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Oral dissolving films of Chlorpheniramine maleate from Wheat Starch/Polymer Blends

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ABSTRACT

The aim of this work was to prepare oral dissolving films of Chlorpheniramine maleate using starch/polymer blends. Formulations of oral disintegrating films of chlorphenarime maleate were prepared from native (NAT), pregelatinised (PGL) and freeze-dried (FRD) wheat starches blended with hydroxypropylmethyl cellulose (HPMC). The material and rheological properties of blends of native and modified forms of the native and modified starches and the blended mixtures were determined. Modified starches were mixed with HPMC to form the starch/polymer blends. Chlorphenirame maleate was incorporated into the starch-polymer blends by dissolution. Films were obtained through the solvent evaporation method and evaluated for strength and drug release. The ranking for viscosity for the blends was NAT/HPMC > FRD/HPMC > PGL/HPMC. Film flexibility ranged from 18 to 41 in the order PGL/HPMC> NAT/HPMC > FRD/HPMC. Drug release for all films was within 10minutes. Flexible oral disintegrating film formulations of chlorpheniramine maleate were obtained from the wheat starch/HPMC blends.

Keywords: Oral films, Wheat Starch, Polymer blends, Chlorpheniramine maleate.

INTRODUCTION

An important drawback for oral dosage forms such as tablets and capsules for pediatric and geriatric patients has been difficulty in swallowing. Hence the emergence of oral thin film formulations as an advanced alternative to the traditional dosage forms. Thin films, which are similar in size, shape and thickness to a postage stamp, are typically designed for oral administration. They are usually administered by placing the strip on or under the tongue (sublingual) or along the inside of the cheek (buccal) (Alur *et al.*, 2001). Films offer an advantage over creams and ointments in that they deliver a measured dose of drug to the site of administration (Chinna and Madhusudan, 2010).

Starch, which is the second most abundant renewable polymer in nature, is inexpensive, fully biodegradable and has been widely studied for many years in the field of materials (Doane, 1992; Shogren *et al.*,1994; Odeniyi *et al.*, 2011a). It is a glucose polymer $(C_6H_{10}O_5)_n$ abundant in the seeds of cereal plants and in bulbs and tubers. Starches are generally non-toxic, biocompatible, biodegradable, abundant (Cascone *et al.*, 2001) and non-interacting with most drugs. However, as polysaccharides dissolve easily in water, cannot form stable hydrogels, an effective approach is to modify the native polymer and make them into a polymer gel networks to form polysaccharide and synthesized polymer blend hydrogels, which will serve as drug delivery systems.

Starch-based hydrogels have received increased attention due to their abundant availability, high swellability in aqueous solutions, as well as good biocompatibility and biodegradability (Zhang et al., 2005; Toshio et al., 2006; Seidel et al., 2001). However, only a few studies on starch/polymer blend hydrogels have been reported (Hashim et al., 2000; Kunal et al., 2006, Odeniyi and Ayorinde, 2012). These gels could be cast into films as a convenient dosage form.

This work was aimed at formulating oral thin films of chlorpheniramine from hydrogels prepared by physically blending native and thermally modified starches obtained from wheat (Triticum aestivum) with hydroxypropylmethylcellulose.

MATERIALS AND METHODS

The materials used were Wheat grains (Triticum aestivum), Hydroxypropylmethyl cellulose Methocel ®, K15M (Colorcon, England) Chlorpheniramine maleate powder (Sigma Chemicals, St. Louis, USA). All other reagents were of analytical grade.

Methods

Preparation of wheat starch powders

Wheat starch was extracted following the method of Riley et al., (2008).

Starch modification

The native wheat starch was modified to yield the freeze-drieed and pregelatinized forms according to method described by Odeniyi and Ayorinde (2012).

Preparation of the blends

Wheat starches were mixed with HPMC in different ratios to obtain the starch/Polymer blends.

Physicochemical properties of starches

Angle of repose

A 10g quantity of each the starch powders were poured into an open-ended glass cylinder with its bottom resting on a horizontal surface. On raising the cylinder vertically, the granules formed a conical heap at angle with the horizontal base, known as angle of repose. The height of the cone was measured and the angle of repose (θ) is given by the equation:

$$\theta = \tan^{-1} h/r$$

Where h = height of conical powder heap

r = radius of circular base

Determination of particle density

The particle density of starch powders were determined by the pycnometer method using xylene as displacement fluid (Odeniyi et al., 2011b).

