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$AlCl_3$ Cross-Linked and Spray Dried Carboxymethyl Sago Cellulose Microspheres as Potential Carriers for the Enteric Delivery

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Abstract

A semisynthetic polymer of carboxymethyl sago cellulose (CMSC) was synthesized from Malaysian sago biomass and further used in the development of drug delivery system. Recently, we have reported spray-dried carboxymethyl sago cellulose (CMSC) microspheres for enteric release and dissolution enhancement of piroxicam. In the present investigation, an attempt has been made to improve the enteric release property of CMSC microspheres using aluminium chloride as a cross-linker in the spray drying process and prednisolone as a model drug. CMSC microspheres loaded with prednisolone were prepared using a cross-linker concentration of 0%, 0.01%, 0.025% and 0.05%. All the drug-loaded microspheres were found to have high drug entrapment efficiencies (DEE) ranging from 99% to 106.1%. FT-IR spectroscopy has confirmed the cross-linking in CMSC microspheres as well as intact and amorphous nature of the entrapped drug. Field Emission Scanning Electron Microscope (FESEM) results have shown agglomeration of microspheres and the presence of drugs on the surface. Cross-linked microspheres have shown better efficiency than the uncross-linked microspheres in restricting drug release in stomach pH. Only about 5% of the loaded drug was released from cross-linked microspheres at pH 1.2 while 10% of the drug was released from uncross-linked microspheres. Also, cross-linked microspheres have exhibited faster drug release in pH 6.8 than the uncross-linked microspheres. Spray-dried and $AlCl_3$ cross-linked CMSC microspheres have shown promising results in enteric drug delivery as well as dissolution enhancement.

Keywords

Microspheres, Carboxymethyl Sago Cellulose, Drug Delivery, Prednisolone

1. Introduction

Metroxylon sagu is known as sago palm that rich source of starch and it serves as one of the various forms of staple food for communities across the globe. Malaysia (particularly in Johor Bharu and Sarawak) is one of the highest producers and exporters of sago starch and at the same time generates a large amount of sago biomass, which poses an environmental problem. It is therefore favourable if sago biomass can be converted into useful products that would greatly decrease the amount of water pollution contributing to the environment. A semi-synthetic polymer of carboxymethyl sago cellulose (CMSC) was synthesized from Malaysian sago biomass in our lab and further used in the development of drug delivery system [1] [2].

Spray drying is a common method used to prepare microspheres or microcapsules for loading and administration of various drugs [3] [4]. It is a relatively rapid and simple technique that can produce a good yield with high drug entrapment efficiency [3]. In spray drying, the polymer is firstly dissolved into a homogenous solution under high-speed homogenization. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range of 1 - 100 μm. Microspheres products are then separated from the hot air by cyclone separator while the trace of solvent is removed by vacuum drying [4]. In previous work [4] we have exploited hydrophilicity of CMSC to increase the dissolution of poorly water-soluble drug piroxicam by producing drug-loaded spray-dried CMSC microparticles.

Prednisolone is a steroid medication that is used to treat a certain type of allergies, inflammatory conditions, and autoimmune disorders [5]. Poor dissolution and gastric ulcerations are two main issues in the oral administration of prednisolone. An ideal delivery system should restrict prednisolone release in the stomach and at the same time should improve drug dissolution in the small intestine. Hence in the present investigation, an attempt has been made the first time to formulate spray-dried and $AlCl_3$ cross-linked CMSC microspheres for the ideal delivery of prednisolone. Prednisolone loaded CMSC microspheres were synthesized by spray drying using different % of aluminium chloride and characterized by entrapment efficiency, Fourier-transform infrared spectroscopy (FT-IR), field emission scanning electron microscopy (FE-SEM) and *in vitro* release studies.

2. Experimental

2.1. Material

CMSC (0.6 degree of substitution) was synthesized by a method established in our lab as indicated in our previous publication [1] [6]. Prednisolone was purchased from Lianyungang Zhongyi International, China. $AlCl_3$ was obtained from Friedemann Schmidt, Malaysia. All other reagents used were of analytical grade.

