Development of Pharmaceutical Gel Base Containing Sodium Carboxymethyl Mungbean Starch

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ABSTRACT

A high-viscosity sodium carboxymethyl mungbean starch (SCMMS), prepared by a carboxymethylation reaction with monochloroacetic acid in an alkaline condition, using methanol as a solvent, was investigated for the potential use as a pharmaceutical gelling agent. Gel bases were originally prepared from four commercial polymers, including carbopol (CP), hydroxypropylmethylcellulose (HPMC), methylcellulose (MC) and sodium carboxymethylcellulose (SCMC) to yield starting gel bases at different concentrations. The appropriate concentrations of gelling agents in gel bases were found to be 1.5% w/w for Carbopol 941, 4% w/w for HPMC and MC and 2%w/w for SCMC. SCMMS was then used to partially substitute the commercial gelling agents at the commercial polymer to SCMMS ratio of 3:1, 1:1 and 1:3. Six mixed-gelling agent formulations with good appearances and viscosity were selected and, along with the four starting formulations, were subjected to the satisfaction evaluation in 34 volunteers. The results showed that the formulations containing CP-SCMMS at ratio of 1:1 and 1:3, HPMC-SCMMS at ratio of 1:1 and MC-SCMMS at ratio of 3:1 yielded gel bases with higher scores of satisfaction, compared to their starting sole gelling agent formulations. Statistical analysis revealed that the satisfaction was influenced significantly by the spreadability (p = 0.001) and the ease of rubbing (p = 0.009). The incorporation of ibuprofen into the selected gel base formulations showed no evidence of separation and resulted in only slight decrease of viscosity, while the clarity and stability remained unchanged. These results exhibited the potential of SCMMS, which can be produced domestically, either as a partial substitute to the commercial gelling polymers or, with more intensive study, as a new, effective, sole gelling agent for topical gel preparation.

Key words: Mungbean starch, Gel base, Carboxymethylation, Modified starch, Ibuprofen gel, Product's satisfaction, Descriptive statistic, SPSS

INTRODUCTION

Sodium carboxymethyl starch (SCMS), a chemically-modified starch, is officially listed in the United States Pharmacopeia (USP) and the British Pharmacopoeia (BP) and has been widely used in the food industry. This starch ester derivative is soluble in unheated water and forms paste with smoother texture, higher flexibility and strength than those of pregelatinized starches (Mishra et al., 1990). The viscosities of SCMS pastes are varied, depending on the reaction conditions used in the preparation, including the acid-to-base ratio, the amount of water in the reaction, time and temperature of the reaction and the type of solvent. In addition, SCMSs prepared from different types of native starch (e.g., tapioca, rice, corn, etc.) exhibit different physicochemical properties which lead to a broad application of SCMSs as many types of pharmaceutical excipients, for examples, binder (Pitaksuteepong, 1995), disintegrant (Teruya, 1995) and suspending agent (Suwannapakul, 1997). Our group has recently reported the preparation and physicochemical properties of sodium carboxymethyl mungbean starches (SCMMSs) (Kittipongpatana et al., 2006a), the evaluation of SCMMSs as a potential suspending agent (Kittipongpatana and Sirithunyalug, 2006) and as a film-former for tablet coating (Kittipongpatana et al., 2006b). At similar viscosities, SCMMS paste also shows the highest degree of clarity compared to SCMSs prepared from other types of starch and therefore, can potentially be employed in the development of an aqueous gel base for topical gel preparations, either solely or in combination with other gelling agents. In this study, a high-viscosity SCMMS is investigated as a new potential gelling agent and is employed to partially substitute four commercial gelling agents, including carbopol (CP), hydroxypropylmethylcellulose (HPMC), methylcellulose (MC) and sodium carboxymethylcellulose (SCMC) (Allen et al., 2005) in the preparation of pharmaceutical gel bases.

MATERIALS AND METHODS

Materials

Mungbean starch was obtained from Sitthinan Co. Ltd. (Pine brand, Thai Industrial Standard, TIS 948-2533). Chemicals and solvents used in the preparation and analysis of modified starches were of analytical grade or equivalent. Methanol used to wash the final products was of commercial grade but was double-distilled before use. Commercial gelling polymers included carbopol (CP), hydroxypropylmethylcellulose (HPMC), methylcellulose (MC) and sodium carboxymethylcellulose (SCMC). Ibuprofen was a gift from Siam Pharmaceutical Co. Ltd. Chemicals used to prepare gel formulations were of pharmaceutical grade or equivalent.

