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Development and characterization of tripolymeric and bipolymeric composite films using glyoxal as a potent crosslinker for biomedical application

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ABSTRACT

For various biomedical applications, biopolymeric films are often crosslinked using chemical crosslinker such as glutaraldehyde, which is considered as a toxic chemical. In this report, we have prepared and characterized biopolymeric films using different combinations of chitosan, CMC, alginate and PVA using glyoxal as the crosslinker. The prepared films were subjected to various physico-chemical and mechanical characterizations such as swelling index, surface pH, surface morphology analysis using SEM, interact ion study using XRD, flexibility study using tensile testing and hardness testing. Glyoxal crosslinking resulted in variation of physico-chemical and mechanical alteration of the chitosan-PVA films while it had the negligible effect on the CAP film. Further, the hardness of the films demonstrated a decrease in value in the crosslinked films as compared to non-crosslinked films. We have interpreted that glyoxal is a potential crosslinker for chitosan-based composite polymers while in this case, it did not show any significant effect on CMC and alginate based composite structures. Therefore, using this type of films would be the cheap, safe and new alternative in drug delivery and other biomedical applications.

1. Introduction

Biopolymers have been a boon for various biomedical applications such as drug delivery, tissue adhesives, wound healing coverings and scaffolds for tissue engineering. They are being employed attributed to their properties of biodegradability, biocompatibility, adhesiveness and non-immunogenicity. Various natural, semi-natural and synthetic polymers such as chitosan, silk, alginate, cellulosic polymers, poly acrylic acid (PAA), poly-lactic acid (PLA), poly (lactic-*co*-glycolic acid) (PLGA), polycaprolactone (PCL) have been employed for various applications. Natural and semi-synthetic biopolymers have added advantage of being readily biodegradable and a few are bioadhesive too and therefore they are widely utilized for drug delivery applications [1,2].

Chitosan, the deacetylated version of the parent polymer chitin, is one of the most exploited biopolymers. Apart from being biodegradable and biocompatible, it has a great anti-microbial activity. Chitosan is a natural bioadhesive too. Being a cationic polymer, it interacts with anionic groups easily and forms a strong bond. A few examples of its bioadhesive application are its mucoadhesive drug delivery system and bioadhesive surgical sutures [3]. Some other natural and semi-natural mucoadhesive polymers are alginate (ALG), carboxymethyl cellulose (CMC), Hydroxypropyl methyl cellulose (HPMC) while poly acrylic acid is the most utilized synthetic mucoadhesive polymer [4]. Mucoadhesive biopolymeric blended films are being clinically and experimentally tested for transbuccal and transdermal drug delivery systems. Transbuccal delivery of drugs primarily depends upon the interaction of the polymer and the mucin protein of the mucous membrane, permeation enhancing effect of added permeation enhancer and the swelling behaviour of the formulated films [5]. Though mucoadhesive polymers specifically do not show adhesiveness over skin, the formulated patches often are backed by an adhesive layer which could hold back the patch over skin for transdermal application. The polymeric films are also incorporated with special permeation enhancers which could make it easier for the drug to permeate through the highly keratinized epidermis [6]. Wound healing covering is another wide area of application of polymers. Being a great anti-microbial compound, chitosan is being used alone or as the primary ingredient of various patches used as wound covering [7]. A lot of in vitro, preclinical and clinical studies have been reviewed by Dai et al. regarding the antimicrobial and wound healing effect of chitosan based formulations [8].

Abbreviations: ASTM, American Standard Testing Materials; CMC, carboxy methyl cellulose; HPMC, hydroxypropyl methyl cellulose; IS, Indian standard; NaOH, sodium hydroxide; PVA, poly vinyl alcohol; PAA, poly acrylic acid; PLA, poly lactic acid; PLGA, poly lactic-*co*-glycolic acid; SEM, scanning electron microscopy; XRD, X-ray diffraction.

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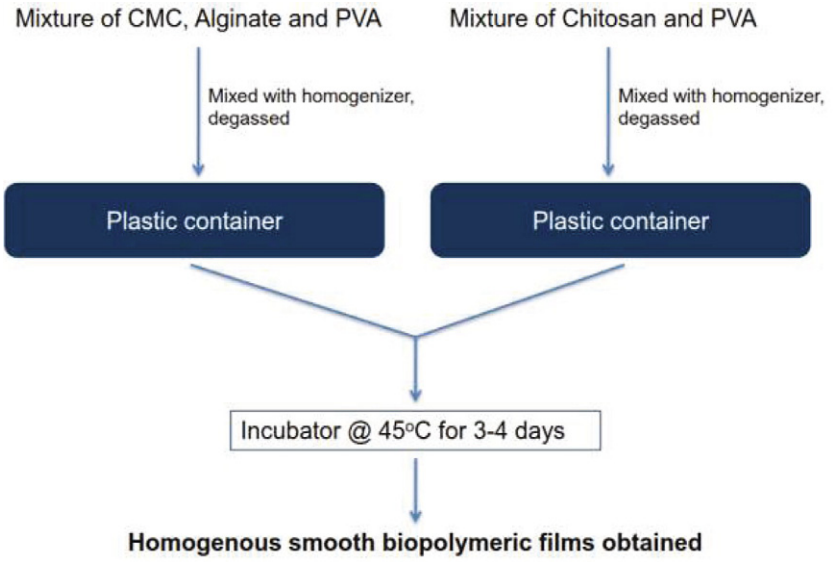

Fig. 1. A brief pictorial demonstration of solvent casting method.