2.2. Preparation of the CMSC Microspheres

CMSC microspheres were synthesized using a scheme indicated in Figure 1. A 2% (w/v) of 125 mL CMSC solution was prepared and 25 mg of drug was added. The mixture was stirred at 800 rpm for 10 min using a stirrer (Thermo Scientific Cimarec, Malaysia) and sonicated (Hielscher UIP500hd, Germany, 80% amplitude for 4 min) to prepare a homogenous solution. The aluminium chloride solution of 0.05%, (w/v) of 125 mL was prepared separately. To prepare the 1:1 volume ratio of CMSC and $AlCl_3$ solution, 125 mL of each of the above solution was mixed (Table 1) and stirred for 30 min using a magnetic stirrer at 50 rpm. To prepare the 2:1 ratio of volume, 166.67 mL of 2% CMSC/drug mixture and 83.33 mL of 0.05% w/v $AlCl_3$ were added together and stirred for 30 min using a magnetic stirrer at 50 rpm. Spray drying was performed in SD-06 spray drier (Lab Plant, UK) using 1 mm nozzle. The following conditions were used in the production: inlet temperature of 160˚C, pump speed (30 mL/min), and deblocker speed (medium).

The same procedure was used to formulate various batches of prednisolone loaded CMSC microspheres with reduced $AlCl_3$ concentrations of 0.025%, 0.01%, and 0% w/v. Similarly, unloaded microspheres were also prepared for characterization. All microsphere formulations were kept in well-closed glass containers and stored in a desiccator until further analysis.

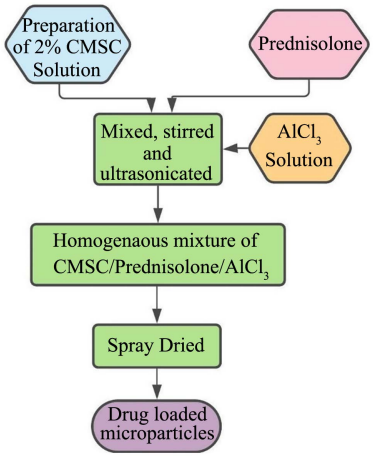

Figure 1. Shows the schematic representation of microparticle synthesis.

Table 1. Concentrations of CMSC, $AlCl_3$, and its ratio used in optimizing spray drying mixture. Total volumes of the mixture consist of CMSC and $AlCl_3$ is fixed as 250 mL.

Concentration of CMSC (w/v)	Concentration of $AlCl_3$(w/v)	Ratio of CMSC: $AlCl_3$ (v/v)
2.5%	0.05%, 0.5%, 0.025%, 0.01%	1:1
5%	0.05%, 0.5%, 0.025%, 0.01%	1:1
2%	0.05%, 0.025%, 0.01%	2:1
2.5%	0.05%, 0.025%, 0.01%	2:1
5%	0.05%, 0.025%, 0.01%	2:1

2.3. Drug Entrapment Efficiency

One hundred milligrams of drug-loaded microspheres were hydrolysed overnight at room temperature using 10 mL of 1 M NaOH solution. Samples were filtered using Whatman filter paper (No 40). The filtrate was diluted with distilled water and the prednisolone content was measured 247 nm [7] using a UV-Visible spectrophotometer (Shimadzu-1800, Kyoto, Japan). The theoretical drug loading (%) was calculated using Equation (1).

Theoretical Drug Loading = (Weight of drug added (g))/(Weight of polymers and drug added (g)) × 100 (1)

Drug entrapment efficiency (DEE) was calculated using Equation (2).

