Mechanical, Mucoadhesive and Biocompatibility Behavior of Hydrogel Films: A Slow Anticancer Drug Delivery System

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Abstract: Systemic administration of anticancer drugs is associated with a number of side effects. Therefore, it needs some targeted drug delivery system to deliver the drug which would ensure relief from side effects along with the direct delivery of drug to the site of action in a controlled manner. Keeping in view the importance of mucoadhesive polymers in site specific drug delivery, in the present work, an attempt has been made to prepare, polysaccharide gum, PVA and AAm based mucoadhesive polymeric films for use as slow, site specific drug delivery system for oral cancer drug 5-fluorouracil. Characterizations of polymers have been carried out by SEMs, EDAX, FTIR, TGA/DTA/DTG, XRD and swelling studies. The in vitro release dynamics of drug and some important biomedical properties of hydrogel films (like blood compatibility, mucoadhesion, tensile strength, relaxation, resilience and bursting strength) have also been studied. The values of maximum detachment force ($F_{max}$) and work of adhesion ($W_{ad}$) of polymeric films have been observed $(1.026\pm0.175$ N) and $(0.073\pm0.010$ N mm) respectively. The release of drug in simulated saliva fluid occurred through Fickian diffusion mechanism and polymer films have been observed to be biocompatible nature.

Keywords: Polymers Matrix, Mucoadhesive, Hydrogels, Drug Delivery, Anticancer, Biocompatibility

1. Introduction

Bioadhesive drug delivery systems offer a new approach for the treatment of certain local and systemic diseases. A prolonged duration of drug action and optimization of drug delivery are some of the advantages that may be offered by bioadhesive systems. Such systems have been used for rectal, gastrointestinal, vaginal, nasal, ocular and buccal drug delivery. Among these various sites available, mucosa of the buccal cavity has been found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms [1,2]. Hydrogels are appropriate materials for the buccal drug delivery due to mucoadhesiveness, sustained-release property, good feel in the mouth, and safety [3,4]. Hydrogels are three-dimensional polymeric networks which swell quickly by imbibing a large amount of water. Several polymeric hydrogel systems have been prepared from natural and synthetic polymers [5]. Polysaccharides gums are promising biodegradable, nontoxic, freely available and less expensive polymeric materials which have been used to develop various hydrogel drug delivery devices [6,7].

Drug delivery to the oral cavity can have versatile applications in local treatment of diseases of the mouth, such as periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers. Long-term adhesion of the drug containing hydrogels against copious salivary flow, which bathes the oral cavity mucosa, is required to achieve this local drug delivery. For this purpose, many types of bioadhesive hydrogels systems have been devised [8-11]. In one study, buccal adhesive system containing propranolol hydrochloride has been found to be stable in natural human saliva and buccal adhesive has been observed to be comfortable in the human buccal cavity [12]. Llabot and coworkers [13] have designed a mucoadhesive 2-layered tablet for potential use in the treatment of oral candidosis containing nystatin. McQuinn and co-workers [14] have assessed oral mucosal delivery in human volunteers of opiate analgesic buprenorphine from a thin non-eroding mucoadhesive polymeric disk.

Keeping in view the importance of mucoadhesive polymers in site specific drug delivery, in the present work an
attempt has been made to prepare tragacanth gum, polyvinyl alcohol (PVA) and acrylamide (AAm) based mucoadhesive polymeric films for use as slow, site specific drug delivery system for oral cancer. In brief, the tragacanth gum is a dried gum exudation obtained from the stems and the branches of species Astragalus (family Leguminosae). It is generally recognized as safe (GRAS) by the Food and Drug Administration (FDA) [15]. Like other hydrocolloids, it has also good adhesive properties and good compatibility with synthetic polymer like PVP, to form polymeric blends [16]. Tragacanth gum has been used as mucoadhesive penicillin drug delivery system for delivering the bioactive agent to the oral mucosa [17]. PVA is a water-soluble, non-toxic and non-carcinogenic polymer. It has film forming and adhesive properties which make it excellent candidate for use in biomaterials. Poly(acrylamide) gels have been widely used as filler for reconstructive plastic and cosmetic surgery [18]. 5-FU is an anti-metabolite chemotherapy agent which is used to treat colorectal, pancreatic, breast, anal, stomach, skin, oropharyngeal and other cancers [19].

