus, Varicella Zoster virus⁵.

Antiviral Drugs

Antiviral drugs are those which are being used to treat viral infections. Many antiviral drugs are available now and most of them are capable to act against viruses like herpes viruses, HIV, influenza A and B viruses, hepatitis B and C viruses. Researchers are going on to find antiviral drugs for pathogens in other families.

Dosage forms of antiviral drugs

The conventional dosage forms like tablets, capsules etc., available for the antiviral drugs are sometimes inefficient due to the low solubility of the compound, less bioavailability, short half-life, toxic effects etc. The drug administration through oral and parenteral route also faces some disadvantages such as gastric irritation, first-pass metabolism, difficult to swallow and poor patient compliance which recommends the search for new delivery systems. So the formulation of new drug delivery systems is necessary for the efficient delivery of the drugs. Various novel formulations are recently developed for the antiviral drugs which include hydrogels, micro emulsions, liposomes, microspheres, niosomes, submicronemulsions, solid dispersions, ocular inserts etc., The new drug delivery systems provides less dosing frequency and short period of treatment which makes the treatment easy, patient compliance and cost effective. The target delivery of drugs, biocompatibility and biodegradability as well as non-toxicity are the main

Table 1: Description of various hydrogel formulations of antiviral drugs.

Type of Hydrogel	Material	Drug	Route	Organism affected	Reference
Thermosensitive and mucoadhesive	Ploxamer/Hyaluronic acid	Acyclovir	Nasal	Herpes simplex virus	9
pH-sensitive	Acrylic acid(AA) and polyethyleneglycol monolaurylether monoacrylate(PEGLA)	Acyclovir	Oral	Herpes simplex virus	10
Mucoadhesive hydrogel	Poly vinyl pyrrolidone(PVP)/Chitosan /Carbopol	Acyclovir	Nasal	Herpes virus	11
Hydrogel patch	Sodium carboxymethyl cellulose	Acyclovir	Transdermal	Herpes virus	12
-	-	Monocaprin	Intravaginal/ Intracutaneous	Herpes simplex virus 2	14
Micro-emulsion based hydrogel	-	Penciclovir	Topical	Herpes virus	15
Superporous hydrogel	Acrylic acid and acrylamide monomers	Zidovudine	Oral	HIV	18
Iontropically gelled hydrogel	Sodium alginate and chitosan	Stavudine	Oral	HIV	19
Thermosensitive	Methyl cellulose	Tenofovir	Intravaginal	HIV	20
-	Acrylamide and 2-acrylamido-2 methyl propane sulphonic acid	Indinavir sulphate	-	HIV	22

advantages of the new drug delivery carrier systems⁵. Hydrogel which works on the swelling mechanism is an efficient drug delivery system due to its biocompatibility and controlled release behavior.

Hydrogels

Hydrogels consisting of various crosslinks are insoluble in water but works on the swelling mechanism in the aqueous environment. The presence of hydrophilic groups in the polymer backbone helps them to absorb water while the crosslinks resist their dissolution. The various chemical residues such as hydroxylic, amidic, carboxylic, etc., contributes to the hydrophilicity of the hydrogel networks^{6,7}.

Physical and Chemical forms of hydrogel

The crosslinks in the hydrogel can be physical crosslinks or chemical crosslinks. Hydrogen bonding, crystallisation, Van der Waals interactions, complexation, electrostatic interactions, physical entanglements and so on, results in physical crosslinks, while chemical crosslinks are due to the ionic or covalent bonds. Depending on the type of the crosslinks, physical or chemical hydrogels can exist⁸.

Antiviral Drugs in Hydrogels

Acyclovir

Acyclovir is being used to treat the infections caused by Herpes simplex virus and it has been studied by many researchers for preparing hydrogels of Acyclovir with different methods. Mayol L *et al* prepared hydrogel using poloxamer along with hyaluronic acid for thermosensitive as well as mucoadhesive platform for the delivery of Acyclovir and studied its rheological, mucoadhesive and

in vitro release properties. The polymeric platform was optimized and the *invitro* drug release studies showed that Acyclovir release could be prolonged or controlled for about 6h⁹. A modified form of pH sensitive Poly Acrylic Acid(PAA) hydrogels, P(AA-co-PEGLA) were prepared by MaJing *et al* to study the drug loading and release characteristics of less water soluble drugs such as Naproxen, Ibuprofen, Diclofenac sodium and Acyclovir. The mechanism of modified PAA hydrogel preparation involved the radical polymerization of a newly synthesized amphiphilic poly ethylene glycol(PEG) macromonomer, polyethylene glycol monolaurylether monoacrylate (PEGLA) and PAA with ethylene glycol dimethacrylate(EGDMA) as crosslinker which was induced by UV using 2-oxoglutaric acid as photoinitiator. The results showed that as the PEGLA concentration increases, the drug loading capacity was improved due to the high swelling ratio of modified hydrogel in the drug loading solvent because of the amphiphilic nature of the PEG macromonomer. The drug release rate could also be regulated in accordance with the PEGLA content in the hydrogel which resulted in some hydrophobic interaction of hydrocarbon tails in PEGLA that contributes an additional crosslinking¹⁰. Hydrogels which were made from mucoadhesive polymers such as polyvinyl pyrrolidone(PVP), chitosan and carbopol were compared and studied for the nasal delivery of Acyclovir with an irradiation dose of 15kGy for the crosslinking. In the study release of acyclovir was found to be dependent on the composition of gels and when compared to chitosan and