Determination of pH

The pH of 1% dispersion of native, pregelatinized, freeze dried and starch/HPMC blends in water were determined using a pH meter.

Swelling capacity

A 5gm quantity of native and modified starch, and starch/HPMC blends in different ratio were weighed into a measuring cylinder. The tapped volume (Va) of the powders were determined. Each of the starch powders was dispersed in 100ml water. The volume of the sediment (Vb) in each solution was taken after 24hours. The swelling capacity was estimated as:

Swelling capacity = Va/ Vb……(1)

Where Va = tapped volume

Vb = volume of sediment after 24 hours

Determination of viscosity

Viscosity of the native and modified starches, and starch/HPMC blend in the different solutions were determined, using a viscometer (a Brookfield Model – DV-11 + Pro viscometer). Viscosity was determined at different temperatures (30, 40, 50, 60, 70 and 80 ºC).

Viscoamylography

Viscosity profiles of the native and modified starches and starch/polymer blends were obtained using a heating and cooling viscometer, series 3RVA (Rapid Visco Analyser) coupled with Thermocline for Windows software (Newport Scientific Pty. Ltd. Warriewood, NSW Australia). Heating of the slurry in the equipment was done under a constant rate of shear, and the increase in viscosity of material was measured as torque on the spindle and a curve was traced (Thomas and Atwell, 1999).

Parameters determined from the trace were peak viscosity, peak time, peak temperature, trough viscosity, breakdown, final viscosity, setback from trough and setback from peak.

Film Dosage Preparation

Starch and starch/polymer (5%w/v) mixtures were prepared using distilled water. Chlorpheniramine was added to the film base solutions, followed by thorough mixing. A 15ml volume (containing 1g chlorpheniramine and 1g of the starch mixture) of the prepared solution was poured into a plastic petri dish (diameter 54mm). The films were dried in the oven at 50 ºC for 12hours. Film formation was judged to have failed if a film could not be removed from the bottom of the dish.

Film Thickness

Film thickness was measured at 5 points on each film using a digital micrometer screw gauge. The folding ability of the films along its length and breadth was noted. The average thickness was obtained and the standard deviation calculated.

Film Flexibility Determination

The thin film (20×20 mm) from each formulation was repeatedly folded at the same place. The total number of foldings made before the film cracked was denoted as film flexibility value. The film was examined for cracks over the area of the bend under strong light. Three samples were examined for each formulation.

Uniformity of Drug Content

Samples (20×20 mm) from each formulation were cut and placed in 50mls of distilled water. The samples were allowed to dissolve at 37 ºC and drug content determined by UV spectrophotometer at 265nm (Unico, UV2102 PC). Determination was done in triplicate for each formulation.

Dissolution Test

The film produced was cut into 10x10mm and placed in the dissolution test apparatus basket USPXX III Basket Method (DBK- Dissolution Rate Test Apparatus, England). A 200ml of distilled water was placed in the glass container. This was done 100 revolutions per minute at 37 ºC. Aliquots of 5mls were taken at intervals of 1, 3, 5, 7 and 10 minutes. Absorbance was measured by UV Spectrophotometer (Unico, UV2102 PC) at 265nm.

STATISTICAL ANALYSIS

Statistical analysis was done on the results obtained using Students' t-test and ANOVA. At 95% confidence interval, p value lower or equal to 0.05 was considered the limit of significance.

RESULTS

The formulations developed in this study were simple easy to prepare and relatively economical. Films from the natural and modified starches were brittle, hence the need for incorporation of HPMC. The results presented are for the starch/HPMC 1:1 blends as they were found be coherent and easy to remove from the petri dishes.

The physicochemical properties of the native and modified wheat starch are presented in table 1. The rheological properties of the starches and starch/HPMC blends are presented in Table 2 and Figures 1 and 2.