2. Experimental

2.1. Materials and Methods

Tragacanth gum (TG) [Loba Chemie Pvt. Ltd., Mumbai-India], polyvinyl alcohol (PVA) (M. Wt. 1,45,000) and acrylamide (AAm) [Merck Specialities Private Limited Mumbai-India], N,N'-methylene bisacrylamide (NN-MBA) [ACROS organics, New Jersey-USA], ammonium persulphate (APS) [Qualigens Fine Chemicals Mumbai-India], The drug used i.e. 5-Fluorouracil (5-FU) was obtained from Unimark Remedies Ltd., Mumbai-India.

2.2. Preparation of TG-cl-Poly(VP-co-AAm) Hydrogels

Reaction was carried out with known amount of tragacanth gum, definite concentration of PVA, initiator (APS), monomer (AAm), plasticizer (glycerol) and crosslinker (NN-MBA), taken in the aqueous reaction system in a beaker and these contents were stirred at constant speed for definite time to get homogeneous reaction mixture. Resultant mixture was poured into a petridish and polymer films were prepared by solution casting method. The crosslinked composite polymer matrix was then stirred first in distilled water and then in ethanol to remove the soluble fractions left in the film after polymer reaction. This polymer matrix was then dried in oven at 40ºC and was named as of TG-cl-poly(VP-co-AAm) hydrogel. The optimum reaction parameters for synthesis of hydrogels were evaluated by varying [AAm] from 0 to 0.35 mol/L and NN-MBA from 3.24×10⁻³ to 16.22×10⁻³ mol/L. The optimum reaction conditions for the synthesis of hydrogels were obtained as tragacanth gum = 5% (w/v), [AAm] = 0.28 mol/L, PVA = 2.5% (w/v), NN-MBA = 9.73×10⁻³ mol/L, APS = 6.57×10⁻³ mol/L and glycerol = 0.34 mol/L. The hydrogels prepared at optimum reaction conditions were used for further studies.

2.3. Characterizations

Scanning electron micrography (SEM) and electron dispersion X-ray analysis (EDAX) were taken on FEI SEM Quanta 256, Model D9393 (Singapore). Fourier transformed infrared spectroscopy (FTIR) of polymers were taken in KBr pellets on Nicolet 5700 FTIR THERMO (USA). Thermal degradation of polymers was studied with the help of thermo gravimetric analysis (TGA) on EXSTAR TG/DTA 6300 thermal analyzer. These thermograms are obtained in the range 30-800ºC under air atmosphere at 10ºC/min heating rate. X-ray Diffraction (XRD) measurement of polymers was made by using PAN-analytical X’Pert Pro powder diffraction system (The Netherland). Swelling studies were carried out by gravimetric method [20].

2.4. Drug Release Studies

The release dynamics of drug from the drug loaded hydrogel was determined by using the power law expression given by Ritger and Peppas [21,22] i.e. M(t)/M∞=kt^n. Where M(t)/M∞ is the fractional release of drug in time t, ‘k’ is the constant characteristic of the drug-polymer system, and ‘n’ is the diffusion exponent characteristic of the release mechanism. M(t) and M∞ is drug released at time ‘t’ and at equilibrium respectively.

2.5. Biomaterial Properties of Hydrogels

2.5.1. Blood Compatibility

The haemocompatibility was evaluated according to procedure reported in the International Standard Organization (ISO) (ISO10993-4,1999) [23] and two types of blood interactions were studied i.e. thrombogenicity and haemolytic potential. In thrombogenicity, the evaluation of thrombus formation on polymeric film surface was carried out by a gravimetric method [24]. Haemolytic potential was determined by using procedure as described in American Society for Testing and Materials (ASTM) [25].

