DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(15), 1701-1708 (1992)

CHITOSAN AS A TABLET BINDER

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ABSTRACT

Chitosan was evaluated as a binder for chlorpheniramine maleate tablets in comparison with other cellulose binders such as sodium carboxymethylcellulose, hydroxypropylmethylcellulose and methylcellulose. The effects of binder concentration on the mechanical properties of granules and tablets as well as on disintegration time and dissolution profiles were studied. Results showed that granules prepared with methylcellulose had lowest percentage of fines and friability. Chitosan tablets showed best dissolution profiles. The rank order correlation for binder efficiency was: hydroxypropylmethylcellulose > chitosan > methylcellulose > sodium carboxymethylcellulose.

INTRODUCTION

Several reports have been published on the use of various materials as binders and their effects on tablet properties (1-3). Since binders affect a number of tablet properties, the evaluation of their performance is not a simple task. Mendes and Brannon (1) suggested that an evaluation of binder efficacy based on the properties of tablet hardness and friability be provided by combining these into a single parameter to offer an arbitrary rating scale. This was accomplished by dividing the

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hardness by the friabrasion value to get the HFR or "hardness-friabrasion ratio". Georgakopoulos and Malamataris (2) obtained another parameter by dividing HFR by disintegration time (HFR/DT). This parameter should be more useful in that it not only measures the efficiency of the binder by measuring hardness and friability but also includes any negative effects on disintegration.

Chitosan is a potentially useful excipient and has extremely low toxicity, good biocompatibility and biodegradability (4). It is a cationic polyelectrolyte having a gel-like structure in acidic environment. It is structurally analogous to cellulose (5) and has been evaluated as a direct tablet compression aid (6-7) and sustained release vehicle (8-9). The purpose of this study was to evaluate chitosan as a granulation binder in tablet formulations for chlorpheniramine maleate using lactose as a diluent. The performance of chitosan as a binder was evaluated by comparison with other cellulosic agents such as hydroxypropylmethylcellulose (HPMC), methylcellulose (MC) and sodium carboxymethylcellulose (Na CMC).

EXPERIMENTAL

Materials: Lactose N.F. and Na CMC U.S.P. were obtained from Amend Drug and Chemical Co., Irvington, NJ. Chlorpheniramine maleate was a gift of Sandoz Research Institute, Lincoln, NE. HPMC, E50 LV (premium grade) was from Dow Chemical, Midland, MI. MC (400 cps grade) and magnesium stearate U.S.P. were obtained from Ruger Chemical Co., Irvington, NJ . Chitosan was obtained from Sigma Chemical Company, St. Louis, MO and Ac-Di-Sol from FMC Corporation, Newark, DE.

Granulation: Lactose and chlorpheniramine maleate granules (500 gm) were prepared by wet granulation using 2 to 5 % w/v solutions of Na CMC, HPMC, MC and chitosan. Chitosan solutions were prepared in 2% lactic acid in water. All other binder solutions were prepared by dissolving approproate quantities of binders in purified water. The drug (4 mg per tablet) was mixed with lactose (188 mg per tablet) by a geometric dilution method, transferred to a planetary mixer (Hobart, Model no. 50) and mixed for 10 minutes. Binder solutions were added to dry powders in the blender and mixed for 10 more minutes. The wet mass was then forced through a # 12 U.S. standard sieve and the resultant granules were dried overnight at 50°C. The dried granules were passed through a # 20 mesh and

mixed with 1% magnesium stearate and 1% Ac-Di-Sol in a Twin Shell blender (Patterson-Kelley) for 10 minutes. Finally, the granules were compressed into tablets on a single punch tablet machine (Stokes Model E) using 5/16 inch standard concave punches.

Properties of granules: Carstensen's funnel method (10) was used to determine hopper flow rates. Fines were removed by shaking a known weight of granules on a # 80 sieve. The contents remaining on sieve were weighed and % fines calculated. A graduated cylinder was used to determine bulk density (11). The granule friability was determined by subjecting 10 gm of the 20/80 mesh fraction and 100 glass beads (average diameter 4mm) to falling shocks for 100 revolutions in a friabilator (Vanderkamp). The abraded samples were sieved on an 80 mesh screen for two minutes. The amount retained on the sieve was weighed and % friability calculated.