DEE = Experimental Drug loading/theoretical drug loading × 100% (2)

2.4. FT-IR Spectroscopy

The infrared spectrum of the samples was measured between 100 and 4000 cm^{-1} in a Varian 640-IR FTIR spectrophotometer (Agilent Technologies, US) using an attenuated total reflection accessory. Further to confirm the cross-linking during spray drying, Diffused Reflectance-Fourier Transform Infrared (DR-FTIR) (Perkin Elmer, Spectrum RX FT-IR System, Japan) spectroscopy was used.

2.5. Field Emission Scanning Electron Microscopy

A field emission scanning electron microscope (SU8010, Hitachi, Tokyo, Japan) was used to study the shape, size, and surface morphology of all the samples. Samples were fixed in stubs using double-faced adhesive tape and coated with a thin layer of platinum using a Quorum (Q150RS) sputter coating system (Lewes, UK) before being observed at desired magnifications.

2.6. *In-Vitro* Release

The *in vitro* release study was carried out using USP TDT-08L dissolution tester (Electro Lab, India) with vessels containing 675 mL of 0.1 N HCl (pH 1.2) maintained at 37˚C ± 0.5˚C and stirred at 50 rpm to simulate the stomach environment [8]. The microspheres containing 25 mg of prednisolone were used and the dissolution rates were measured. Five mL aliquots of samples were withdrawn from the flask for every 30 min and the same volume of fresh acid mediums was replaced. After 120 min, 225 mL of a 0.2 M solution of trisodium orthophosphatethat has been equilibrated to 37˚C ± 0.5˚C was added and the pH was adjusted to 6.8 using 1 M HCl or 1 M NaOH to simulate the intestinal environment. Dissolution was continued at 50 rpm until 240 min. The drug contents of the samples were measured at 247 nm using a UV visible spectrophotometer (Shimadzu-1800, Kyoto, Japan).

2.7. Statistical Analysis

Drug dissolution data were analysed by ordinary two-way ANOVA using the

Geisser-Greenhouse correction (GraphPad Prism 8.4.3 software, La Jolla, CA 92037 USA). The *p*-value of <0.05 were identified as statistically significant. Uncorrected Fisher's LSD multiple pair-wise comparisons of the data were conducted to determine the statistical significance of the release of the drug from different batches of microparticles.

3. Result and Discussion

CMSC solutions are known for cross-linking with ferric [9] and aluminium chloride [2]. Ferric cross-linking was more intensive and reported to have a very slow release which might not be suitable for oral drug delivery [9]. In contrast, aluminium cross-linking was less intensive and more suitable for extended drug delivery [2]. Based on this information from the literature $AlCl_3$ was selected to generate CMSC microspheres. Formation of gels, clumps, and precipitates was visually observed by adding dilute, low concentration of $AlCl_3$ solutions to CMSC solutions of different %w/v as indicated in **Table 1**. This is an important step to avoid nozzle blockage during the spray drying process.

Mixing solutions of high concentrations of CMSC and $AlCl_3$ resulted in higher precipitation due to increased cross-linking leading to particle aggregation. It was found that 2% (w/v) of CMSC with 0.01%, 0.025% and 0.05% of $AlCl_3$ was suitable and also adapted for producing drug-loaded microspheres. All other tested concentrations have produced precipitates and complexes and hence resulted in nozzle clogging while spray drying.

Product yield was calculated using Equation (3) [10].

$$\text{Product yield (\%)} = (\text{Mass of product obtained from spray dryer})/(\text{Total mass of dissolved solids}) \times 100\% \quad (3)$$

The product yields (**Table 2**) obtained varied between 29.4% - 39.5%, which is close to the acceptable range. This might be due to the loss of particles in the aspirator or due to the high molecular weight of the CMSC used [11] in the encapsulation process.

As shown in **Table 2**, the drug loading of CMSC microsphere cross-linked with 0%, 0.01%, 0.025% and 0.05% w/v% of $AlCl_3$ was 19.5%, 21.5%, 18.7% and 20.8% w/w, respectively. The percentage drug entrapment efficiency of these

Table 2. Product yield, drug loading, and entrapment efficiency of CMSC microspheres loaded with 20% w/v of prednisolone.

