ORIGINAL PAPER

Nig. J. Pharm. Res. 2017, 13 (1) pp 13-18
ISSN 0189-8434 Available online at http://www.nigjpharmres.com

The effect of formulation additives on the properties of films prepared using *Terminalia randii* Baker F Gum

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Natural polymers are becoming useful excipients in pharmaceutical formulations due to their non-toxic and biodegradable properties. One of their common uses is in the manufacture of polymeric films.

Objective: This present work is to evaluate the effect of plasticizer type and polymer type on the properties of Terminalia films.

Method: Films were prepared by solvent casting method using Terminalia, xanthan gums and hydroxylpropy lmethylcellulose (HPMC). Terminlia was also combined with xanthan, HPMC at different ratios using propylene glycol and glycerol as plaasticizers. The films were characterized using adherence, folding endurance and mechanical properties were determined using tensile strength and percent elongation. Disintegration was carried out in a disintegration apparatus using distilled water, 0.1M HCl (pH 1.2) and phosphate buffer pH 6.8.

Result: Films prepared with Terminalia and those prepared by combining Terminalia and xanthan gums showed adherence. Films plasticized with glycerol had higher folding endurance and tensile strength. When HPMC was combined with Terminalia, the disintegration of the films produced was significantly ($p<0.05$) reduced at pH 6.8

Conclusion: Glycerol plasticizer produced films with optimal properties, while combination of Terminalia gum and HPMC, produced films with optimal properties. Therefore, plasticizer and polymer must be carefully chosen for film formulations.

Keywords: Film, Plasticizer, Terminalia gum, Polymers, Tensile strength, Fold endurance

INTRODUCTION

Pharmaceutical industries are looking at ways of improving conventional dosage forms (Haque and Sheela 2015). One of such is the formulation of the drugs as films which was introduced about four decades ago, to overcome the problem of swallowing exhibited by tablets and capsules (Irfan *et al* 2016). These films have been shown to improve onset of action, reduce dose frequency and improve efficacy (Borges *et al* 2015). The films are made from polymeric materials and they could be mucoadhesive (Kassem *et al* 2017), buccoadhesive (Trastullo *et al* 2016), oral disintegrating films (Sharma *et al* 2016) and transdermal patches (Wang *et al* 2015).

Polymers on their own cannot form acceptable films (Panda et al 2014), therefore, there is need to add other excipients such as plasticizers. Plasticizers are small organic molecules added to polymers to reduce brittleness, impart flexibility, improve toughness, and reduce crystallinity, lower glass transition and melting temperatures (Vieria *et al* 2011). Contacts between polymers is also reduced thus decreasing rigidity of the three-dimensional structure thereby allowing deformation without rupture (Mekonnen *et al*. 2013).

Terminalia gum obtained from the incised trunk of *Terminalia randii* Baker F (family Combretaceae) has been found useful as a directly compressible excipient in controlled delivery of carvedilol (Bamiro *et al* 2012), as a binder in carvedilol tablet formulation (Bamiro et al 2010), as suspending agent (Bamiro *et al* 2014). In the light of the above uses of Terminalia gum, and in our search for other uses of this gum, we found that it has not been used in film formulation. Therefore, in this study, three polymers Terminalia gum (test polymer), xanthan gum and hydoxylpropy[methylcellulose (standards) and their mixtures in various ratios with Terminalia gum will be prepared as films by solvent casting method, using propylene glycol and glycerol as plasticizers. The influence of polymer type and plasticizer on the film properties will be evaluated.

MATERIALS AND METHODS

Materials

The materials used were Xanthan (M.A.F. by shanghai blueway trading co Ltd china), Hydroxyl propyl methyl cellulose (HPMC) E15 Premium LV (Jiangsu Guo Tahiintl Group Huatal Imp and Exp. Co. Ltd., China), *Terminalia randii* (Extracted in the Pharm. Tech. Lab. of Olabisi Onabanjo, Ago-Iwoye, University), Propylene glycol (PG) ((Karnataka fine chem. industries, Bangalore, India) and Glycerol (Gapuma Ltd, U.K).

Method

Extraction of Terminalia gum

Extraction of Terminalia gum has been described elsewhere (Bamiro *et al.,* 2010). Briefly gums collected from incised trunk of *Terminalia randii* was soaked in chloroform double strength water for 5 days with intermittent stirring. The mucilage was strained through a calico cloth and precipitated with 95% ethanol. The precipitated gum was filtered and washed with diethyl ether and dried in hot air oven. The dried gum was milled and passed through sieve size No 60.