Properties of tablets: The disintegration times of the tablets were determined according to USP XXII (12). Friability was determined by subjecting twenty tablets to 100 revolutions in a friabilator. Hardness of the tablets was determined with the Pfizer hardness tester. Ten independent measurements were averaged for each formulation. Drug content was determined by dissolving composite samples in 0.1 N HCl and analyzing spectrophotometrically (Hewlett Packard) at 264 nm. The dissolution rates were determined according to the USP Paddle method (12) using 0.1 N HCl as the dissolution medium.

RESULTS AND DISCUSSION

The properties of the granulations prepared with various concentrations of binders are shown in Table 1. A decrease in the percentage of fines, friability of the granules and flow rate was observed with an increase in the binder concentration for all the binders employed. The results of friability testing and percent of fines suggest that all the binders used were more effective as their concentrations increased. An increase in binder concentrations also resulted in granules with lower bulk density. This presumably results from the larger volume of intra-particulate voids associated with the larger size of granules (2).

The physical properties of tablets prepared with different binders are outlined in Table 2. An increase in concentration of the binders caused an increase in the

TABLE 1

Physical properties of chlorpheniramine maleate granules

Granulating fluid (% w/v)	Fines (%)	Friability (%)	Bulk density (g/ml)	Flow rate (g/s)
Chitosan				
2	19.0	13.6	0.51	7.22
3	17.5	11.6	0.49	7.01
4	14.0	9.1	0.48	7.12
5	11.5	8.2	0.48	6.89
HPMC				
2	18.2	12.1	0.50	7.40
3	14.2	9.9	0.49	7.28
4	11.2	8.7	0.48	7.12
5	9.0	7.8	0.47	6.95
MC				
2	15.5	10.9	0.52	7.40
3	14.2	9.3	0.51	7.24
4	12.5	8.5	0.50	7.14
5	10.2	7.2	0.49	6.66
Na CMC				
2	20.0	14.8	0.54	7.12
3	18.5	10.8	0.53	6.89
4	9.1	9.1	0.51	6.72
5	8.5	8.5	0.49	6.18

hardness values and disintegration times of the tablets and a decrease in friabiliy. Chitosan and Na CMC yielded tablets of roughly the same hardness. The results of friability testing confirmed those of hardness; as the hardness increased, the friability decreased. The maximum friability was obtained with 2% Na CMC and the minimum with 5% MC. In terms of friability and hardness, all binders yielded acceptable tablets. Additionally, there was a reduction in disintegration times of tablets prepared with chitosan as the binder.

HPMC produced tablets with high HFR/DT values (Table 2). This indicates that HPMC exhibits an optimum balance between binding and disintegration properties compared to the other binders. Thus, due to its superior binding properties, HPMC was chosen as the standard binder for calculating HFR/DT index (HDI) values. These were obtained by dividing the HFR/DT of the test binder by the HFR/DT of the standard and multiplying by 100. Based on the HDI values, the performance of