Very often, blended polymeric films are crosslinked during their formulation to impart them strength. The most common chemical crosslinker applied is glutaraldehyde. Glutaraldehyde, however, is considered toxic for respiratory tract, eyes and skin and therefore alternative cross-linkers are being utilized for the polymeric films [9]. A few works has reported that glutaraldehyde crosslinked polymers pose risk of post implantation depolymerisation and further release of monomers. Glutaraldehyde has further been reported to accelerate the calcification of the implanted prostheses [10]. On the other hand, glyoxal has been shown to be cytocompatible and support viability of the cells [11]. In the experiment reported here we have developed a tripolymeric and a bipolymeric film having natural and semi-natural biopolymers using glyoxal as the crosslinker and reported a few physicochemical and mechanical properties of these biopolymeric films crosslinked with glyoxal compared to those without any crosslinker.

2. Materials and method

2.1. Materials

Chitosan [GRM9358] and CMC [GRM329] were procured from HiMedia laboratories India. Sodium Alginate [CAS 9005383] and PVA [CAS 9002895] were purchased from Loba Chemicals India while Glyoxal [92245072735] was purchased from SRL Chemicals. Glycerol [Merck; AK7AF57508] was used as the plasticizer. Acetic acid [Merck; AB8A580103] was used as the solvent content for dissolving chitosan.

2.2. Preparation of polymeric solutions

Chitosan, being soluble in acidic solution, was dissolved in 2% acetic acid (v/v) to form 1% (w/v) chitosan solution. CMC (1% w/v), Alginate (1% w/v) and PVA (5% w/v) were dissolved in double distilled water. All the solutions were kept for 4 h stirring on magnetic stirrer. The solutions were kept undisturbed overnight to get degassed.

2.3. Preparation of blended films

The blended films were formed in two combinations; Bipolymeric (Chitosan + PVA or ChPVA films) and Tripolymeric (CMC + Alginate + PVA or CAP films). A total of 4 films were developed, 2 with crosslinker and 2 without crosslinker. Initially, CMC (1% w/v), Alginate (1% w/v), chitosan (1% w/v in 2% acetic acid) and PVA (5% w/v) were prepared as the stock polymer solution. Glycerol (10% v/v) was used as the plasticizer for all the formulations. Glyoxal (5% v/v) was used as the crosslinker for 1 formulation each of both sets. The individual ingredients were mixed thoroughly on a magnetic stirrer and were further mixed under a homogenizer to get a clear uniform solution. The solution was further kept overnight to get degassed. The films were prepared using the established solvent casting method as described by Dong et al. [12]. (Fig. 1) Individual mixed solutions were then poured in plastic containers and kept in an incubator at 45 °C for 3–4 days. The films were carefully peeled off from the plastic plates for further evaluations. The quantitative details of all the ingredients are provided in Table 1.

2.4. Thickness measurement of films

The thickness of the films was measured using a manual vernier caliper. The thickness was measured at different portions and an average was calculated. The least count of the vernier caliper was 0.1 mm.

2.5. Surface pH measurement

The surface pH of the polymeric films is an important consideration for drug delivery at particular site. An acidic or alkaline pH of the film surface could be erosive for the buccal mucosa or epidermal surface. For transbuccal and transdermal drug delivery, the surface pH should be between 6.5 and 7.4, as per the physiological considerations. The films were washed with NaOH followed by distilled water to bring the pH to physiological level in accordance with buccal mucosa and epidermal surface. The pH was measured using a pocket-size pH meter by Eutech Instruments. The experiment was replicated to cross-check each value obtained

Table 1
Quantitative details of the ingredients in polymeric films.

Film formulation	CMC	Alginate	Chitosan	PVA	Glycerol	Glyoxal
F1 (CAP)	10 ml	10 ml	–	10 ml	3 ml	1.5 ml
F2 (CAP + G)	10 ml	10 ml	–	10 ml	3 ml	1.5 ml
F3 (ChPVA)	–	–	15 ml	15 ml	3 ml	1.5 ml
F4 (ChPVA + G)	–	–	15 ml	15 ml	3 ml	1.5 ml