Preparation of films

Polymeric films were prepared by solvent casting method. The components of the film formulations are presented in Table 1. The required amount (1.5 g) of polymer was weighed and dispersed in water and left for 8 hours for uniform dispersion. The plasticizer required was also mixed with water and the two mixtures were mixed with a magnetic stirrer (model H400S, Benchmark, USA) for 1 hour. The mixture was allowed to stand for 3 hours to allow removal of entrapped air. The mixture was poured into a petri dish, dried in hot air oven (Ketan Thermostated Oven, CAT NO 65118, India) at 50^{o}C for 8 hours.

The films were peeled from petri dishes, cut into 2 x 2 cm and stored in desiccator over silica until ready for use.

Tack test

Film strips were pressed between paper for 5 minutes and the degree of adherence of the film to the paper was determined (Chaudhary *et al* 2013).

Determination of film thickness

The measurement was taken at five different locations (centre and the four peripheral edges) with a micrometre screw gauge and the average was determined (Ofori-Kwakye *et al.,* 2012).

Folding endurance

The folding endurance was determined by repeatedly folding the film at a particular point. The number of times taken for the film to fold without breaking was taken as the endurance of fold (Meyer *et al.,* 2013).

Determination of the mechanical strength of films

The method of Ofori-Kwakye *et al.* (2012) was used with slight modification. Briefly, film free from air bubbles was held with a clamp. Different loads/weights were attached to the film strip, the load at break and elongation were recorded. Tensile strength and percent elongation were calculated from the following equations:

Tensile strength (Nmm^2) = load at break (N)/(strip thickness$\times$strip width)

% elongation =change in length/ original length $\times$ 100

Table 1: Components of film formulations

Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Terminalia randi (g)	1.5	1.5	_	_	_	_	0.75	0.75	0.5	0.5	1.0	1.0	0.75	0.75	0.5	0.5	1.0	1.0
Xanthan (g)	_	_	1.5	1.5	_	_	0.75	0.75	1.0	1.0	0.5	0.5	_	_	_	_	_	_
HPMC (g)	_	_	_	_	1.5	1.5	_	_	_	_	_	_	0.75	0.75	1.0	1.0	0.5	0.5
Propylene glycol (g)	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_
Glycerol (g)	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2	_	0.2
Water to (mL)	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

Disintegration of film

Disintegration was carried out on the film using a disintegration apparatus (BP, 2009). The disintegration was carried out in distilled water, 0.1M HCl and phosphate buffer pH 6.8 at a temperature of 37±0.5 ^{o}C.

Statistical Analysis

Statistical analysis was done to compare the effect of plasticizer type and polymer type on film properties using ANOVA (GraphPad Software Incorporation, San Diego, USA). At 95% confidence interval, p values of ≤ 0.05 were considered significant.

Results and Discussion

Tack test

Tack is the ability of a material to adhere instantaneously to a solid surface when brought into contact by a light pressure. This test is used to show the degree of dryness of a material, but it can also be used as the degree of adhesion. The results are presented in Table 2. When individual polymers were made into films, there was slight adherence. This adherence increased when Terminalia gum was combined with Xanthan gum. There was no adherence when Terminalia was combined with HPMC. Films showing adhesion to the paper indicates that the films have adhesive properties, therefore, they can be useful as bio-adhesive films.

Film thickness

The thickness of the films was between 0.22 mm and 0.44 mm. Films made from Terminalia gum alone produced the thinnest film. The result of the film thickness is presented in Table 1. Thickness determination is of importance as this is directly proportional to dose accuracy of the film (Nair *et al.*, 2013).

Folding endurance

The folding endurance of the films was between 67 - >400. Folding endurance of Terminalia gum film alone could not be determined because it was brittle. The results are presented in Table 2. Folding endurance is the ability of a film to withstand breaking when folded or bended repeatedly along the same plane (Patel *et al.*, 2009). The folding endurance of Terminalia film could not be determined because it was too brittle. The folding endurance of xanthan film containing glycerol was >400 (F4) while F3, that contained propylene glycol was 67. It was observed generally, that folding endurance of films formulated with glycerol was significantly higher ($p<0.05$) than those containing propylene glycol. This indicates that the type of plasticizer used had effect on the folding endurance. Plasticizers reduce glass transition temperature, thus making the films to be more flexible (Bharkatiya et al 2010). Without plasticizers, a brittle film will be formed. Plasticizers helps in breaking up bonds such as hydrogen bonds or Vander Waal's forces present in polymers, thus making them more flexible (Panda *et al.,* 2014). Polymer type also affected the folding endurance. Xanthan film (F3) containing glycerol with a folding endurance of >400 decreased when Terminalia gum was added (F10 & F12). When HPMC was used (F6), folding endurance was 180, when Terminalia gum was added (F16 & F18), folding endurance increased to >400.