The characteristics of the films obtained from the blends are given in Table 3 and include film thickness, weight, film description, flexibility and percentage drug content. The effect of temperature on the viscosity profiles of the starch/HPMC blends are presented in Figure 3. The release profiles of chlorpheniramine maleate from the starch/HPMC films are shown in Figure 4.

Table 1: Physicochemical properties of the starches

Starch forms	Particle density (g/cm^3)	Angle of repose (°)	pH	Swelling capacity
Native	0.99±0.01	68.83±0.02	4.67±0.01	0.81
Freeze-dried	1.03±0.03	59.93±0.01	5.83±0.01	0.83
Pregelatinized	1.07±0.01	59.67±0.02	5.31±0.13	0.29

Table 2: Rheological properties of starches and starch/polymer blends

Test Sample	Peak viscosity (cP)	Trough viscosity (cP)	Breakdown (RVU)	Final Viscosity (cP)	Pasting Temp (°C)
NAT	2561	1619	942	1098	71.1
FRD	5447	3217	2230	2240	91.2
PGL	4696	2578	2118	4166	79.9
NAT/HPMC1:1	1042	602	440	193	72.5
FRD/HPMC 1:1	1692	1182	510	923	91.2
PGL/HPMC 1:1	1292	597	695	860	70.9

Table 3: Characterization of Films of Natural Polymer Blends

FILM COMPOSITION	Film thickness (mm)	Weight (mg)	Description	Film flexibility	Drug Content (%)
NAT/ HPMC 1:1	1.954± 0.21	10.91± 0.11	Transparent	20.2 ± 2.4	96.8 ± 1.2
FRD/ HPMC 1:1	1.388± 0.16	9.04± 0.15	Transparent	18.7± 3.1	98.6 ± 1.5
PGL/ HPMC 1:1	1.251±0.14	8.91±0.01	Transparent	41.2 ±1.6	95.3± 2.4

