Research Article

Preparation and Chracterization of Polysaccharide Based Capsule Shells

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ABSTRACT

To Prepare and Characterize Polysaccharide based capsule shells. Traditionally gelatin capsules have been used for the encapsulation of drugs and medicines. Since gelatin is from animal origin its use as a capsule material brings religious and dietary restrictions. Gelatin is also reactive and may react with the selective encapsulated drugs. Hygroscopic drugs cannot be encapsulated. Considering the above drawbacks in the present study efforts are being made for the development of polysaccharide based capsules. For the preparation of capsule shells large number of polysaccharides either in natural or modified forms are the material of choice. Polysaccharides explored in the present work are potato and maize starch, dextrins, cellulose, modified starch (Pure-cote B793) and modified cellulose (Hydroxypropyl methyl cellulose-HPMC). Biochemical characterization of these polysaccharides was carried out. In order to increase the gelling potential of polysaccharides gelling agents and gelling promoters were used. Also different plasticizers were used independently and in combinations. Formulations of polysaccharides alone, as well as their combination were tried to cast capsules of desirable characteristic properties by dipping method using stainless steel (ss316) make pins. Formulation containing hydroxyl propyl methyl cellulose (HPMC-5 cps) and Pure cote B793 in proportion of 60:40 in presence of gellangum-F(5%) as a gelling agent, Sodium acetate and EDTA-Na_2 as gelling promoters and sorbitol (5%) as a plasticizer was found to be most suitable for making capsules. Capsules prepared from the above formulation were found to have comparable properties with gelatin and HPMC capsules in terms of disintegration time, dissolution time and dimensions.

Keywords: Polysaccharides, gelling agents, gelling promoters, plasticizers, capsule shells, stainless steel (ss316) make pins.

INTRODUCTION

Traditionally gelatin capsules have been used for encapsulation of drugs and medicines. The capsule is one of the oldest forms in pharmaceutical history, to the ancient Egyptians[1]. The first patent for gelatin capsule was granted to the pharmacist Joseph Gerard Auguste Dublanc and the pharmacy student Francois Archille Barnabe Mothes in 1884[2]. Gelatin is obtained from animal tissues by prolonged boiling action of acid and alkali on collagen of connective tissues such as bones, ligaments, tendons etc. Since gelatin is from animal origin its use as capsule material brings religious and dietary restrictions. In addition some possibility of cattle disease like mad cow disease makes it risky to consume animal product.

Gelatin is also reactive and may react with the selective drugs encapsulated resulting into delay in the dissolution time. Gelatin capsules have moisture level of 13-14% which makes hygroscopic drug unstable for encapsulation. Considering the above, a growing need is felt for the development of encapsulation material (capsule) for drug delivery, which will be of completely vegetarian origin and economical.

Present research work is an attempt to prepare polysaccharide based capsule by utilizing natural or modified polysaccharides alone or in combination by dipping method. Number of gelpromotors, gelling agents and plasticizers are tried and the best choice is made so as to make capsule shell with properties comparable to that of hard gelatin and hydroxyl methyl propyl cellulose capsules.

MATERIALS AND METHODS

Polysaccharides used in the present work are potato and maize starch, dextrins, cellulose, modified starch (Pure cote B793) and modified cellulose (hydroxyl propyl methyl cellulose-HPMC 5, 6, 15 cps). In order to enhance the gelling potential of polysaccharides gelling agents used are; guar gum, xanthan gum, tamarind kernel powder, carrageenan (food grade) and gellan gum-F.

In order to enhance the gelling potential of gelling agents gelling promoters used are; Potassium Chloride, Sodium Chloride, Sodium acetate and Ethylene diamine tetra acetic acid (Na – dehydrate).

The plasticizers used are Sorbitol, Glycerol, Triethyl Citrate and Polyethylene glycol (PEG-400). Other Chemicals/ biochemicals used are; Acetic acid, Iodine, Potassium Iodide, Dextrose, maltose, 3,5 dinitro salicylic acid, Sodium hydroxide, Sodium dihydrogen phosphate, Phenol sulphuric acid, D_20, Ethanol and n-butanol.

Biochemical characterization of the above polysaccharides was done which includes, determination of blue values, α and β amylolysis limits, chromatographic separation and determination of dextrose equivalents for starches, determination of particle size for starches, HPMC and Pure cote B793. ^1H and ^{13}C NMR and IR spectral analysis for Pure cote B793 was done to analyze the nature of modification.