2.5.2. Mucoadhesion

Mucoadhesion testing of the polymeric films was carried out using texture analyzer (TA.XT Stable micro System UK) with 5 kg load cell equipped with mucoadhesive holder. The maximum force required to separate the probe from the goat intestinal mucosa (i.e. maximum detachment force; Fmax in N) was directly recorded in the instrument and the total amount of work involved in the probe withdrawal from the tissue (i.e. work of adhesion; Wad) was then calculated from the area under the force versus distance curve in Nmm [26].

Wad = Area under the curve (force versus distance)
2.5.3. Tensile Strength

The tensile strength test of polymeric films (dimension 10 cm × 4 cm) was carried out in texture analyzer (TA.XT Stable Micro System UK) with 50 kg load cell. The tensile strength and elongation at break were calculated [27]. The area of the polymeric film of thickness (1.0 mm) used for each experiment was (10×4) cm². However 15 mm film was within the clamps, so the initial length of the film in the formulae was taken as 70 mm. Each test was carried out in triplicate. The instrumental parameters were fixed for this test.

2.5.4. Relaxation, Resilience and Bursting Strength

The relaxation, resilience and bursting strength of the polymeric films (dimensions 30 ×30 mm) was carried out in texture analyzer (TA.XT Stable Micro system UK) with 50 kg load cell. Each test was carried out in triplicate. A film strip was fixed in the frame and a probe was pressed down from fixed distance at definite force for a fixed time. The instrumental parameters were fixed for this test.

3. Results and Discussion

3.1. Characterizations

3.1.1. Scanning Electron Micrography (SEM) and Electron Dispersion X-ray Analysis (EDAX)

SEMs of TG-cl-poly(VA-co-AAm) hydrogels showed that the crosslinked polymer matrix has structural heterogeneity and some crosslinked networks found (Fig. 1). This may be due to grafting and crosslinking of AAm/PVA on to the polymeric backbone ‘tragacanth’. Energy dispersion X-ray analysis (EDAX) for elemental composition analysis of polymers showed C = 47.74, O = 26.24 and N = 24.92% in the samples. Presence of nitrogen in polymers indicates the incorporation of the monomer AAm and crosslinker NN-MBA in polymer matrix.

3.1.2. Fourier transformed infrared spectroscopy (FTIR)

FTIR spectra of TG-cl-poly(VA-co-AAm) hydrogels are presented in Fig. 2. In the FTIR spectra of TG-cl-poly(VA-co-AAm) polymer, the broad band at 3403.7 cm⁻¹ due to –OH and N-H stretching, band at 1670.3 cm⁻¹ due to C=O stretching (amide I band), band at 1611.0 cm⁻¹ due to N-H in plane bending (amide II band), band at 1247.1 cm⁻¹ due to C-N stretching (amide III band) of the amide group present in the networks and band at 1452.8 cm⁻¹ due to CH₂ bending vibrations have been observed. Further, some absorption bands at 2926.2 cm⁻¹ (due to C–H stretching modes of -CH₂ group), 1731.5 cm⁻¹ (due to stretching vibration of C=O groups of free carboxylic acid of the galactouronic acid of the gum), 1369.9 cm⁻¹ (due to C–H bending vibration modes of the methylene groups), and at 1076.5 cm⁻¹ (due to the C–O stretching vibrations of ethereal linkage present in the gum) have also been observed apart from usual bands in tragacanth and PVA [28-30]. These observations indicate the incorporation of poly(AAm) in the networks.
3.1.3. X-ray Diffractometry (XRD)

The powder X-ray diffraction patterns of TG-cl-poly(VA-co-AAm) polymer are shown in Fig. 4. In case of crosslinked TG-cl-poly(AAc) hydrogel there is no crystalline region in its XRD spectrum and a broad peak of less intensity shows amorphous nature of crosslinked hydrogels. Mishra and co-workers have also reported amorphous nature of okra-cl-poly(AAm) crosslinked hydrogels [31].

