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PREPARATION AND EVALUATION OF STARCH PHOSPHATE- A NEW MODIFIED STARCH AS A DISINTEGRANT IN TABLET FORMULATIONS

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ABSTRACT

Starch phosphate prepared by reacting potato starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures was found to be a white, crystalline, non-hygroscopic powder. Starch phosphate prepared exhibited excellent flow characteristics. Starch phosphate was insoluble in water and aqueous fluids of acidic and alkaline pHs. It also exhibited good swelling (400%) in water. It has no pasting or gelling property when heated at 100°C in water for 30 min. As starch phosphate exhibited good swelling in water, it is considered as a promising disintegrant in tablet formulations and was evaluated as disintegrant in tablet formulations. Tablets of (i) sulfamethoxazole (100 mg) and (ii) paracetamol (120 mg) were prepared by wet granulation method employing starch phosphate at 5 and 10% strength as disintegrant and were evaluated. For comparison tablets were also prepared employing crospovidone (a super disintegrant) as disintegrant at 5 and 10% strength in the tablets. Paracetamol and sulfamethoxazole tablets formulated employing starch phosphate (both wet and dry addition) disintegrated within 3 min. Wet addition of starch phosphate gave relatively fast disintegration than dry addition with both the drugs. Paracetamol and sulfamethoxazole tablets formulated employing starch phosphate as disintegrant gave rapid and higher dissolution of the contained drug when compared to those formulated with crospovidone and commercial product in each case. Wet addition of starch phosphate gave relatively faster dissolution with both the drugs than dry addition. Thus starch phosphate, a new modified starch, was found to be a promising disintegrant in tablet formulations and can be used in a concentration of 5-10% as an efficient disintegrant.

Key words: Modified starch, Starch phosphate, Disintegrant, Tablets, Sulfamethoxazole, Paracetamol.

INTRODUCTION

Disintegrant is critical ingredient in tablets. Disintegration and subsequent dissolution are the rate limiting steps in the absorption of a poorly soluble drug administered

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in a tablet dosage form. Though several disintegrants such as native starches, modified starches and cellulose derivatives are available, there is a continued need to develop new, safe and effective disintegrants for tablets. The objective of the present study is to prepare and evaluate starch phosphate, a new chemically modified starch as a disintegrant in tablets. Starch and modified starches such as sodium starch glycolate (Primogel), pregelatinized starch, dextrin and cyclodextrins have been used in tablets and capsules as fillers, disintegrants and dry binders. Starch citrate, a chemically modified starch has been reported[1] as disintegrant in tablet formulations.

Starch phosphate is one of the modified starches used in the frozen food industry[2,3]. It is produced by phosphorification of free hydroxyl groups of anhydroglucose units of starch molecule. They are esterified with phosphate reagents. Phosphate reagents for starch phosphate monoester are orthophosphate salts[4]. Starch phosphate production is normally by using wet process[2]. No reports are available on its use as pharmaceutical excipient.

In the present study, starch phosphate is prepared, characterised and evaluated as disintegrant in tablets prepared by granulation method. Tablets of (i) sulfamethoxazole (100 mg) and (ii) paracetamol (120 mg) were prepared by wet granulation method incorporating starch phosphate as disintegrant at 5 and 10% strength in the formula. In each case starch phosphate was added before granulation (wet addition) and after granulation (dry addition). For comparison sulfamethoxazole and paracetamol tablets were also prepared employing crospovidone, a super disintegrant. The tablets prepared were evaluated in comparison to commercial brands in each case. The results are presented in this paper.

EXPERIMENTAL

Materials and methods

Sulfamethoxazole, paracetamol and crospovidone were gift samples from M/s Natco Pharma Ltd, Hyderabad. Potato Starch and di-sodium hydrogen orthophosphate anhydrous (Qualigens) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Preparation of starch phosphate

Starch phosphate was prepared based on the method of Choi et al.[5] with some modifications. Potato starch (100 g) and di-sodium hydrogen orthophosphate anhydrous (30 g) were suspended in 100 mL of water and continuously stirred for 20 min. This starch slurry was then filtered and the wet starch mixture was conditioned for 12 h at room

temperature (28^{o}C). To enhance phosphorylation, this mixture was heated in a forced air oven at 130^{o}C for 3 h. The product obtained was grounded and sized.

Characterization of starch phosphate

The starch phosphate prepared was evaluated for following :

Solubility

Solubility of starch phosphate was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether.

pH

The pH of a 1% w/v slurry was measured.

Melting point

Melting point was determined by using melting point apparatus.

Viscosity

Viscosity of 1% dispersion in water was measured using Ostwald Viscometer.