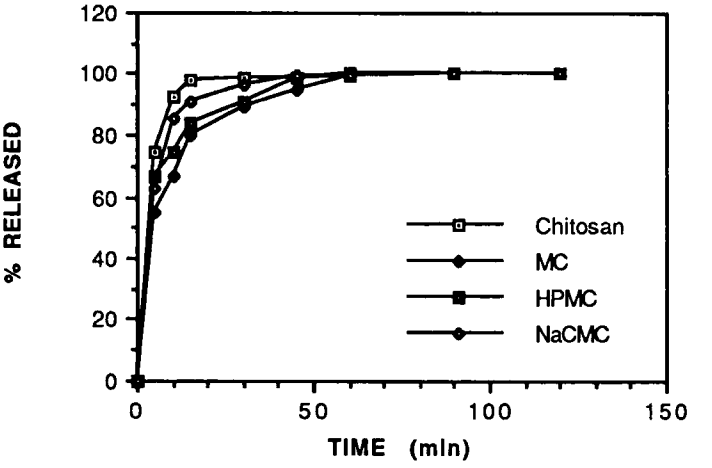
TABLE 2

Physical properties of chlorpheniramine maleate tablets

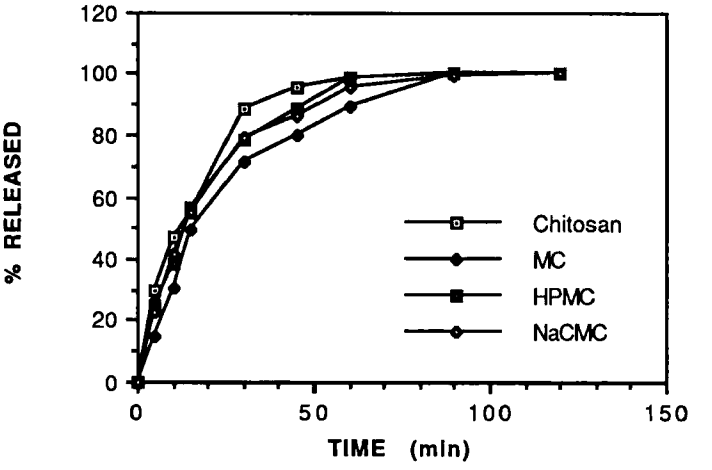
Granulating fluid (% w/v)	Friability (%)	Hardness (kg)	Disintegration Time (sec)	HFR	HFR/DT	HDI	% Dissolved in 5min	% Dissolved in 30min
Chitosan								
2	0.48	2.90	51	5.90	0.116	53.95	74.13	99.00
3	0.29	3.80	156	12.96	0.083	51.87	54.56	88.82
4	0.24	4.12	178	17.02	0.095	79.83	42.62	87.59
5	0.20	5.10	255	24.51	0.096	90.56	30.06	88.97
HPMC								
2	0.22	4.17	88	18.95	0.215	100.00	60.32	90.77
3	0.21	4.80	142	22.65	0.160	100.00	49.33	87.84
4	0.20	5.20	240	28.57	0.119	100.00	43.17	79.10
5	0.18	5.80	298	31.86	0.106	100.00	25.49	73.79
MC								
2	0.24	3.47	139	14.16	0.101	46.97	55.28	89.23
3	0.21	4.10	242	18.98	0.078	48.75	49.90	78.78
4	0.18	5.80	380	31.52	0.082	68.90	36.47	77.25
5	0.16	7.50	512	44.91	0.087	82.07	15.25	71.42
NaCMC								
2	0.58	2.85	130	4.88	0.037	17.20	62.60	96.37
3	0.31	3.90	238	12.58	0.052	32.50	39.49	89.03
4	0.24	4.75	280	19.58	0.069	57.98	34.29	80.61
5	0.20	5.00	496	24.75	0.049	46.22	23.02	78.94

the binders was found to be in the following order: HPMC > chitosan > MC > Na CMC.

The amounts of drug dissolved in 5 min and 30 min from tablets prepared with different binders are listed in Table 2 and release profiles (2% and 5% binder concentrations) are shown in Figure 1. In general, an increase in the binder concentration casused a decrease in the dissolution rate. Chlorpheniramine maleate tablets containing chitosan as a binder demonstrated superior dissolution profiles. About 75% of the drug dissolved within 5 minutes when 2% chitosan was employed and 30% dissolved with 5% chitosan. When MC was used as a binder, only 55% and 15% of the drug dissolved in 5 minutes at 2% and 5% concentrations, respectively. Similar dissolution profiles were obtained for 3% and 4% binder concentrations. It is postulated that at higher binder concentrations, while hardness increases, porosity and capillary pore size are reduced. Thus,



(a)



(b)

Figure 1. Dissolution profiles of chlorpheniramine maleate tablets (a) 2% w/v binder concentration (b) 5% w/v binder concentration

wicking of water into the tablet is markedly reduced and consequently disintegration and dissolution are slowed.

CONCLUSIONS

The results of this investigation showed that chitosan is an effective tablet binder. The relative binder efficiency parameter (HDI) revealed that the binders ranked in the following order: HPMC > chitosan > MC > Na CMC. In addition, tablets made with chitosan exhibited rapid dissolution.

ACKNOWLEDGMENT

The authors wish to gratefully acknowledge Dr. Myron Slotsky of Marion Merrell Dow Inc., for reviewing this manuscript.

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