![Fig. 3. XRD spectra of tragacanth gum.](image1)

![Fig. 4. XRD of TG-cl-poly(VA-co-AAm) hydrogels](image2)

3.2. Swelling Studies

3.2.1. Swelling of Hydrogels as a Function of Feed [AAm]

The swelling trends indicate the increase in swelling with the increase in feed monomer concentration during the synthesis of polymers (Fig. 5.1). The increase in feed [AAm] in the reaction system during the polymerization has resulted into the formation of more hydrophilic hydrogels. Generally increase in monomer concentration is responsible for decrease in swelling of the polymeric material due to increase in crosslinking density. But reverse trends in the present case may be due high hydrophilicity of the acrylamide which may be probably dominate over the network density factor. Xinming and coworkers have also observed increase in swelling of hydrogels with increase in AAm concentration [32]. It is worthy to mention here that during the synthesis of hydrogels, when the [AAm] was varied, the all other contents kept fixed.

3.2.2. Swelling of Hydrogels as a Function of Crosslinker

At the optimum monomer concentration the hydrogels prepared with different crosslinker concentration and their swelling behavior was studied. The increase in crosslinker has not exerted a strong effect on the swelling (Fig 5.2). However in general the swelling first increased and then decreased with increase in feed crosslinker concentration during polymerization reaction. It means, after formation of optimum pore size in the polymer network, crosslinking density increased with further increase in crosslinker concentration in the reaction system. Hiremath and coworkers [33] have also observed similar trends of swelling with increasing [NN-MBA] in hydrogels. The swelling of the hydrogels as a function of monomer and crosslinker concentration occurred through Fickian diffusion mechanism. The values of initial diffusion coefficients are presented in Table 1.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Parameters</th>
<th>Diffusion exponent ‘n’</th>
<th>Gel characteristic constant ‘k’ ×10^2</th>
<th>Diffusion coefficients (cm²/min)</th>
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<td>Initial D_i × 10⁶</td>
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<td>Diffusion coefficients (cm(^2)/min)</td>
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<td>Initial (D_i \times 10^6)</td>
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<td>3.113</td>
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Effect of [NaCl]

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<td>0.410</td>
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</table>

Effect of temperature

3.2.3. Swelling of Hydrogels as a Function of pH, [NaCl] and Temperature of Swelling Medium

To study the effect of pH of swelling medium on the swelling of the TG-cl-poly(VA-co-AAm) hydrogels, the swelling of polymeric networks was taken in pH 2.2 buffer, pH 7.4 buffer, simulated saliva fluid (SSF ~ 6.75 pH) and distilled water (figure 5.3). Swelling is observed more in pH 7.4 buffer (4.208±0.026 g/g of gel) and SSF (4.063±0.028 g/g of gel) as compared to the pH 2.2 buffer (3.799±0.061 g/g of gel) solutions. Swelling of hydrogels increased with increase in pH of the swelling medium. At lower pH, the –CONH\(_2\) groups do not ionize and keep the polymer networks at its collapse state. At higher pH solution, these groups get partially ionized, and the –COO\(^-\) groups repel each other and were responsible for opening of pores and more swelling [31,34]. The water uptake by the hydrogels in 0.9% NaCl solution (4.083±0.078 g/g of gel) was less as compared to the distilled water (6.517±0.530 g/g of gel). This is due to a screening effect of the additional cations causing a non-perfect anion–anion electrostatic repulsion between –COO\(^-\) ions. This will decrease the osmotic pressure (ionic pressure) difference between the hydrogel networks and the external solution. The presence of ions in the swelling medium has a profound effect on the swelling behavior of the hydrogels because of charge screening effect. Swelling of hydrogels increased with increase in temperature of swelling medium. These swelling trends may be due to the increase in diffusion of water molecules in the polymer matrix and increase in the
segmental mobility of polymer. Swelling of the hydrogel occurred through Fickian diffusion mechanism in different media (Table 1).