Demineralized water in steel beaker was heated to 90 °C on water bath and beaker was transferred to hot plate having attached with magnetic stirrer. Gelling promoters in different combinations were added and solution was further stirred with magnetic stirrer for 5 minutes. Then gelling agent was added with continuous stirring till complete dissolution was obtained. In order to get better homogeneity stirring was further continued for 15 minutes. At this point plasticizers were added for required formulation only. Finally maize starch/ dextrin/cellulose/PC/HPMC/ HPMC: PC blend with different proportions were added with continuous stirring. The solution was cooled and maintained at 60°C under constant stirring for 8-10 hours. Minimum quantity of this solution was used for the gellation temperature (cooling curve) study which is very important for deciding the dipping temperature for making capsules. Viscosity measurements were done using MCR 301 Rheometer. In the double gap rheo tube 14–15 ml solution at 60°C was placed. System was attached to cooling system (Liquid Nitrogen Unit) which cooled the solution from 60–40 °C at the rate of 2 °C per minute. The viscosity was continuously monitored and recorded automatically. Viscosities measured were represented in the form of cooling curves. In the solutions maintained at 60°C lubricated stainless steel (ss316) make pins were separately dipped into the solution and withdrawn. Pin temperature was monitored during each dipping trials with the digital thermometer. The dipping time was maintained between 4-5 seconds and withdrawal time in between 4-8 seconds. Stainless steel pins were air dried so as to obtain capsules.

The capsule shells were characterized by determining % moisture, weight, thickness, microtensile properties, dimensions, disintegration time and dissolution time.

RESULTS

Blue Values for native and modified starch samples are indicated as, Potato starch 0.52, maize starch 0.38, Pure cote B793 0.28. With ^{13}C and ^{1}H NMR spectra the presence of propyl group was confirmed in pure cote B793. Thus Pure cote B793 was a propylated starch. Gellation temperatures for different biopolymers formulations are depicted in Table 1.

The dipping temperatures were about 7-10 °C above the gellation temperature. Capsules were made by dipping process. The following compositions were explored, polysaccharides alone, polysaccharides in presence of gelling agent, polysaccharides + gelling agent + gelling promoters, polysaccharides + gelling agent + gelling promoters + plasticizer. Polysaccharides (potato starch, maize starch, cellulose, dextrins) alone were unable to form films. Heavy run down of the solution on the stainless steel pins was observed after withdrawing from the dipped solution. Further addition of gelling agents (guar gum, xanthan gum, tamarind kernel powder) did not support the Capsule film formation. Further addition of gelling promoters (KCl, CH_3C00Na + EDTA-Na_2) also did not produce any positive results. However all the above polysaccharides in presence of gellan gum–F and CH_3C00Na + EDTA-Na_2 as gelling promoter could form capsules, but they were very brittle and opaque.

Table 1: Gellation Temperatures for different bio-polymers and Formulations

S. No.	Bio-polymers/Formulations	Gellation Temperature (°C)
1	Gellangum (G)	29.4
2	Gellangum + gelling promoters(GP)	33.1
3	Purecote- B793(PC)	44
4	5 cps HPMC (hydroxyl propyl methyl cellulose)	45
5	6 cps HPMC	49.5
6	15 cps HPMC	49.8
7	5 cps+G+GP	42.6
8	6 cps+G+GP	47.5
9	15 cps+G+GP	48.5
10	5 cps+PC+G+GP	41.5
11	6 cps+PC+G+GP	44
12	15 cps+PC+G+GP	44.5
13	5 cps+PC+G+GP+(S-5%)	41.5
14	5 cps+PC+G+GP+(S-10%)	41.5
15	5 cps+PC+G+GP+(PEG-400-5%)	41.5
16	5 cps+PC+G+GP+(PEG-400-10%)	41.5
17	5 cps+PC+G+GP+(TEC-5%)	41.5
18	5 cps+PC+G+GP+(TEC-10%)	41.5
19	5 cps+PC+G+GP+(S+PEG+TEC-5%)	41.5
20	5 cps+PC+G+GP+(S+PEG+TEC-10%)	41.5
21	6 cps+PC+G+GP+(S-5%)	44
22	6 cps+PC+G+GP+(S-10%)	44
23	6 cps+PC+G+GP+(PEG-400-5%)	44
24	6 cps+PC+G+GP+(PEG-400-10%)	44
25	6 cps+PC+G+GP+(TEC-5%)	44
26	6 cps+PC+G+GP+(TEC-10%)	44
27	6 cps+PC+G+GP+(S+PEG+TEC-5%)	44
28	6 cps+PC+G+GP+(S+PEG+TEC-10%)	44
29	15 cps+PC+G+GP+(S-5%)	44.5
30	15 cps+PC+G+GP+(S-10%)	44.5
31	15 cps+PC+G+GP+(PEG-400-5%)	44.5
32	15 cps+PC+G+GP+(PEG-400-10%)	44.5
33	15 cps+PC+G+GP+(TEC-5%)	44.5
34	15 cps+PC+G+GP+(TEC-10%)	44.5
35	15 cps+PC+G+GP+(S+PEG+TEC-5%)	44.5
36	15 cps+PC+G+GP+(S+PEG+TEC-10%)	44.5
37	Gelatin	35.8