Methods

Preparation of Sodium Carboxymethyl Mungbean Starch

A high-viscosity sodium carboxymethyl mungbean starch (SCMMS) was prepared and the physicochemical properties were determined according to the procedures described by Kittipongpatana et al., (2006a). In brief, 40 g of mono-

chloroacetic acid was dissolved in 200 g of methanol then, while stirring, 140 g of native mungbean starch powder was added into the solution, followed by 80 mL of 50% sodium hydroxide solution. The mixture was heated to 70°C where it was maintained for 60 minutes, with continuous stirring. At the end, the reaction was stopped by neutralization with glacial acetic acid. The liquid supernatant was decanted and the powder product was washed several times with 80% methanol and a final wash with 100% methanol. The modified starch was oven-dried at 50°C for 6 hours and was passed through sieve no.60.

Preparation of Gel base Formulations

Carbopol (CP) was used at concentrations between 0.5 to 2% w/w while hydroxypropylmethylcellulose (HPMC), methylcellulose (MC) and sodium carboxymethylcellulose (SCMC) were used at concentrations between 1 to 5% w/w. The formulation was as follow:

Polymer

Propylene glycol	10.0	mL
Denatured alcohol	8.0	mL
Triethanolamine	1.5	mL
Water qs. to	100.0	g

The viscosity, spreadability and general appearances of each gel base formulation were noted. The pH of each formulation was also recorded.

Preparation of mixed-polymer gel bases and selection of gel base formulations

Based on the viscosity and general appearances of the gel bases, one concentration for each polymer was selected and SCMMS was used to partially replace the original gelling agent in different ratios of commercial polymer : SCMMS (3 : 1, 1 : 1, 1 : 3). The polymer blends were mixed and their viscosities determined. Six mixed-polymer formulations were selected based on clarity, gel textures, viscosity and spreadibility, along with four commercial gel base formulations, for satisfaction assessment by volunteers.

Physicochemical properties of selected gel base formulations and volunteers' satisfaction assessment

Viscosity

Apparent viscosity of each formulation was measured, using a Brookfield R/S-CPS rheometer (for semisolid). The measuring system was CC48 DIN. The mode used was CSR (controlled shear rate). The measured parameters consisted of three steps: (1) an increase of rotation speed from 0 to 1,000 rpm in 1 min, (2) held at 1,000 rpm for 1 min, and (3) a decrease of rotation speed from 1,000 to 0 rpm in 1 min. All measurements were performed in triplicate, at a controlled temperature of 25±1°C. The data were analyzed with a Brookfield Rheo 2000 software. The apparent viscosity for all samples in this study was measured at a shear rate of 1,000 s^{-1}. Viscosity was expressed in mPa s.

Clarity

Gel base (2.5 mL) was placed in a disposable cuvette and the absorption was measured at 700 nm on a spectrophotometer against a water blank.

Volunteers' satisfaction on the products

The product satisfaction was assessed in 34 volunteers (n=34) from a workplace by using a questionnaire. Each volunteer was asked to evaluate ten formulations by applying approximately 0.1 g of the products on the skin and to rate each formulation from a scale of 1 to 5; 1 being the least satisfaction or the worst quality, while 5 being the most satisfaction or the best quality. The questionnaire consisted of two main parts: (1) volunteer's personal data, including age (divided into ranges of 10-20, 21-30, 31-40 and above 40-years-old) and gender and (2) the formulation data. The topics of evaluation included texture, spreading, grittiness, disappearance after applying, ease of rubbing, irritation and volunteer's satisfaction. The data were statistically analyzed using multiple regression method. The results were used in the selection of suitable formulations for further study.

Preparation of Ibuprofen Gel

Three gel base formulations with the highest satisfaction scores were employed in the preparation of a medicated gel. An anti-inflammatory agent, ibuprofen, was used as model drug at the concentration of 0.5% w/w. The general appearances, viscosity and spreadability of the medicated formulations were assessed and compared to those of the gel bases.