Swelling index

Starch phosphate (200 mg) was added to 10 mL of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes were allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

$$S.I\ (\%) = \frac{\text{Volume of sediment in water - Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \times 100$$

Test for Gelling property

The gelling property (gelatinization) of the starch and starch phosphate prepared was evaluated by heating a 7% w/v dispersion of each in water at 100^{o}C for 30 min.

Moisture absorption

The hygroscopic nature of starch phosphate was evaluated by moisture absorption studies in a closed desiccator at 84% relative humidity and room temperature.

Particle size

Particle size analysis was done by sieving using standard sieves.

Density

Density (g/cc) was determined by liquid displacement method using benzene as liquid.

Bulk density

Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

Angle of repose

Angle of repose was measured by fixed funnel method.

Compressibility index

Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V) after hundred tappings of a sample of starch phosphate in a measuring cylinder. CI was calculated using equation

$$\text{Compressibility index (CI)} = \frac{V_o - V}{V_o} \times 100$$

Preparation of tablets

Tablets of (i) sulfamethoxazole (100 mg) and (ii) paracetamol (120 mg) were prepared by conventional wet granulation method employing acacia (2%) as a binder, lactose (q.s) as diluent, talc (2%) and magnesium stearate (2%) as lubricants and water as granulating fluid. Starch phosphate was included in the formulations as disintegrant at 5 and 10% strength in each case. For comparison tablets were also prepared employing crospovidone (a super disintegrant) as disintegrant at 5 and 10% strength in the tablets. Two series of tablets were made in each case. In one series starch phosphate was added before granulation (wet addition) and in the other series it was added after drying the granules and before compression (dry addition). The granules were compressed into tablets on a tablet punching machine (M/s Cadmach Machinery Co. Pvt. Ltd) to a hardness of 7 kg/cm^2 using 9 mm round and flat punches. In each case 100 tablets were compressed.

Evaluation of tablets

Hardness of tablets was tested using Monsanto Hardness tester. Friability of the

tablets was determined in a Roche friabilator. Disintegration time was determined in a Thermonic tablet disintegration test machine using water as test fluid.

Estimation of drug content in the tablets

From each batch of tablets prepared five tablets were accurately weighed and powdered. Tablet powder equivalent to 20 mg of drug was taken for assay into a 100 mL conical flask and extracted with 3 x 10 mL quantities of methanol. The methanolic extracts were filtered and collected into a 50 mL volumetric flask and the volume was made upto 50 mL with methanol. The solution was then suitably diluted with 0.1 N hydrochloric acid in the case of sulfamethoxazole and with phosphate buffer of pH 7.8 in the case of paracetamol. The absorbance of the solutions was measured at 265 nm for sulfamethoxazole and at 249 nm for paracetamol. Drug content of the tablets were calculated using the standard calibration curve in each case.

Dissolution rate study

Dissolution rate of the tablets prepared was studied using 8 station dissolution rate apparatus (M/s Lab India Disso 2000) employing a paddle stirrer at 50 rpm and at 37 + 1^{o}C. Hydrochloric acid 0.1 N (900 mL) was used as dissolution fluid for sulfamethoxazole and Phosphate buffer of pH 7.8 (900 mL) was used as dissolution fluid in the case of paracetamol tablets. Samples of dissolution fluid, 5 mL each, were withdrawn at 5, 10, 15, 20, 25, 30, 40, 50, 60 min. through a filter (0.45 µ). The samples were suitably diluted with the corresponding dissolution fluid and assayed for sulfamethoxazole at 265 nm and paracetamol at 249 nm using the corresponding dissolution fluid as blank. Each sample withdrawn was replaced with an equal amount of drug free dissolution fluid. All dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Starch phosphate was prepared by reacting starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures. The reactions involved are shown in Fig. 1. Starch phosphate prepared was found to be white, crystalline, non hygroscopic powder and can easily be grounded to different sizes. Powder which passes through mesh No. 80 and retained on mesh No. 120 was collected. This powder has an average particle size of 152 µm. The starch phosphate prepared was characterised by determining various physical properties. The properties of starch phosphate prepared are summarised in Table 1.

