Colloids and Surfaces B: Biointerfaces 144 (2016) 125–134

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Statistical modelling of the rheological and mucoadhesive properties of aqueous poly(methylvinylether-*co*-maleic acid) networks: Redefining biomedical applications and the relationship between viscoelasticity and mucoadhesion

David S. Jones *, Thomas P. Laverty, Caoimhe Morris, Gavin P. Andrews

School of Pharmacy, Queen's University Belfast, Medical Biology Centre, 97, Lisburn Road, Belfast BT9 7BL, United Kingdom

ARTICLE INFO

Article history:
Received 17 December 2015
Received in revised form 29 February 2016
Accepted 2 March 2016
Available online 4 March 2016

Keywords:
Poly(methylvinylether-*co*-maleic acid)
Viscoelastic
Mucoadhesion
Statistical modelling
Multiple linear regression
Rheology
Pharmaceutical
Biomedical

ABSTRACT

Poly(methylvinylether-*co*-maleic acid) (PMVE/MA) is commonly used as a component of pharmaceutical platforms, principally to enhance interactions with biological substrates (mucoadhesion). However, the limited knowledge on the rheological properties of this polymer and their relationships with mucoadhesion has negated the biomedical use of this polymer as a mono-component platform. This study presents a comprehensive study of the rheological properties of aqueous PMVE/MA platforms and defines their relationships with mucoadhesion using multiple regression analysis. Using dilute solution viscometry the intrinsic viscosities of un-neutralised PMVE/MA and PMVE/MA neutralised using NaOH or TEA were $22.32 \pm 0.89\ dL\ g^{-1}$, $274.80 \pm 1.94\ dL\ g^{-1}$ and $416.49 \pm 2.21\ dL\ g^{-1}$ illustrating greater polymer chain expansion following neutralisation using Triethylamine (TEA). PMVE/MA platforms exhibited shear-thinning properties. Increasing polymer concentration increased the consistencies, zero shear rate (ZSR) viscosities (determined from flow rheometry), storage and loss moduli, dynamic viscosities (defined using oscillatory analysis) and mucoadhesive properties, yet decreased the loss tangents of the neutralised polymer platforms. TEA neutralised systems possessed significantly and substantially greater consistencies, ZSR and dynamic viscosities, storage and loss moduli, mucoadhesion and lower loss tangents than their NaOH counterparts. Multiple regression analysis enabled identification of the dominant role of polymer viscoelasticity on mucoadhesion ($r > 0.98$). The mucoadhesive properties of PMVE/MA platforms were considerable and were greater than those of other platforms that have successfully been shown to enhance *in vivo* retention when applied to the oral cavity, indicating a positive role for PMVE/MA mono-component platforms for pharmaceutical and biomedical applications.

1. Introduction

Poly(methylvinylether-*co*-maleic anhydride) is a 1:1 copolymer of methyl vinyl ether and maleic anhydride that is available in various grades, including the free acid form, poly(methyl vinyl ether-*co*-maleic acid) (PMVE/MA) [1]. The low toxicity and excellent biocompatibility of PMVE/MA have resulted in its widespread use throughout the pharmaceutical and cosmetic industry [2,3]. In particular, this polymer has found use within toothpastes, mouthwashes, denture adhesives, hairsprays, transdermal patches, periodontal drug delivery systems and within stoma adhesive pastes [4–8].

PMVE/MA has been reported to form adhesive interactions with mucin-coated epithelial surfaces (termed mucoadhesion) [9–11] and, as a result, has been used as a component of a range of biomedical implants where retention at the site of application is important, e.g. as mucoadhesive nanospheres and microspheres, mucoadhesive buccal tablets, mucoadhesive implants for application to the periodontal pocket and microneedle transdermal systems. In such applications mucoadhesion has been shown to enhance the retention of the implant at the site of application, thereby facilitating controlled drug release and offering site specific mechanical properties [6,9,12,13]. The mucoadhesive properties of PMVE/MA are accredited to its large molecular weight, its favourable chemical functional groups and anionic charge, all of which aid interaction with the mucus layer through polymer mucin interpenetration and the formation of various hydrogen bridges [9,14,15].

* Corresponding author.
E-mail address: d.jones@qub.ac.uk (D.S. Jones).

http://dx.doi.org/10.1016/j.colsurfb.2016.03.008
0927-7765/

The successful pharmaceutical and biomedical applications of PMVE/MA have predominantly required the formation of networks with other polymers, most notably poly(vinylpyrrolidone, PVP). For example in a series of publications, Jones et al. described the formulation of networks of PMVE/MA and PVP that were designed for use as implants within the oral cavity [6,12,13]. In these studies it was shown that the rheological properties of the networks were engineered through modification of both the ratio of PMVE/MA to PVP and polymer concentration. Other studies have described the design of biomedical implants that involve the use of PMVE/MA in association with other polymers. For example, Moreno et al. described the formulation of thermosensitive hydrogels of PMVE/MA and Pluronic F127 that were designed for the controlled release of proteins [16]. Whereas the combined use of PMVE/MA and poloxamer 407 and hydroxypropylcellulose gels designed for the treatment of oropharyngeal cancer has been described [17]. Most recently however Jones et al. highlighted a significant concern regarding the use of interactive polymer networks involving PMVE/MA. The combination of PMVE/MA and poly(vinyl alcohol) produced rheologically structured, mucoadhesive networks. However, upon storage, the viscoelastic and mucoadhesive properties of the networks were observed to significantly and detrimentally change thereby obviating their use as biomedical implants. Conversely, there was no alteration of the rheological properties of mono-polymeric PMVE/MA systems on storage [18]. The use of binary polymeric networks involving PMVE/MA must therefore be treated with extreme caution.