Formulation	Product Yield (% w/w)	Drug Loading (% w/w)	Entrapment Efficiency (% w/w)
2% CMSC, 0% $AlCl_3$	34.5	19.5 ± 1.7	99.7 ± 6
2% CMSC, 0.01% $AlCl_3$	29.4	21.5 ± 1.4	106.1 ± 12
2% CMSC, 0.025% $AlCl_3$	39.5	18.7 ± 4.5	98.7 ± 9.6
2% CMSC, 0.05% $AlCl_3$	38.2	20.8 ± 1.7	105.8 ± 16.4

microspheres ranged between 99.1% and 106.1% w/w which confirms high entrapment efficiency of the proposed encapsulation method. The same phenomenon was also reported by Darvari and Hasirci [12], where the presence of a higher concentration of $AlCl_3$ crosslinking agent gave rise to higher loading of 2', 7'-dichlorofluorescein and aldicarb in CMC microspheres. The presence of $AlCl_3$ also gave rise to higher drug loading. This could be due to the replacement of Na^+ found in CMSC with Al^{3+} ions that causing further entrapment of the drug [13]. The drug entrapment efficiencies of the microspheres were above 100% in certain formulations. This could be due to the loss of unloaded or less loaded microspheres through the exhaust tube during the spray drying process [3] [4].

The IR spectrums of prednisolone and CMSC/Prednisolone physical mixture were presented in **Figure 2**. Both have shown characteristic bands of the OH group at 3200 - 3500 cm^{-1} (OH involved in intermolecular association) confirms the presence of three hydroxyl groups of prednisolone [14]. The characteristic stretching vibrations of carbonyl groups C=O at 1700 cm^{-1} and C=C at 1660 cm^{-1} appear as very strong bands in the spectrum of prednisolone (**Figure 2(c)** and **Figure 2(d)**). These functional group peaks were intact in the spectrum of prednisolone loaded spray dried CMSC microspheres (**Figure 2(a)**). Besides, peaks present in the spectrum of drug-loaded microspheres (**Figure 2(a)**) are the summation of the characteristics peaks of prednisolone (**Figure 2(c)**, **Figure 2(d)**) and the crosslinked CMSC microspheres (**Figure 2(b)**) which confirms successful encapsulation of the drug [4]. The reduction in the intensity of the peaks of the drug in the formulation relative to the physical mixture (**Figure 2(c)**) is due to the changes in the crystallinity of the drug during the spray drying process [15].

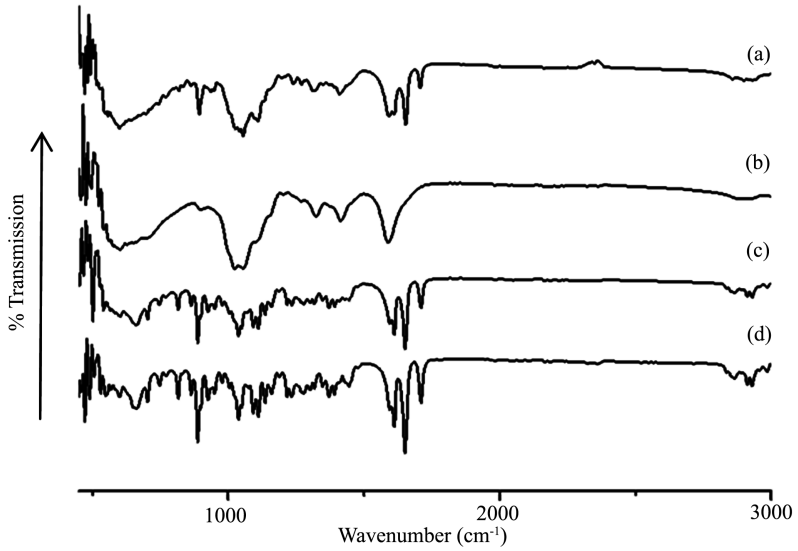

Figure 2. ATR-FTIR spectra of 0.05% $AlCl_3$ cross-linked CMSC microspheres with (a) and without (b) prednisolone; 1:1 physical mixture of prednisolone and CMSC (c); prednisolone (d).