carbopol gels, PVP gels were found to have high release rate and in the presence of glycerol or PEG the drug release rate of PVP was found to get increased¹¹. Acyclovir hydrogel patch in matrix formulation was optimized and the influencing factors were investigated by Zhang Ling *et al* using orthogonal design method for choosing the optimized formulation and L9 table for the experiment in which the drug release from the patch was found to be 55.03% at 6h and a peeling strength of 58.4s¹².

Monocaprin

A number of saturated as well as unsaturated fatty acids and their monoglycerides containing hydrogel formulations were developed and evaluated by Kristmundsdottir T and *et al* to study which of them was most active in short incubation time against herpes simplex virus, HIV and bacteria like Chlamydia trachomatis and neisseria gonorrhoeae. The results showed that monocaprin which is the 1-monoglyceride of capric acid and lauric acid could cause a reduction of virus of 100000-fold in 1 minute at 20mM concentration. Monocaprin exhibited full activity while lauric acid was negligibly active. Also hydrogel formulations with 20mM concentration of Monocaprin showed high virucidal activity in *in vitro* and about 100000-fold inactivation of HSV-1 in human semen within 1 min¹³. Neyts J and *et al* have studied the effect of hydrogel containing Monocaprin in the prevention of intravaginal and intracutaneous infections in mice by HSV-2. At 20mM concentration of Monocaprin, the intravaginal and intracutaneous infections of HSV-2 was found to be prevented and also irritation and toxic effects were negligible when applied in the skin and vaginal mucosa¹⁴.

Penciclovir

Microemulsion based hydrogel (MBH) formulation of Penciclovir was studied by Zhu W and *et al* to analyse its effectiveness in topical administration. Compared to commercial creams available the microemulsion and MBH was found to have more permeation to both dermis and epidermis in the *in-vivo* study conducted in mice¹⁵.

Valganociclovir

Valganociclovir is the prodrug of ganciclovir used to treat the cytomegalovirus infections. Hydrogel microspheres of chitosan and hydroxypropyl cellulose (HPC) prepared by emulsion-crosslinking method with glutaraldehyde (GA) as crosslinker was employed for the encapsulation of Valganociclovir hydrochloride (VHCl) by B Mallikarjuna *et al*. The hydrogel microspheres showed an encapsulation efficiency upto 80% and a prolonged release of the drug was observed for 12h. The effect of drug release by varying the concentrations of VHCl crosslinking agent (GA) and HPC was also reported in the study which showed a fast release of drug at low concentration of crosslinking agent and high concentrations of HPC and vice versa. The increase in the concentration of crosslinking agent resulted in slow drug release due to the rigidity of polymeric chains at higher GA concentration and contraction of microvoids which resulted in the slow drug release through polymeric matrices. At low drug loading more void spaces were free through which only a less number of drug molecules could be transported. The hydrophilic nature of HPC resulted in

high swelling of the polymeric matrix at high HPC concentration which made the drug release faster¹⁶.

HIV Drugs in Hydrogels

Entry inhibitors

Polystyrene 4-sulfonate which is an entry inhibitor of HIV-1 was formulated in the microgel form and its enzymatically triggered release was studied by Meredith R Clark *et al*. The crosslinker used for the synthesis of microgel contained a peptide substrate specific to the seminal serine protease prostate specific antigen (PSA). Depending upon the PSA substrates GISSFYSSK and GISSQYSSK the microgel particles were composed of N-2 hydroxypropylmethacrylamide and bis-methacrylamide functionalized peptides. When the microgel was exposed to human seminal plasma (HSP) the network degraded and triggered the release of entrapped drug. The degradation of microgel particles in HSP with GISSFYSSK substrate was 17 times faster than with GISSQYSSK substrate. Microgel with 1 mol% GISSFYSSK peptide crosslinker was degraded completely in 30h in the presence of human seminal plasma at 37°C and polystyrene 4-sulfonate was released and reached 10µg/ml concentration within 30 minutes¹⁷.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Superporous hydrogel has been prepared and characterized for the effective release of zidovudine using acrylic acid and acrylamide as monomers and N, N methylene bisacrylamide as crosslinking agent and N,N,N,N' tetramethylethylenediamine ammonium persulphate as initiator pair for polymerization by Kotha Ashok Kumar *et al*. To help in the formation of pores in the superporous hydrogels sodium bicarbonate was used as blowing agent of gas. Superporous hydrogels were succeeded to prolong the therapeutic activity of zidovudine¹⁸. Hydrogel beads which were ionotropically gelled have been formulated and studied for the prolonged release of Stavudine by J S Patil *et al* using anionic gellan gum as the primary polymer with its counter ion to form gel and chitosan as the polyelectrolyte. The results showed that formulations with copolymer had a sustained release of Stavudine for 12h while the other with gellan gum alone showed a release for 10h and also the chitosan based formulations exhibited more encapsulation efficiency¹⁹. Stearic acid modified thermosensitive hydrogels of methylcellulose (MCS) is evaluated for the delivery of tenofovir by Li N *et al* and the Tenofovir loaded MCS hydrogel showed a sustained release for 10h without having a burst release²⁰. Supramolecular hydrogels that had the self delivering capacity was formulated by converting anti-HIV prodrugs. Reverse transcriptase inhibitors were covalently conjugated to a self assembled motif to form the supramolecular nanofibers that formed hydrogel matrices in weak acidic condition. The elasticity of hydrogels was found to be enhanced on treatment with prostate acid phosphatase and the formulation was found to exhibit good sustained release of anti-HIV drugs²¹.