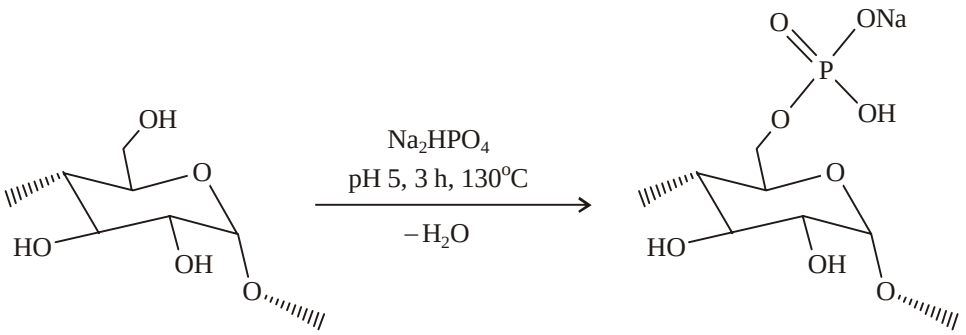

Fig. 1: Phosphorification of potato starch to produce starch phosphate

Table 1: Physical properties of the starch phosphate prepared

Property	Result
Solubility	Insoluble in all aqueous and organic solvents tested
pH (1% w/v aqueous dispersion)	7.25
Melting Point	Charred at 210°C
Viscosity (1% w/v aqueous dispersion)	2.11 cps
Swelling index	400
Gelling property	No gelling and the swollen particles of starch phosphate separated from water. Whereas in the case of starch, it was gelatinized and formed gel.
Moisture absorption	4.0 %
Particle size	152 µm (80/120 mesh)
Density	1.667 g/cc
Bulk density	0.534 g/cc
Angle of repose	20.04^0
Compressibility index	11.01 %

When tested for m.p., it was charred at 210°C. Starch phosphate prepared was insoluble in water, aqueous fluids of acidic and alkaline pH and several organic solvents tested. In water it exhibited good swelling (400%). No gelling/pasting was observed with starch phosphate when its aqueous dispersion was heated at 100°C for 30 min, where as

potato starch formed a paste/gel during the above heat treatment. In the micromeritic evaluation, the angle of repose and compressibility index values revealed the excellent flow characteristic of starch phosphate. As starch phosphate exhibited good swelling in water it is considered as a promising disintegrant in tablet formulations and was evaluated as disintegrant in tablet formulations. Tablets of (i) sulfamethoxazole (100 mg) and (ii) paracetamol (120 mg) were prepared by wet granulation method employing starch phosphate at 5 and 10% strength as disintegrant in each case. In one series starch phosphate was added before granulation (wet addition) and in another series it was added after drying the granules and before compression (dry addition) to evaluate starch phosphate as disintegrant in both the methods.

All the tablets were evaluated for weight variation, drug content, hardness, friability, disintegration time and dissolution rate and dissolution efficiency. For comparison commercial brands in each case were also evaluated. The physical properties of all the tablets formulated as well as commercial brands tested are given in Tables 2 and 3.

Table 2: Drug content, hardness, friability, disintegration time of paracetamol tablets formulated employing starch phosphate and crospovidone as disintegrant

Disintegrant	Type of addition & concentration	Drug content	Hardness	Friability	Disintegration time
	(Wet/Dry)	(mg/tab)	(Kg/cm^2)	(%)	(min-sec)
Starch Phosphate	Wet (5%)	118.9	6.5	1.4	3-0
	Wet (10%)	119.2	5.5	0	1-30
	Dry (5%)	119.1	6.0	0	2-0
	Dry (10%)	119.4	6.5	1.1	1-14
Crospovidone	Wet (5%)	119.7	5.5	1.0	0-37
	Wet (10%)	119.3	6.5	1.5	0-25
	Dry (5%)	119.5	5.5	2.7	2-04
	Dry (10%)	119.5	6.0	0.88	0-42
Commercial	-	119.4	6.5	1.05	1-21

In the test for uniformity of weight the percentage deviation was less than 4.5% in all the cases. Drug content was within 100 + 3% of the labelled claim in each case. Hardness of

the formulated tablets was in the range 5.5-7.5 Kg/cm^2. Weight loss in the friability test was less than 2.70%. All the formulated tablets including both wet and dry addition of starch phosphate, disintegrated within 3 min. Wet addition of starch phosphate gave relatively fast disintegration than dry addition with both the drugs. Paracetamol tablets formulated employing crospovidone were also disintegrated within 2 min. Whereas sulfamethoxazole tablets formulated employing crospovidone exhibited relatively slow disintegration (Table 3). As such, all tablets formulated employing starch phosphate were of good quality with regard to weight variation, hardness, friability and drug content and disintegration time.