Despite the (growing) number of publications that describe the use of PMVE/MA-based platforms for biomedical applications (particularly for drug delivery applications), there is a paucity of studies that have examined the physicochemical properties of PMVE/MA regarding its suitability as a monopolymeric platform for biomedical applications. This oversight is of scientific relevance for two reasons. Firstly, without an understanding of the rheological and mucoadhesive properties of PMVE/MA, the formulation of existing biomedical implants may not be optimal, with detrimental consequences on their clinical usage. Secondly, full understanding and knowledge of the rheological and mucoadhesive properties will offer possibilities for the use of this polymer for an enhanced range of applications, *e.g.,* as pharmaceutical implants, drug delivery applications and as mucoadhesive, viscoelastic implants designed to facilitate cataract removal [19].

Therefore, this study aims to provide a comprehensive description of the rheological properties of PMVE/MA and, for the first time, to specifically statistically examine the relationship of these properties to the mucoadhesive properties. In particular the generated data and the relationships between the various rheological and mucoadhesive properties will be statistically modelled, thereby providing a comprehensive characterisation of the relationship between these parameters. In so doing this study will offer a beneficial insight into the potential biomedical applications of PMVE/MA and of the contribution of physicochemical properties of PMVE/MA to mucoadhesion, an area as yet not fully clarified.

2. Materials and methods

2.1. Materials

Poly(methylvinylether-*co*-maleic acid, PMVE/MA) (Gantrez® SBF97) with an average molecular weight of approximately 1,200,000 Da was kindly donated by ISP, Surrey, UK. Sodium hydroxide (NaOH) pellets and triethylamine (TEA) were purchased from Sigma Aldrich, Dorset, England. All other chemicals were purchased from BDH Laboratory supplies Dorset, England and were of AnalaR grade, or equivalent quality.

2.2. Methods

2.2.1. Manufacture of dilute PMVE/MA solutions

Stock solutions (0.2–0.6 g/dL) of PMVE/MA were prepared by adding the required mass of polymer to an appropriate volume of deionised water (pH 5.0–5.2). The polymeric solutions (five replicate batches) were subsequently agitated using a mechanical stirrer. Dilution of stock solutions was carried out to obtain the desired concentration, with the final volume being corrected after neutralisation of the relevant systems. Neutralisation of suitable solutions was carried out *via* the drop wise addition of sodium hydroxide solution (30% w/w NaOH) or Triethylamine (TEA) until a pH value of 7.4 was obtained (measured using a Hanna Instruments pH meter). The solutions examined reflected a range of un-neutralised, TEA and NaOH neutralised PMVE/MA systems.

2.2.2. Manufacture of bulk aqueous PMVE/MA systems

PMVE/MA systems were manufactured *via* the slow addition of the appropriate amount of polymer (5–30% w/w) to deionised water under mechanical mixing *via* a mechanical stirrer. A number of gels had their pH adjusted to pH 7.4 using either a 30% w/w NaOH solution or TEA; with gel pH determined using a flat faced gel pH probe. To remove air, all samples were stored for 24 h prior to testing, with all testing being completed within a 72 h period. Bulk rheological measurements were performed using both continuous shear analysis and oscillatory analysis.

2.2.3. Viscometric analysis of dilute solutions

All viscometric analyses of PMVE/MA solutions (0.2–0.6 g/dL) were performed using Rheotek Ostwald U-tube viscometers sizes O–D. Solutions were added to the tube *via* a pipette until the required level was reached. The U-tube was then placed into a Rheotek water bath pre-set to 37 °C ± 0.5 °C and allowed to equilibrate for 15 min. The time required for the fluid to fall a predetermined distance was measured and used to calculate the kinematic viscosity (υ, mm^2 s^{-1}) (Eq. (1)).

$$\upsilon = kt \tag{1}$$

where: k refers to the U-tube multiplication factor and t refers the solution/solvent flow time (s).

From this the relative viscosity (η_{rel}) was calculated

$$\eta_{rel} = \frac{\upsilon}{\upsilon_o} \tag{2}$$

where: ν and ν_o refer to the kinematic viscosities of the polymeric solution and the solvent in which the polymer is dispersed, respectively.

The specific viscosity (η_{sp}) is then calculated:

$$\eta_{sp} = \eta_{rel} - 1 \tag{3}$$

The reduced viscosity (η_{red}) may be thus expressed as the ratio of the specific viscosity to the concentration:

$$\eta_{red} = \frac{\eta_{sp}}{C} \tag{4}$$

where C is the concentration of the polymer in g/dL [20].

U-tubes were chosen so that the efflux time for each solution was always above 200 s (or 300 s for the O size tube) thus allowing greater accuracy within measured results. The viscometric properties of five replicate solutions were measured in all cases.

Calculation of the intrinsic viscosity of each system [η] was performed using the Huggin's equation (Eq. (5)) or the equation described by Fuoss and Strauss (Eq. (6)) [21–23].

$$\eta_{red} = \frac{\eta_{sp}}{C} = [\eta] + k'[\eta]^2 C \tag{5}$$