Statistical Analysis

Descriptive statistic was used to describe the product's physical properties and subject satisfactions. Multiple regression was employed to determine the factors affecting subject satisfactions at 95% confidence level ($p<0.05$). All analyses were carried out using SPSS for Windows version 10.0.

RESULTS AND DISCUSSION

Preparation of Sodium Carboxymethyl Mungbean Starch

The physicochemical properties of the prepared SCMMS were consistent with those previously reported (Kittipongpatana et al., 2006a). The degree of substitution (DS) was determined to be 0.3482. The powders were freely soluble in unheated water; a 1% w/v solution yielded a pH of 9.0. When dispersed in water and allowed to fully swell, SCMMS formed clear, viscous gel at a concentration between 1 and 4% w/w. At a concentration of 5% w/w or higher, it formed thick gel which suggested a potential use as a sole gelling agent.

Properties of commercial gel base formulations

Comparisons on the viscosity, pH, spreadability and general appearances of the gel base formulations containing varied concentrations of different commercial gelling agents are shown in Table 1.

Table 1. Certain properties of gel bases prepared by using different commercial gelling agents at varied concentrations.

Gelling Agent	Conc. (% w/w)	Viscosity	pH	Spreadability	Textures
CP	0.5	++	7.5	good	foamy
	1.0	+++	7.5	good	foamy
	1.5	++++	7.4	good	foamy
	2.0	++++	7.4	good	foamy
HPMC	1	-	8.9	good	too soft
	2	+	9.0	good	
	3	++	9.1	good	
	4	+++	9.1	very good	
	5	+++	9.1	very good	very sticky
MC	1	-	8.8	good	too soft
	2	+	8.9	good	
	3	+++	9.1	very good	
	4	++++	9.0	very good	
	5	++++	9.2	very good	too hard
SCMC	1	+	9.0	good	too soft
	2	+++	9.1	good	
	3	+++	9.0	require rubbing	
	4	++++	9.1	require rubbing	too hard
	5	++++	9.2	require rubbing	too hard

viscosity; - very low, + low, ++ medium, +++ high, ++++ very high

The formulations containing 1.5% w/w CP, 4% w/w HPMC, 4% w/w MC and 2% w/w SCMC were selected as representatives for each gelling agent, based on their overall properties and textures. Most formulations had pH of 8.8-9.2 due to the presence of the alkaline triethanolamine in the formulation, with the exception of those containing carbopol in which the acidity of the polymer counteracts the alkaline effect to pH 7.4-7.5.

Properties of mixed polymer-SCMMS gel base formulations

Tables 2 to 5 show certain properties of gel base formulations containing mixed commercial polymer and SCMMS, at three different ratio, as gelling agents. The increasing ratio of SCMMS caused a slight increase in the pH of most formulations due to its alkaline property. The clarity of all gel base formulations was not affected, while the viscosity was slightly decreased when the SCMMS ratio in the formulations were increased. All gel base formulations showed good spreadability on the skin.

Table 2. pH, clarity, viscosity, spreadability and general appearances of gel base formulation containing carbopol and SCMMS as gelling agents at different ratios.

Formulation	Ratio	Polymer (%w/w)		pH	clarity	viscosity	spreadability	note
		CP	SCMMS					
CP-A	3 : 1	1.125	0.375	7.5	clear	++++	good, stick well on skin	bubbles, foamy
CP-B	1 : 1	0.75	0.75	7.8	very clear	+++	good, stick well on skin	bubbles, foamy
CP-C	1 : 3	0.375	1.125	8.0	clear	+++	good, stick well on skin	bubbles, foamy

viscosity; - very low, + low, ++ medium, +++ high, ++++ very high

Table 3. pH, clarity, viscosity, spreadability and general appearances of gel base formulation containing HPMC and SCMMS as gelling agents at different ratios.

Formulation	Ratio	Polymer (%w/w)		pH	clarity	viscosity	spreadability	note
		HPMC	SCMMS					
HPMC-A	3 : 1	3.00	1.00	8.9	very clear	++++	very good, stick on skin	
HPMC-B	1 : 1	2.00	2.00	9.2	very clear	+++	very good, stick on skin	
HPMC-C	1 : 3	1.00	3.00	9.1	clear	+++	good, stick on skin	slightly soft texture

viscosity; - very low, + low, ++ medium, +++ high, ++++ very high

Table 4. pH, clarity, viscosity, spreadability and general appearances of gel base formulation containing MC and SCMMS as gelling agents at different ratios.