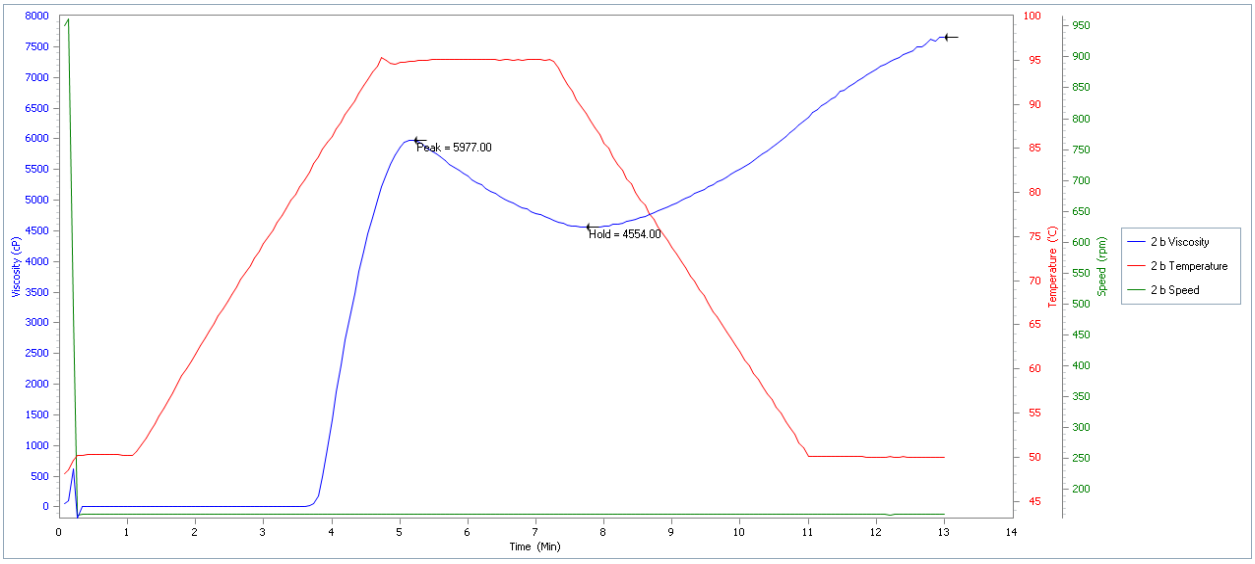

Figure 1: RVA Analysis of Freeze-dried Wheat Starch

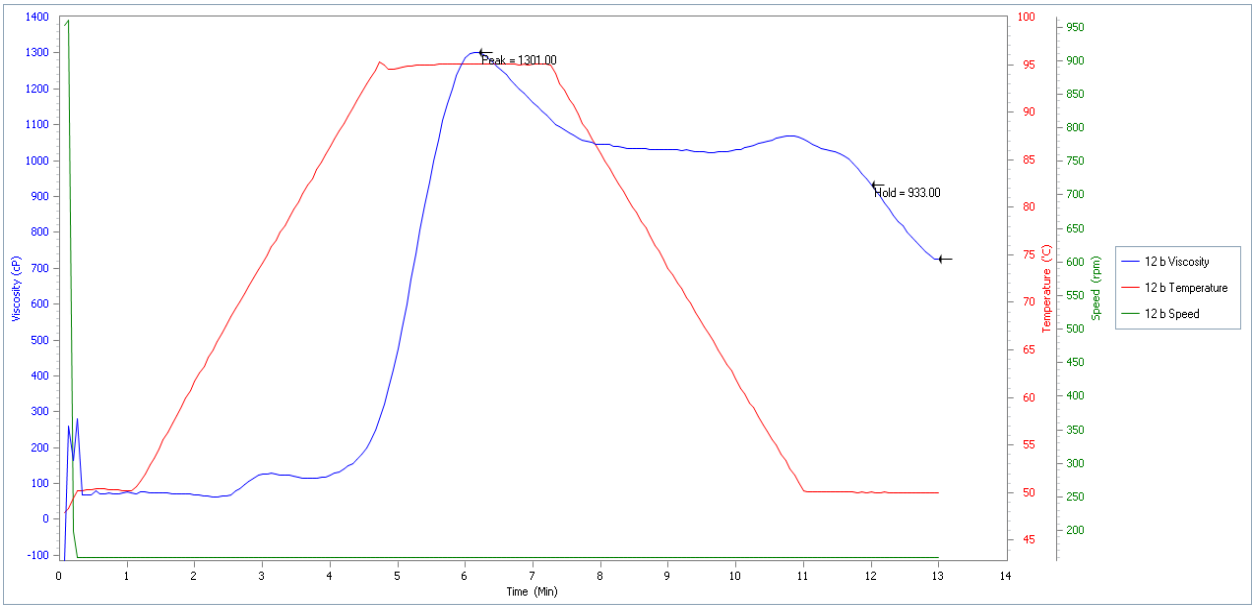

Figure 2: RVA Analysis of FRD / HPMC 1:1 blend

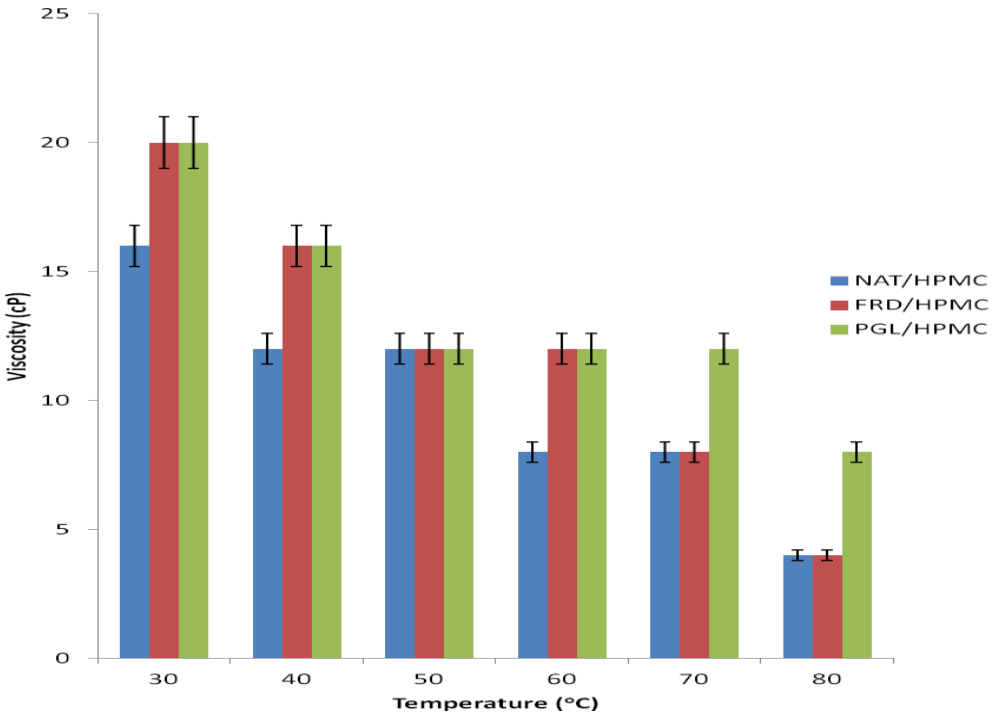

Figure 3 **:** Effect of temperature on the viscosity of Starch/Polymer blend hydrogel (1:1

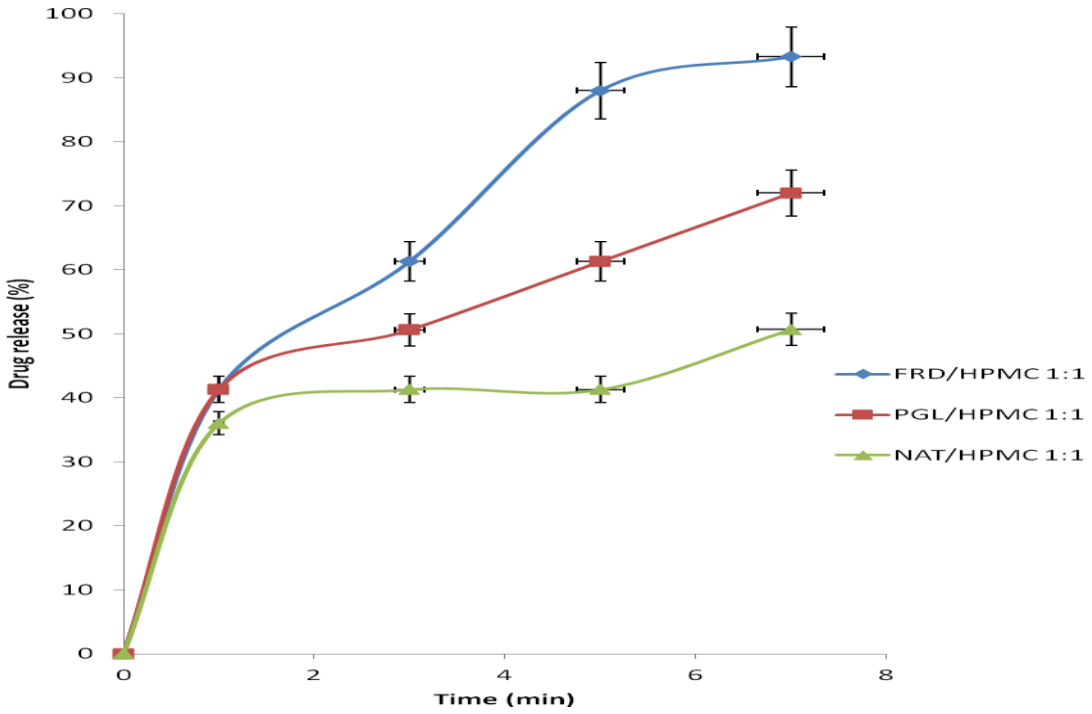

Figure 4: Dissolution profiles of Chlorpheniramine maleate buccal films. Each value represents an average of three determinations. (Mean ± SD,n = 3).

DISCUSSION

Values of angle of repose for the starches are shown in Table 1. This is a measure of the frictional forces between the particles in a loose powder and characterizes powder flow. Values less than 30^{o} represent materials with good flow properties. All the starches were found to have high values of angle of repose of between 59.67^{o} to 68.83^{o} with the ranking in the order: Native starch > freeze dried starch > pregelatinized starch. A slight improvement in the flow properties of the starches was observed. This could be due to the reduction in intermolecular association in the native starch granules (Akintayo and Akintayo, 2009; Odeniyi and Ayorinde, 2012).