Addition of plasticizer did not help to improve the quality of capsules. Pure cote B793 alone could not form capsules. Pure Cote B793 in presence of gellan gum-F and gelling promoter CH_3C00Na + EDTA-Na_2 could form thin and brittle capsules, further addition of plasticizer did not

help to improve the strength of the films. HPMC grades (5, 6, 15 cps) not alone but in presence of gellan gum-F and CH_3C00Na + EDTA-Na_2 as gelling promoter could form flexible and clear capsules. Clarity and elasticity was further improved by addition of plasticizers.

Although HPMC seemed to be the ideal for the production of capsules, use of HPMC alone is not economical. Therefore an attempt was to try blending of HPMC and Pure cote B793 for the capsule formation.

The ratio of HPMC to Pure cote B793 was varied from 90:10 to 50:50 in presence of gellan gum–F and CH_3C00Na + EDTA-Na_2.

The plasticizers used were sorbitol, PEG-400 and TEC alone and in combinations. Capsules could be properly formed by using composition in which HPMC (5 cps): Pure Cote ratio was 60:40. This ratio was found to be satisfactory in % relative humidity, drying time and % moisture for capsules made which is represented in Table 2. The Figure 1 indicates the transparent capsules shells on the stainless steel (ss316) make pins.

The Figure 2 indicates the polysaccharide based capsule shells. Micro-tensile properties for capsule films are depicted in Table 3.

Capsule Films were stable when exposed to polychromatic light in U.V chamber for 6 hours. Disintegration time for capsules made from various formulations are represented in Table 4.

HPMC (5 cps) and pure cote B793 (60:40) in presence of gellan gum-F, CH_3C00Na + EDTA-Na_2 as gel promoter and combination of sorbitol (5%) showed satisfactory tensile strength and modulus.

Comparative Weight, thickness and dimensions for standard and prepared capsules (size 0) are indicated in Table 5. The dissolution time studies for different capsules are indicated in Table 6.

Figure 1: Transparent Capsule shells on stainless steel (ss316) pins

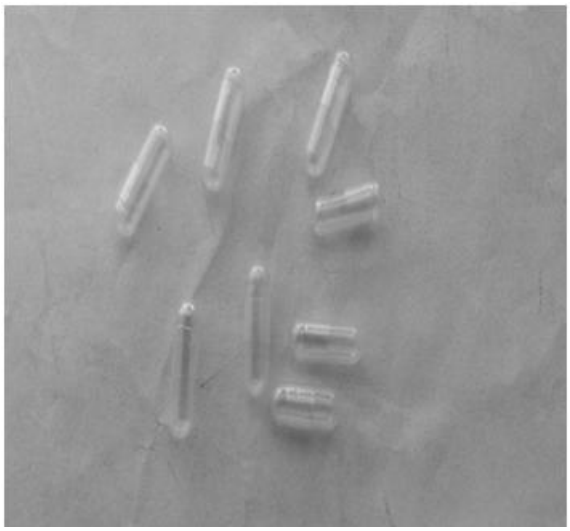

Figure 2: Polysaccharide based capsule shells

Table 2: Drying conditions for capsule shells and % Moisture

Formulations	R.T (°C)	% RH	Drying Time (minutes)	% Moisture (1gm of capsule shells)
5 cps HPMC	28.1	68	80	6.8
6 cps HPMC	28.2	68.2	90	6.5
15 cps HPMC	28.0	67.9	100	6.6
5cps and purecote	27.8	69.1	90	7.0
6cps and purecote	27.6	69.4	100	7.2
15cps and purecote	28.0	68	110	7.4
5cps, purecote and plasticizers	28.5	67.5	110	7.5
6cps, purecote and plasticizers	28.3	68.1	120	7.3
15cps, purecote and plasticizers	28.2	68.2	140	7.8