Formulation	Ratio	Polymer (%w/w)		pH	clarity	viscosity	spreadability	note
		MC	SCMMS					
MC-A	3 : 1	3.00	1.00	8.6	very clear	++++	good, stick well on skin	
MC-B	1 : 1	2.00	2.00	8.8	very clear	+++	good, stick on skin	
MC-C	1 : 3	1.00	3.00	8.9	very clear	+++	good, stick on skin	soft texture

viscosity; - very low, + low, ++ medium, +++ high, ++++ very high

Table 5. pH, clarity, viscosity, spreadability and general appearances of gel base formulation containing SCMC and SCMMS as gelling agents at different ratios.

Formulation	Ratio	Polymer (%w/w)		pH	clarity	viscosity	spreadability	note
		SCMC	SCMMS					
SCMC-A	3 : 1	1.50	0.50	9.0	clear	++	good, stick to skin	Very liquid, not gel-like
SCMC-B	1 : 1	1.00	1.00	9.0	clear	+	good, slightly stick to skin	Very liquid, not gel-like
SCMC-C	1 : 3	0.50	1.50	9.0	clear	+	good, does not stick to skin	Very liquid, not gel-like

viscosity; - very low, + low, ++ medium, +++ high, ++++ very high

Selection of gel base formulations

Viscosity and clarity

The viscosity and clarity of ten selected gel base formulations, six of which contained mixed polymers while the other four contained sole gelling agent, were determined. The spreadability was also noted before being subjected to satisfaction evaluation on volunteers (Table 6). The viscosities of the gel bases, measured by using a semisolid format viscometer, were greater than 10.0 mPa.s, with the exception of gel bases D (SCMC 2%) and G (CP 0.375% + SCMS 1.125%) of which the viscosities were less than 6 mPa.s. However, the viscosity of this magnitude is generally acceptable for use as gel base. All gel bases exhibited very low absorption at UV 700 nm ($A<0.10$) which suggested good clarity of the products.

Volunteers' satisfaction on the products

Of the 34 volunteers, 11 were male (32.35%) and 23 were female (67.65%). The ages of the volunteers were in two ranges, 10-20 years old (14, 41.18%) and 21-30 years old (20, 58.82%). The average scores of subject satisfactions ranged from 3.00±1.07 to 3.76±0.99 (Table 6). Product satisfaction, in a decreasing order, was: G > F > I > A = H = J > D > B > E > C. Multiple regression analysis showed that factors significantly affecting the satisfaction were the spreading of gel base ($p = 0.001$) and the ease of rubbing ($p = 0.009$), while most products received high score on grittiness and disappearance after applying. A mathematic model could be derived as:

Subject satisfaction = 0.37 + 0.572 spreading + 0.544 ease of rubbing
($r^2 = 0.8110$)

Subject satisfaction of product G was higher than others and it accounted for 75% of the total. Subject satisfaction could be maximized by improving physical properties of the products. This determination suggested that subject satisfaction depended mainly on spreading and ease of rubbing, therefore it is necessary to improve these properties in order to maximize subject satisfaction. However, these two

factors can explain only 81% of the variance in subject satisfaction which indicates that there are other factors that may influence subject satisfaction. One possible factor is the texture of the products in which the volunteers' scores varied. Thus, to maximize subject satisfaction, more concerns with the product's other properties should be taken into account.

From the results of both the physicochemical properties and the satisfaction assessment by volunteers, gel bases F, G, I and J were then selected for further studies on the incorporation of the model drug ibuprofen.

Table 6. Viscosity, clarity and volunteers' satisfaction scores on key properties of ten gel base formulations selected for further evaluation.