Table 3: Drug content, hardness, friability, disintegration time of sulfamethoxazole tablets formulated employing starch phosphate and crospovidone as disintegrant

Disintegrant	Type of addition & concentration	Drug content	Hardness	Friability	Disintegration time
	(Wet/Dry)	(mg/tab)	(Kg/cm^2)	(%)	(min-sec)
Starch Phosphate	Wet (5%)	99.7	6.0	2.1	2-25
	Wet (10%)	99.1	5.5	1.0	2-23
	Dry (5%)	99.2	6.5	1.3	2-09
	Dry (10%)	99.6	6.5	0.71	2-27
Crospovidone	Wet (5%)	99.7	7.5	0.89	4-24
	Wet (10%)	99.7	7.0	1.0	4-47
	Dry (5%)	99.2	7.0	0.70	8-40
	Dry (10%)	99.2	7.5	0.7	1-34
Commercial	-	400.5	6.5	0.81	1-37

The dissolution parameters of the tablets prepared are summarised in Tables 4 and 5. The dissolution of both paracetamol and sulfamethoxazole from all the tablets prepared followed first order kinetics with correlation coefficient (R^2) greater than 0.855. All the dissolution parameters ($PD_{10,}$ $DE_{30,}$ T_{50} and K_1) indicated very rapid and higher dissolution of the drug from tablets formulated employing starch phosphate as disintegrant when compared

to those formulated with crospovidone and commercial product in each case. Wet addition of starch phosphate gave relatively faster dissolution with both the drugs than dry addition.

Table 4: Dissolution parameters of paracetamol tablets formulated employing starch phosphate and crospovidone as disintegrant

Disintegrant	Type of addition & concentration (Wet/Dry)	PD_{10} (%)	T_{50} (min.)	DE_{30} (%)	k_1 (min^{-1})
Starch Phosphate	Wet (5%)	72.22	< 5 min	71.40	0.0943
	Wet (10%)	80.49	< 5 min	79.27	0.1352
	Dry (5%)	55.43	6 min	58.70	0.0506
	Dry (10%)	63.28	< 5 min	66.37	0.0673
Crospovidone	Wet (5%)	51.85	9 min	65.17	0.0789
	Wet (10%)	78.19	< 5 min	78.09	0.1054
	Dry (5%)	66.60	< 5 min	71.20	0.0859
	Dry (10%)	69.73	< 5 min	74.89	0.0915
Commercial	-	49.19	11 min	54.94	0.0457

(PD_{10}: Percent Dissolved in 10 min; T_{50}: Time for 50% Dissolution; DE_{30}: Dissolution Efficiency at 30 min; k_1: First Order Dissolution Rate Constant)

Table 5: Dissolution parameters of sulfamethoxazoletablets formulated employing starch phosphate and crospovidone as disintegrant

Disintegrant	Type of addition & concentration (Wet/Dry)	PD_{10} (%)	T_{50} (min.)	DE_{30} (%)	k_1 (min^{-1})
Starch Phosphate	Wet (5%)	74.32	6	70.98	0.0869
	Wet (10%)	79.50	< 5	75.28	0.1585
	Dry (5%)	46.62	12	60.62	0.0683
	Dry (10%)	64.68	6	62.83	0.0751

Cont…

Disintegrant	Type of addition & concentration (Wet/Dry)	PD_{10} (%)	T_{50} (min.)	DE_{30} (%)	k_1 (min^{-1})
Crospovidone	Wet (5%)	65.44	6	68.66	0.0790
	Wet (10%)	67.30	< 5	76.74	0.1490
	Dry (5%)	23.04	23	29.96	0.0205
	Dry (10%)	58.40	8	57.51	0.0691
Commercial	-	41.80	16	40.11	0.0530

(PD_{10}: Percent Dissolved in 10 min; T_{50}: Time for 50% Dissolution; DE_{30}: Dissolution Efficiency at 30 min; k_1: First Order Dissolution Rate Constant)

As the concentration of disintegrant was increased the dissolution rate was also increased. Dissolution of both paracetamol and sulfamethoxazole from the tablets formulated employing starch phosphate was much higher than the official specification (NLT 80 % in 30 min.). The fast disintegration and rapid and higher dissolution observed with the tablets formulated employing starch phosphate is due to its high swelling and easy dispersible nature. All the formulated tablets gave higher dissolution than the corresponding commercial brands.

CONCLUSION

(i) Starch phosphate prepared by reacting potato starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures was crystalline, non-hygroscopic and was insoluble in water and aqueous fluids of acidic and alkaline pHs.

(ii) It also exhibited good swelling (400%) in water. It has no pasting or gelling property when heated at 100^0C in water for 30 min.

(iii) Paracetamol and sulfamethoxazole tablets formulated employing starch phosphate (both wet and dry addition) disintegrated within 3 min. Wet addition of starch phosphate gave relatively fast disintegration than dry addition with both the drugs.

(iv) Paracetamol and sulfamethoxazole tablets formulated employing starch phosphate as disintegrant gave rapid and higher dissolution of the contained drug when compared to those formulated with crospovidone and commercial product in each case. Wet addition of starch phosphate gave relatively faster dissolution with both the drugs than dry addition.

(v) Thus starch phosphate, a new modified starch was found to be a promising disintegrant in tablet formulations and can be used in a concentration of 5-10 % as an efficient disintegrant.

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