Mechanical Strength

Tensile strength is the maximum strength a film can withstand being stretched before necking or cracking (Lim and Hoang 2013). The results of the tensile strength of films are presented in Table 2. The tensile strength of the films was low with individual polymers (2.63-7.58 N/Mm^2). Films with combined polymers had higher tensile strength (5.26-20.45 N/mm^2) except for F11 with a tensile strength of 2.38 N/mm^2. Addition of Terminalia gum to HPMC significantly ($p<0.05$) increased the tensile strength of the films. Mixing or crosslinking of two or more polymers have been shown to improve the Tensile strength of films (Dong *et al.*, 2006). It was also observed that films containing glycerol have higher tensile strength.

Table 2: Effect of polymer type and plasticizer on folding endurance and mechanical properties of films

Film Formulation	Adherence	Film Thickness (mm)	Folding Endurance	Tensile Strength (N/mm^2)	% Elongation
F1	+++	0.24±0.8	ND	ND	ND
F2	+++	0.22±0.98	ND	ND	ND
F3	+	0.38±0.75	67±1.00	2.63	8
F4	+	0.3±0.63	>400±0.00	7.58	4
F5	+	0.3±0	185±2.65	5.00	10
F6	+	0.3±0	180±4.51	5.00	8
F7	-	0.38±0.7	>400±0.00	5.26	10
F8	+	0.3±0.68	>400±0.00	6.58	8
F9	+++	0.44±0.8	100±2.00	5.36	0
F10	+++	0.36±0.8	298±3.79	13.89	4
F11	+++	0.42±0.75	358±3.79	2.38	2
F12	+++	0.28±0.4	240±2.52	7.14	4
F13	-	0.3±0	>400±0.00	8.33	0
F14	-	0.34±0.49	95±4.73	11.76	2
F15	-	0.22±0.4	95±6.08	20.45	4
F16	-	0.22±0.4	>400±0.00	15.91	4
F17	-	0.28±O.4	184±11.27	7.14	4
F18	-	0.28±0.4	>400±0.00	10.71	8

+++ Strong adherence (Difficult to peel from paper) + Weak adherence - No adherence

Percent Elongation is a useful parameter for testing the effectiveness of a plasticizer. The percent elongation results are presented in Table 2. It was observed that the percent elongation of films prepared with individual polymers were generally higher than those with combined polymers. This could have been due to the crosslinking between the polymers hence increase in bonds present within the polymer, thus making it difficult for elongation of the films. The films containing glycerol prepared with individual polymers gave lower percent elongation than films containing propylene glycol. Some researchers observed that when tensile strength was high, there was reduction in elongation (Unar *et al* 2010). This trend was observed with the films prepared with single polymers and some of those prepared with combined polymers

Disintegration time

Disintegration time is the time taken for the films to break up. The results of disintegration time are presented in Table 2. The ranking of disintegration time for Terminalia films (F1-F2) was 0.1M HCl<6.8 phosphate buffer<distilled water. Xanthan films (F3-F4) was distilled water<0.1M HCl=6.8 phosphate buffer and HPMC films (F5-F6) was 6.8 phosphate buffer<distilled water<0.1 M HCl. When Terminalia was combined with HPMC, there was significance ($p<0.05$) decrease in disintegration time at pH 6.8 (F13-F18), while there was significant ($p<0.05$) increase in disintegration time when Terminalia was combined with xanthan (F7-F12). This indicates that films produced by combination of Terminalia with HPMC will be good for oral film since average pH of the buccal cavity is 6.78 (Aframian 2006).

Table 3: Disintegration time (minutes) of films in different media

Film Formulation	Distilled Water	0.1M HCl	Phosphate buffer pH 6.8
F1	26±3.66	6±1.96	14±4.08
F2	25±3.56	6±1.81	15±4.10
F3	29±1.96	>30±0.00	>30±00
F4	26±4.69	>30±0.00	>30±00
F5	4±1.72	11±1.67	3±0.40
F6	4±1.60	13±1.53	3±0.50
F7	27±3.66	29±0.89	>30±0.00
F8	>30±0.00	26±4.94	>30±0.00
F9	>30±0.00	17±3.29	>30±0.00
F10	>30±0.00	15±4.50	>30±0.00
F11	21±4.36	13±3.66	16±0.63
F12	22±2.57	26±2.10	27±0.49
F13	3±1.17	26±1.79	4±0.63
F14	5±1.17	>30±0.00	4±0.98
F15	3±0.49	>30±0.00	6±1.49
F16	4±0.49	>30±0.00	3±1.20
F17	4±0.40	>30±0.00	6±0.98
F18	4±1.02	>30±0.00	7±1.47

Conclusion

The results of this work have demonstrated that when a film formulation is to be made, the polymer and plasticizer must be carefully selected depending on the use of the formulation. Formulations containing glycerol produced films with good optimal properties.

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Conflict of Interest: None declared

Received: 25 February, 2017

Accepted: 1 May, 2017