The swelling capacity of the starches are given in Table 1. The swelling capacity is a measure of the ability of the starch to retain water. It was observed from the results obtained that the degree of swelling was in the order freeze-dried wheat starch > native wheat starch > pregelatinised wheat starch. Freeze drying caused a slight increase in the hydrophilicity of the native starch, while pregelatinization caused a decrease. However, the swelling capacity for all the starch/polymer blends, including HPMC alone, was 100%, showing a 100% capacity to hold water. This shows that the hydrophilicity of HPMC allowed retention of water molecule in the starches, thereby increasing the swelling power (Betancour-Ancona *et al*, 1997). The capacity to capture water influences parameters such as mechanical properties and surface mobility which would be essential in hydrogels and medicated films (Akhila and Emilia, 2006).

Table 2 shows the viscosity profile the native, modified and starch/polymer blends while Figures 1 and 2 show representative viscosity profile for freeze-dried wheat starch and freeze-dried wheat starch/HPMC blend. The profile presents changes in the starch granules that occur during the heating and cooling cycle in the Rapid Visco Analyzer (Thomas and Atwell, 1999). An increase in

viscosity is recorded as granules begin to swell during the obtained at which point there is a majority of fully swollen, intact granules. During the high temperature hold phase (95 oC), the granules begin to break down, polymer solubilization continues, and molecular alignment occurs within the shear field of the instrument. At this point, a drop in viscosity is recorded (Breakdown viscosity). During the subsequent cooling phase, solubilized amylose and amylopectin polymers begin to reassociate (retrogradation) and another rise in viscosity is traced to a final viscosity. This second rise in viscosity is usually referred to as set-back from peak and the difference between final and trough viscosities is called set-back from trough. Low values of these parameters imply that the materials are resistant to changes in viscosity during the heating and cooling cycle (Adedokun and Itiola, 2010). Further, peak time and temperature of viscosity indicate an inverse relative sensitivity of the starches to heat. Viscosity parameters for starches and starch/HPMC blend at ratio 1:1 are given in Table 4. The ranking of pasting temperature for the starches was Freeze-dried > native > pregelatinized, with no significant difference. The same trend was observed for the starch/HPMC blend indicating that effect of HPMC is uniform on the native and modified starches.

The effect of temperature on starch/HPMC blends is given in Figure 3. While there was a general decrease in the blend viscosity with increased temperature, the pregelatinized starch/HPMC blend showed more stability. Changes in the thermal, mechanical and swelling characteristics of the composite blend could be attributed to hydrogen bonding between HPMC and the starch molecules with the modifications influencing the observed response (Lyons et al., 2009).

The physical characteristics of the chlorpheniramine films are given in Table 3. All the films were transparent with insignificant differences in weight and thickness. Film flexibility was found to be significantly ($p<0.05$) different between the formulations. Films obtained from native wheat and freeze-dried starch blends with HPMC were found to be less flexible and were relatively quick to break on folding while that of the pregelatinized starch/HPMC blend did not break until after forty foldings. Pregelatinisation has previously been reported to increase the tensile strength of tablet formulations in which it was initial heating phase. A peak viscosity is included and this may account for the observed flexibility (Odeniyi et al., 2011a). This has implication in the manufature, handling and use of the films. While HPMC alone has been observed to form films, the films were not sufficiently flexible (Kulkarni et al., 2010).

Drug release profiles from the films are shown in Figure 4. All films completely dissolved within ten minutes. The release rate was in the rank order FWS/ HPMC > PWS/HPMC > NWS/HPMC. Drug release from the FWS/HPMC film was above 80% after five minutes, while those of PWS/HPMC and NWS/HPMC were about 60% and 40% respectively.

CONCLUSION

Modification of wheat starch resulted in improved material and viscosity properties. The properties of wheat starch were further improved by inclusion of HPMC to form starch/polymer blends. The freeze-dried formulation of wheat starch/ HPMC blend showed the best formulation properties in terms of release while the pregelatinized starch/HPMC blend was the best in terms of film flexibility.

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