### 3.3. Drug Release Studies

The release profile of the 5-fluorouracil from the drug loaded hydrogel in pH 2.2 buffer, pH 7.4 buffer, simulated saliva fluid (SSF ~ 6.75 pH) and distilled water is shown in Fig. 6. The release of drug is observed more in higher pH and solution of simulated saliva fluid. The trends of drug release from hydrogels are similar to the swelling trends of hydrogel in different medium. The release profile of drug in simulated saliva fluid indicates that these polymeric films may be used for mucoadhesive drug delivery to oral cavity. The release of drug from the drug loaded hydrogels occurred through diffusion mechanism which is approaching towards Fickian diffusion. In Fickian diffusion mechanism, the rate of penetrant diffusion (water ingressiion) is significantly slower than the polymer segment mobility (polymer relaxation) and the mechanism is diffusion controlled. In this mechanism, penetrant diffusion is controlled by the concentration gradient between the center and the outside of the particle.

![Fig. 6. Release profile of 5-flourouracil from drug loaded TG-cl-poly(VA-co-AAm) hydrogels in different medium at 37°C.](image)

### 3.4. Biomaterial Properties of the Hydrogels

#### 3.4.1. Blood Compatibility

Thrombogenicity of TG-cl-poly(VA-co-AAm) hydrogels was studied. The weight of clot formed and thrombose %age for polymers have been obtained as 0.498±0.018 g per 2mL of ACD blood and 82.36±3.33% respectively. It has been observed that clot formation was lower in the membranes than in the control and for this reason, the polymers are classified as non-thrombogenic [35]. Thrombogenic character is a desirable property of any material used for biomedical applications which evaluate its tissue and blood compatibility. Any material used in biomedical field, should not promote haemolysis and biocompatible material should not promote haemolytic in nature.

The haemolytic potential of for TG-cl-poly(VA-co-AAm) polymeric film was studied. The haemolytic %age for hydrogels is found to be 0.13±0.02% and it was observed less than 2% and this value has been assigned to the material which is non haemolytic [35]. Hence, polymeric film can proposed as biocompatible in nature.

#### 3.4.2. Mucoadhesion

Mucoadhesive strength of TG-cl-poly(VA-co-AAm) polymeric film with intestinal mucosa was studied and values of maximum detachment force (F_{max}) and work of adhesion (W_{ad}) have been observed as (1.026±0.175 N) and (0.073±0.010 N mm) respectively. It means that polymeric film binds to mucosal membrane with strong adhesion force. The mucoadhesion may be due to the supermolecular interactions of functional moieties present in the TG-cl-poly(VA-co-AAm) polymeric films and mucin of the goat mucosa of the intestinal membrane. Hassan and coworkers [36] have also obtained the similar observation, in case of mucoadhesion studies of tablet containing ondansetron hydrochloride (anti-emetic agent), in different polymers such as carbopol, sodium alginate, sodium carboxymethylcellulose low viscosity, and hydroxypropylmethylcellulose and ethyl cellulose. The strength was dependent on the property of adhesive polymers, which on hydration, adhere to mucosal surface, as well as on the concentration of the polymer used. The tablets containing a higher proportion of carbopol showed higher mucoadhesive strength for 15 seconds contact time. This high bioadhesive strength of carbopol may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region, as compared to other polymers that only undergo superficial bioadhesion [36]. Tobyn and coworkers [37,38] have found that contact time and force between pig gastric mucosa and sample, removal test speed of the probe, and pre-hydration time of polymer samples significantly affected the result obtained. Eouani and co-workers [39] have studied the comparison of the buccal mucoadhesive performance of different polymeric films using texture analyzer TA-XT2i. It has been observed that various polymers differing in their chemical nature, molecular structure as well as hydration status influences the buccal mucoadhesive performance.