Protease inhibitors

Hydrogels were formulated using the monomers acrylamide and 2-acrylamido 2-methylpropane sulphonic acid to study the dynamic release of Indinavir sulphate and

also the functionalization of psyllium by Baljit singh and Bala. The kinetics of swelling and release was also discussed in the work to understand the swelling mechanism and drug release. In buffer having pH 2.2 the hydrogel showed a drug release mechanism of Fickian diffusion²².

Other Anti-HIV Drugs

Baicalein

Baicalein was isolated from *Scutellaria baicalensis* Georgi which was a herbal medicine found in China. This compound had the activity against the infectivity as well as replication of HIV. Thermoresponsive hydrogel characterized with right gelation temperature for use in vagina was formulated using different grades of poloxomers (P188, P407), sodium alginate, hydroxypropylmethylcellulose and benzalkonium bromide. The physical and chemical stability of baicalein loaded temperature sensitive hydrogel formulation was studied by Qiuna Zhou *et al.* In the study Baicalein was complexed with hydroxypropyl- γ -cyclodextrin to increase its stability as well as solubility in aqueous solutions. The formulation with 18% P407, 0.96% Ba-HP- γ -CD, 0.5% HPMC, 4% P188, 0.02% benzalkonium bromide showed right gelation temperature and good rate of drug release at the site of administration. Ba-HP- γ -CD release from poloxamer hydrogel followed peppas equation which represented the coupled mechanism of corrosion and diffusion²³.

MiniCD4 M48U1

Thermosensitive and mucoadhesive hydrogels made from pluronic was loaded with miniCD4M48U1 as anti-HIV-1 microbicide and the release kinetics was studied by Kawthar Bouchemal *et al.* The drug release studies showed that the pluronic hydrogel [F127/HPMC (20/1 wt%) and F127/F68/HPMC (22.5/2.5/1 wt%)] retains 25% of M48U1 while 93% release of peptide was observed in Hydroxy ethyl cellulose (HEC) hydrogel which was used as control at end of the study of 24 hours. It was found that the M48U1 release was significantly higher in the initial hours which were sufficient to interact with HIV-1. Toxicity study of these pluronic hydrogels was also conducted using HeLa cells which showed less toxicity which make them good delivery devices of M48U1. Finally the evaluation of M48U1 permeation through macaque vaginal mucosa using Ussing chamber revealed no permeation of peptide through the mucosa which satisfied the local delivery effect of M48U1 loaded pluronic hydrogels²⁴.

CONCLUSION

Hydrogels are three dimensional structures mainly made up of hydrophilic polymers and can undergo swelling in aqueous media. Hydrogels are usually made up of biocompatible materials and are good candidates for the bioadhesive and controlled release devices and are highly used as drug and cell carriers and as matrices for tissue engineering. Based on the origin, ionic charge, swelling behavior, network structure and morphology, components present and drug release mechanism the hydrogels can be categorized into different classes. Hydrogels which are

used as good carriers for the delivery of drugs has been used for the delivery of many antiviral drugs such as acyclovir, penciclovir, monocaprin and rutin and anti HIV drugs such as entry inhibitors like sodium poly(styrene-4-sulfonate) and peptide triazole, zidovudine, tenofovir, stavudine, indinavir sulphate and reverse transcriptase inhibitors. These polymeric materials are well known and effectively used in various fields such as biomedical and pharmaceutical field. Hydrogels are being used for cartilage replacement implants, intraocular lenses, spinal disc implants, artificial arteries, muscles, a potential carrier for various drugs including various anti-HIV drugs etc., Recently, 'light guiding hydrogels' have been synthesized and tested for its effect in the suppression of high glucose levels in diabetic mice²⁵. Multilayer hydrogels are also now emerging which can effectively deliver different drugs at a time.

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