Changes in the FT-IR spectrum due to interaction between CMSC and $AlCl_3$ were reported in our previous publication [2]. Briefly, in **Figure 2(b)**, peaks at 1725 cm^{-1} and 1050 cm^{-1} confirms cross-link formation between CMSC and $AlCl_3$. Further, an alternative infrared method was investigated to confirm the cross-linking between CMSC and $AlCl_3$. In **Figure 3**, absorption at 360 cm^{-1} for both CMSC/$AlCl_3$ physical mixture (**Figure 3(a)**) and unloaded CMSC microspheres cross-linked with 0.05% $AlCl_3$ (**Figure 3(b)**) indicates the presence of typical octahedral environment of aluminium chloride [16]. Peak intensity of CMSC (**Figure 3(b)**) functional groups has been greatly reduced and shifted upon cross-linking with $AlCl_3$ (**Figure 3(c)**). Al^{3+} cross-links CMSC via interacting with COO-groups [2] which reduce the intensity of peaks produced by the carboxyl groups (**Figure 3(c)**).

Based on the FE-SEM images of the microspheres in **Figure 4**, it can be established that the spray drying process yielded microspheres of various sizes, and the same phenomenon was observed in both unloaded and drug-loaded microspheres. This is probably due to adsorption forces present on the micron-sized amorphous spray-dried microspheres [3] [4]. The sphericity of the microspheres was relatively good in all non-crosslinked and crosslinked CMSC. However, the surface of the drug-loaded microspheres was slightly wrinkled and distorted. The presence of prednisolone crystals could be seen on the surface of microparticles (**Figure 4(e)**).

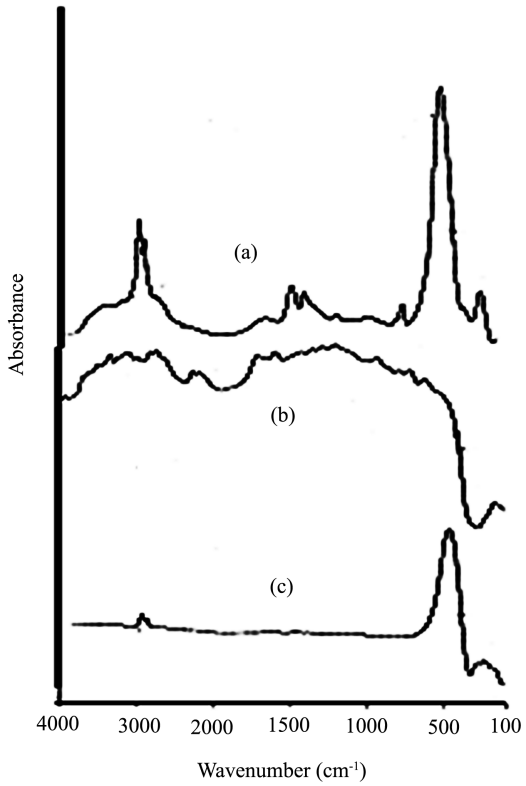

Figure 3. DR-FTIR spectra of (a) CMSC DS 0.6 and $AlCl_3$ physical mixture; (b) CMSC; (c) Unloaded CMSC microspheres with 0.05% $AlCl_3$ crosslinking agent.