Table 3: Micro tensile properties for capsules films

Formulation No.	Tensile Strength (M Pas)	% Elongation	Modulus
1 5CPS+G+GP	18.46	6.35	2.9
2 6CPS+G+GP	24.13	6.8	3.5
3 15CPS+G+GP	30.70	12.17	2.5
4 5CPS+PC+G+GP	22.07	3.37	6.5
5 6CPS+PC+G+GP	17.76	2.31	7.68
6 15CPS+PC+G+GP	18.82	2.72	6.9
7 5CPS+PC+G+GP+(S-5%)	18.80	3.05	6.2
8 5CPS+PC+G+GP+(S-10%)	14.01	4.08	3.43
9 5CPS+PC+G+GP + (PEG-400-5%)	15.02	2.04	7.36
10 5CPS+PC+G+GP+ (PEG-400-10%)	15.02	4.11	3.65
11 5CPS+PC+G+GP + (TEC-5%)	16.77	2.26	7.42
12 5CPS+PC+G+GP + (TEC-10%)	11.69	2.27	5.14
13 5CPS+PC+G+GP + (S+PEG+TEC-5%)	18.40	2.64	6.96
14 5CPS+PC+G+GA + (S+PEG+TEC-10%)	14.49	3.48	4.16
15 6CPS+PC+G+GP + (S-5%)	16.97	2.34	7.25
16 6CPS+PC+G+GP + (S-10%)	13.48	3.02	4.46
17 6CPS+PC+G+GP + (PEG-400-5%)	17.71	2.47	7.17
18 6CPS+PC+G+GP + (PEG-400-10%)	16.70	3.06	5.45
19 6CPS+PC+G+GP + (TEC-5%)	17.10	1.6	10.68
20 6CPS+PC+G+GP + (TEC-10%)	14.11	2.11	6.68
21 6CPS+PC+G+GP + (S+PEG+TEC-5%)	20.41	2.77	7.36
22 6CPS+PC+G+GP + (S+PEG+TEC-10%)	17.06	2.46	6.93
23 15CPS+PC+G+GP + (S-5%)	16.45	2.39	6.88
24 15CPS+PC+G+GP + (S-10%)	17.33	3.31	5.23
25 15CPS+PC+G+GP + (PEG-400-5%)	20.56	2.93	7.01
26 15CPS+PC+G+GP + (PEG-400-10%)	14.01	3.35	4.18
27 15CPS+PC+G+GP + (TEC-5%)	17.33	2.25	7.70
28 15CPS+PC+G+GP + (TEC-10%)	17.18	2.24	7.66
29 15CPS+PC+G+GP + (S+PEG+TEC-5%)	21.81	2.66	8.2
30 15CPS+PC+G+GP + (S+PEG+TEC-10%)	17.87	2.26	7.90
31 GELATIN	33.00	4.55	7.25

Table 4: Disintegration time for capsules made from various formulations

Sample No.	Formulations	Minutes
1	5CPS+G+GP	4.50 SEC.
2	5CPS+PC+G+GP	4.35 SEC.
3	5CPS+PC+G+GP+(S-5%)	6.0 SEC.
4	5CPS+PC+G+GP+(S-10%)	6.30 SEC.
5	5CPS+PC+G+GP + (PEG-400-5%)	8.20 SEC
6	5CPS+PC+G+GP+(PEG-400-10%)	7.15 SEC.
7	5CPS+PC+G+GP +(TEC-5%)	6.30 SEC.
8	5CPS+PC+G+GP +(TEC-10%)	6.15 SEC.
9	5CPS+PC+G+GP +(S+PEG+TEC-5%)	6.50 SEC.
10	5CPS+PC+G+GP +(S+PEG+TEC-10%)	6.10 SEC.
11	6CPS+G+GP	5.55 SEC.