Gel base	Gelling Polymer (%w/w)	Viscosity (mPa s, ±SD)	Clarity (A_{700} nm)	Evaluated Topics						
				Texture	Spreading	Grittiness	Disappearance after applying	Ease of rubbing	Irritation	Satisfaction
A	CP 1.5%	16.89±0.15	0.024	3.35±1.01	3.29±0.97	4.38±0.95	4.26±1.02	3.35±0.85	4.38±0.85	3.38±0.95
B	HPMC 4%	15.46±0.34	0.042	2.85±1.37	3.26±0.96	4.12±0.95	4.35±0.98	3.32±0.81	4.24±0.85	3.15±1.08
C	MC 4%	17.63±0.39	0.032	4.00±1.04	3.06±1.01	4.29±0.80	3.76±1.33	3.06±1.07	4.12±1.07	3.00±1.07
D	SCMC 2%	5.81±0.02	0.064	3.56±0.99	3.18±1.06	3.65±1.45	4.24±1.13	3.44±1.05	4.35±0.92	3.32±1.04
E	CP 1.125% + SCMS 0.375%	13.96±0.13	0.036	2.65±1.30	3.18±0.90	4.08±0.97	4.38±0.78	3.50±0.75	4.38±0.82	3.12±1.04
F	CP 0.75% + SCMS 0.75%	10.82±0.21	0.041	3.03±1.49	3.85±0.93	4.32±0.88	4.47±0.75	3.38±0.77	4.41±0.82	3.65±0.98
G	CP 0.375% + SCMS 1.125%	5.09±0.07	0.056	3.47±1.48	3.88±1.01	4.53±0.61	4.47±0.79	3.91±0.93	4.35±0.92	3.76±0.99
H	HPMC 3% + SCMS 1%	12.48±0.04	0.048	3.65±0.88	3.47±1.05	4.29±0.97	4.18±1.09	3.29±1.12	4.32±0.98	3.38±0.92
I	HPMC 2% + SCMS 2%	10.17±0.03	0.070	3.50±1.21	3.35±0.88	4.41±0.78	4.44±0.82	3.65±0.88	4.47±0.79	3.47±1.02
J	MC 3% + SCMS 1%	15.35±0.04	0.050	3.62±1.04	3.26±0.99	4.38±0.82	4.29±0.97	3.35±0.85	4.29±0.94	3.38±1.07

Preparation of ibuprofen gel

The pH and clarity of ibuprofen gel products formulated, using a mixed ratio of commercial gelling agent and SCMMS, and their viscosity, spreadability and appearances in comparison with the non-medicated gel bases are presented in Table 7. Changes in the viscosity of formulations F and G were possibly due to the presence of carbopol in the formulations. Carbopol is pH-sensitive and generally exhibits highest viscosity at neutral pH (7.0-7.5). A significant drop of pH upon the incorporation of the acidic ibuprofen caused a viscosity decrease in carbopol-containing formulation and increased the turbidity (A700 nm) of the product compared to that of the gel bases. The properties and appearances of formulations I and J, on the other hand, remained mostly unchanged upon the addition of ibuprofen.

Table 7. pH, clarity, viscosity, spreadability and general appearances of ibuprofen gel base formulations (0.5% w/w) prepared using polymer-SCMMS gel base formulations.

Formulation	pH	Clarity (A_{700} nm)	Viscosity compared to gel base	Spreadability	Appearances
F	5.5	0.087	decreased	Easily, but skin stickness decreased	Slightly cloudy gel
G	5.8	0.108	decreased	Easily, but skin stickness decreased	Slightly cloudy gel
I	7.5	0.075	unchanged	unchanged	clear gel
J	7.5	0.065	unchanged	unchanged	clear gel

CONCLUSION

Sodium carboxymethyl mungbean starch (SCMMS) can be used to partially substitute commercial gelling agents in the preparation of aqueous gels. The viscosity and clarity of SCMMS gel texture are comparable with those of the commercial gelling agents. The optimum amount of substitution can be up to 50% of the original gel base amount to obtain a stable and good texture gel while the viscosity still remains in an acceptable range. At higher substitution ratio, the viscosity is partially sacrificed but certain desirable characteristics can still be achieved. Gel bases containing mixed HPMC/SCMMS and MC/SCMMS gelling agents can be used to formulate ibuprofen gel while those containing mixed CP/SCMMS require further formulation adjustment to overcome stability problem due to pH. The results from this study suggest the potential and possible use of SCMMS as gelling agent in topical gel formulation, which is the first step towards the development of SCMMS as a sole gelling agent in the medicated gel products.

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