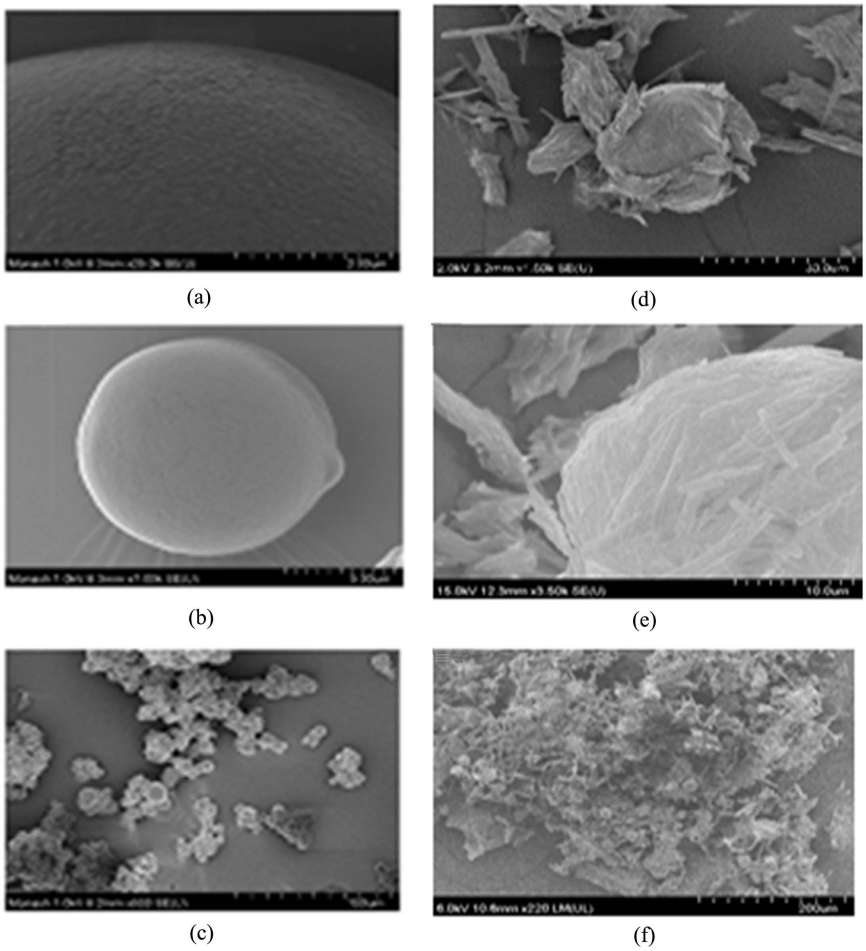

Figure 4. FESEM images of CMSC unloaded and uncross-linked microspheres at a magnification of (a) 25,000× (b) 7000× and (c) 500×. It also shows prednisolone-CMSC microspheres cross-linked with 0.005% $AlCl_3$ at a magnification of (d) 25,000× (e) 15,000× and (f) 450×.

As shown in **Figure 5**, all formulated CMCS microspheres have shown restricted drug release in simulated gastric fluid and faster release in the simulated intestinal condition. $AlCl_3$ cross-linking greatly reduced the drug release in the stomach than the non-cross-linked microspheres. It could be due to a reduction in the diffusion of dissolution medium in the cross-linked microspheres [2]. Cross-linking is well known to cause reduced drug release due to the formation of cross-linking in the polymeric network. Cross-linked microspheres have released only 5% of the loaded drug while uncross-linked has released about 10% of the loaded drug in the first 2 hours' time. The data confirms the better efficiency of the cross-linked microspheres in enteric releasing. A similar observation was reported in CMSC beads cross-linked with aluminium.