12	6CPS+PC+G+GP	5.10 SEC.
13	6CPS+PC+G+GP +(S-5%)	8.10 SEC.
14	6CPS+PC+G+GP +(S-10%)	7.50 SEC.
15	6CPS+PC+G+GA + (PEG-400-5%)	9.55 SEC.
16	6CPS+PC+G+GP +(PEG-400-10%)	11.50 SEC.
17	6CPS+PC+G+GA +(TEC-5%)	10.10 SEC.
18	6CPS+PC+G+GP + (TEC-10%)	12.05 SEC.
19	6CPS+PC+G+GP + (S+PEG+TEC-5%)	12.10 SEC.
20	6CPS+PC+G+GP + (S+PEG+TEC-10%)	11.55 SEC.
21	15CPS+G+GP	17.37 SEC.
22	15CPS+PC+G+GP	14.20 SEC
23	15CPS+PC+G+GP + (S-5%)	52.30 SEC.
24	15CPS+PC+G+GP + (S-10%)	48.50 SEC.
25	15CPS+PC+G+GP + (PEG-400-5%)	49.20 SEC.
26	15CPS+PC+G+GP + (PEG-400-10%)	51.32 SEC.
27	15CPS+PC+G+GP + (TEC-5%)	52.40 SEC.
28	15CPS+PC+G+GP + (TEC-10%)	49.40 SEC.
29	15CPS+PC+G+GP + (S+PEG+TEC-5%)	53.30 SEC.
30	15CPS+PC+G+GP + (S+PEG+TEC-10%)	48.35 SEC.
31	GELATIN	5.40 SEC

Table 5: Weight, Thickness and Dimensions for capsules (Size 0)

Size 0 Capsules	Standard Capsules Specifications (average of 10 Capsules)	Polysaccharide based Capsules (average of 10 Capsules)
Length(mm) Body	18.5	18.7
Length(mm) Cap	10.9	10.8
Thickness (micron)	120	130
Outside diameter(mm) Body	7.34	7.63
Outside diameter(mm) Cap	7.64	7.87
Closed joined length(mm)	21.4	21.2
Weight Capsule (mg)	96	110

Table 6: Dissolution test for capsules (SIZE 0)

Tests	Samples	Specifications	% drug release in 45 minutes	% drug release in 60 minutes
Dissolution test in 0.1M Hcl at 100 RPM	polysaccharide based Capsules	NLT 80% in 45 minutes	86.37	96.24
Dissolution test in 0.1M Hcl at 100 RPM	Gelatin Capsules	NLT 80% in 45 minutes	95.74	98.25
Dissolution test in 0.1M Hcl at 100 RPM	HPMC capsules	NLT 80% in 45 minutes	98.41	99.0

DISCUSSION

Naturally occurring polysaccharides have unique combinations of functional properties and environmentally friendly features. The long chain structures of polysaccharides provide good mechanical properties for applications such as fibres, films, adhesives, drug delivery agents, emulsifier etc. They are renewable materials and are non-toxic and biodegradable. Commercially available products are starch, cellulose and their derivatives, dextran, xanthan gum, carrageenan, gellan gum. Starch and cellulose (native and modified) are the two biopolymers which have been exploited for the preparation of capsules.

In the present work an attempt has been made to prepare capsules using starch and cellulose. Native starch (potato and maize) alone, as well as cellulose alone were unable to form capsules. Failure for dextrins for capsule formation can be due to α 1→6 linkages which hinders the film formation. Therefore pure cote B793, a commercially available modified gelatinized starch was tried.

For capsules blend of HPMC (5 cps) and pure cote B793 (60:40) in presence of gellan gum-F, CH_3C00Na + EDTA-Na_2 as gel promoter and combination of sorbitol (5%) was found to be most suitable. Though HPMC alone could form very good capsules, but it is not economical. Therefore blend of HPMC and Pure Cote was used which can be commercially viable for the production of capsules.

CONCLUSION

Alternative to gelatin capsules is very important in order to overcome the draw backs. Present work aimed at utilization of bio-polymers i.e. starch, cellulose (native and modified), gelling agents (gums), gelling promoters and plasticizers for the preparation of polysaccharide based capsule shells.

Initially biochemical characterization of the biopolymers was carried out which includes, paper chromatography, blue values, particle size and α, β amylolysis limit determination. Pure cote B793 is a gelatinized modified starch and economical. By IR and NMR studies presence of propyl group in pure cote B793 was confirmed.

Cooling curves were studied for different formulations in order to know the gellation temperatures from which dipping temperatures were decided. For capsules preparation blend of HPMC-5 cps and pure cote B793 (60:40) in presence of gellangum–F, gel promoters-CH_3C00Na + EDTA-Na_2 and combination of sorbitol-(5%) was found to be the most suitable.

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