#### 3.4.3. Tensile, Relaxation and Resilience and Bursting Strength

The tensile testing gives an indication of the strength and elasticity of the film and it is shown by tensile strength, and elongation at break [27]. The tensile strength of TG-cl-poly(VA-co-AAm) polymeric films was determined by texture analyzer with 50 kg load cell. The results showed that the breaking force, tensile strength and elongation at break of polymeric films of area of cross section (40×1) mm² are 122.1±21.4 N, 3.05±0.54 N/mm² and 110.89±11.52 % for TG-cl-poly(VA-co-AAm) polymeric films respectively. Relaxation and resilience properties of the TG-cl-poly(VA-co-AAm) polymeric films were determined by texture analyzer with 50 kg load cell and the percentage resilience...
of polymeric films of dimensions (30×30 mm²) and thickness (1.08±0.13 mm) has been found as 34.58±1.70 %, while its relaxation (% retained force) was 44.63±0.182%. Bursting strength of (76.13±6.35) N and distance at burst was (8.58±0.48) mm.

Overall, in the present studies, it has been observed that the TG-cl-poly(VA-co-AAm) polymeric films have numerous hydrophilic functional groups which allow hydrogen bonding with the substrate. It is responsible for the swelling in saliva fluid present in the buccal cavity. The swollen polymers have the maximum distance between their chains leading to increased chain flexibility and efficient penetration in to the mucus membrane. The presence of saliva within the oral cavity is also important in providing the moisture to allow adhesion to occur. It also provides medium for drug dissolution prior to absorption. The results of the mechanical properties, mucoadhesion studies and biocompatibility indicate that these polymeric films can be used conveniently and comfortably to the patients. The sufficient adhesion will keep the drug loaded TG-cl-poly(VA-co-AAm) polymeric film in place and deliver the drugs site specifically. This localization in the targeted tissue could be an improvement in its pharmacokinetic profile [40,41]. Woolfson et al. [42] designed a bioadhesive cervical patch containing 5-FU for the treatment of cervical intraepithelial neoplasia. The patch present a bilaminar design with a drug-loaded bioadhesive film cast from a gel containing 2 % (w/v) Carbopol® 981 plasticised with 1 % (w/w) glycerine. It has been observed that, despite the hydrophilic nature of 5-FU, substantial drug release through human cervical tissue samples is achieved during 20 h. The polymer based slow drug delivery systems will further give the relief from side effects which otherwise are associated with systemic administration of anticancer drugs. These polymeric patches are not only meant for drug delivery to the oral cancer but can be applied to the other system like rectal, gastrointestinal, vaginal, nasal and wounds, for the release of therapeutic agents. In our earlier studies, sterculia crosslinked PVA and sterculia crosslinked PVA-poly(AAm) hydrogel wound dressings have been reported and these polymeric films have absorbed 4.80±0.15 and 6.32±0.15 gram/g of gel of simulated wound fluid respectively and swelling occurred through Case II diffusion mechanism. The release of antibiotic drugs occurred through non-Fickian and Case II diffusion mechanisms respectively. These polymeric films have been observed to be permeable for oxygen and water vapor but have shown impermeability to the micro-organism. Sterculia-PVA hydrogel wound dressing has shown more blood compatibility as compared to the other film. All these results indicated that these hydrogel films have potential to be used as site specific slow mucoadhesive drug delivery system.

3.5. Conclusions

It is concluded from the foregone discussion that the composition of the polymer matrix and nature of the swelling medium influence the network structure and swelling of the hydrogels. Swelling and release of 5-FU from the drug loaded hydrogels have been observed more in solution of higher pH buffer and simulated saliva fluid. The TG-cl-poly(VA-co-AAm) polymeric films are classified as non-thrombogenic, non-haemolytic and hence, these films can proposed as biocompatible in nature. Further the results of mechanical properties and mucoadhesion studies indicate that materials possess a strong adhesive force which is essential requirement for developing the oral drug delivery system. Slow release anticancer drug 5-FU from the drug loaded polymeric films will be further provide the site specific delivery of drug besides diminishing the various side effects which otherwise are possible in systemic delivery of drug used in case of oral cancer. Overall, hydration, drug release and mucoadhesion results indicate that these polymeric films can act as a potential material for future biomedical applications may be used as mucoadhesive drug delivery system. However, further in vitro and in vivo research is needed in order to optimise the performance of polymeric films as oral delivery system and to make their use in practical applicability.

References