Surprisingly, cross-linked microspheres have shown faster dissolution of the drug than the uncross-linked microspheres at intestinal pH. This an added advantage of drugs exhibiting poor solubility and hence CMSC microspheres expected to increase the bioavailability of prednisolone. The trivalent Al^{3+} cation

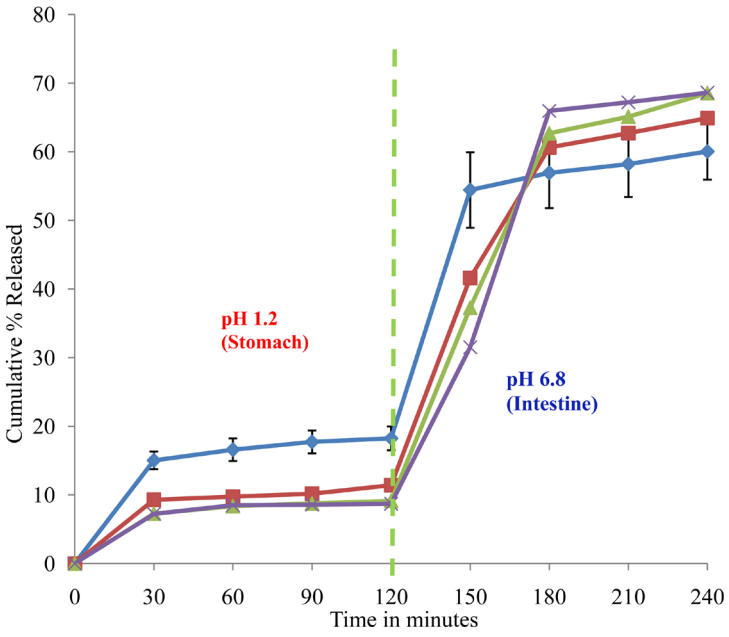

Figure 5. *In vitro* release profiles of prednisolone from various microspheres with (—◆—) 0%, (—■—) 0.01%, (—▲—) 0.025% and (—×—) 0.05% w/w of $AlCl_3$ cross-linking. Each data point indicates an average of six determination and error bars indicated standard deviation. Error bars for cross-linked microspheres were omitted for clarity purposes.

could form ionic inter and intra-molecular crosslinks with the CMSC polymer chains. This occurs through ionic substitution of the monovalent Na^+ cation with the trivalent Al^{3+} cation at the carboxylate (COO-) sites of CMSC [2]. Because of the trivalency of Al^{3+} cation, three chains within and of separate CMSC can be connected at each site, therefore forming extensive crosslinking. Increasing the concentration of crosslinking agent leads to increasing crosslinking density [9] [17] in the microspheres. In an acidic environment, these cross-linked microspheres are hydrophobic due to the protonation of the COOH (pKa approx. 4) group as well as cross-linking. However, these functional groups will ionise in the alkaline pH to release the entrapped drug. Also, Al-CMSC (hydrophobic) will be displaced by sodium at pH 7.2 to form Na-CMSC which is more hydrophilic and enhances water permeation and drug dissolution. CMSC microspheres cross-linked with 0.05% $AlCl_3$ has shown faster enteric drug release than the other formulations.

Two-way ANOVA analyses of the entire release profile of uncrosslinked and cross-linked microspheres showed no significant difference in the prednisolone release pattern ($p > 0.05$). In contrast, when the analysis was conducted using the release profile obtained in the acidic pH, a significant release difference ($p < 0.05$) found between non-crosslinked and cross-linked microspheres. Among the cross-linked microspheres, no significant difference in the drug release ($p > 0.05$) at pH 1.2 was observed between 0.025% and 0.05% w/v $AlCl_3$ cross-linked microspheres. This statistical analysis confirms the enhanced acid resistance associated with the cross-linked microspheres.

4. Conclusion

Prednisolone loaded CMSC microspheres were successfully prepared using a spray drying method. The concentrations for CMSC and $AlCl_3$ that were found to be optimal for the spray drying technique were 2%, and 0.025%, respectively. The drug entrapment efficiency of these microspheres was high and ranged from 98% - 106.1% w/v. Spray-dried and $AlCl_3$ cross-linked CMSC microspheres have shown promising results in enteric drug delivery as well as dissolution enhancement. In addition, the proposed methodology has used sago biomass and aqueous solvent in the formulation, thus helpful in sustainability and maintains a green environment.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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