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International Journal of Pharmaceutics 173 (1998) 87–92

international journal of pharmaceutics

Evaluation of the disintegrant properties for an experimental, crosslinked polyalkylammonium polymer

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Received 21 January 1998; received in revised form 22 April 1998; accepted 25 June 1998

Abstract

The swelling and water sorption properties of an experimental, cross-linked polyalkylammonium polymer and three other super disintegrants, i.e. crospovidone, sodium starch glycolate, and croscarmellose sodium, were evaluated via water vapor uptake, water uptake, and dry/wet particle size measurements. Direct compression formulations containing either aspirin or hydrochlothiazide as a model drug, dibasic calcium phosphate as a bulking agent, and the aforementioned disintegrants at two levels (0.25 and 1%) were tableted on a single station Manesty F-3 press. The disintegration and dissolution tests demonstrated that the crosslinked polyalkylammonium polymer possesses effective disintegrant properties, e.g. consistently fast disintegration, rapid dissolution, and is effective at low concentrations.

Keywords: Disintegrant; Crosslinked polymer; Hydrochlorothiazide; Aspirin; Dissolution

1. Introduction

The importance of quick tablet disintegration and dissolution to ensure rapid availability of the active ingredient(s) for absorption is well recognized. A number of agents have been formerly used as tablet disintegrants but are now archaic. Only a few acceptable disintegrants are currently available to pharmaceutical scientists. The plain starches were the most widely used disintegrants but could not be used in low concentrations to effectively break apart the tablet. Most compendial and industry standards for the disintegration time of a compressed tablet are considerably shorter than they were in the early 1970s. This shorter disintegration time requirement stimulated continuous efforts in the search for new, more efficient disintegrating agents (Baichwal and Moghe, 1971; Bal and Joshi, 1974; Deshpande

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0378-5173/98/$ - see front matter
PII S0378-5173(98)00218-X

Table 1
Formulation compositions of the tablets prepared with different super disintegrants

Ingredient	Amount (mg per tablet)			
ASA	80.00	80.00	—	—
HCTZ	—	—	25.00	25.00
Dibasic calcium phosphate	211.00	213.25	269.75	272.00
Disintegrant[a]	3.00	0.75	3.00	0.75
Magnesium stearate	—	—	3.00	3.00
Stearic acid	6.00	6.00	—	—
Tablet weight	300.00	300.00	300.00	300.00

[a] The disintegrants studied include croscarmellose sodium (Ac-Di-Sol®, FMC), crospovidone (Polyplasdone XL®, International Specialty Products), sodium starch glycolate (Explotab®, Edward Mendell), and DMP 504 (crosslinked polyalkylammonium polymer, DuPont Merck Pharmaceutical).

and Panya, 1987; Bhargava et al., 1991; El-Khawas and El-Khodairy, 1995; Duru et al., 1995), other than the most widely used plain starches.

Traditional tablet disintegrants can be classified as starch (e.g. corn, wheat, potato, rice and pregelatinized starch), macromolecules (e.g. alginic acid, sodium alginate, polacrilin potassium, and guar gum), finely divided solids (e.g. colloidal silicon dioxide and magnesium aluminum silicate), and cellulose (e.g. powdered cellulose, microcrystalline cellulose, carboxymethylcellulose, methylcellulose, and low-substituted hydroxypropylcellulose). Wicking and swelling were found to be the primary mechanisms of action for tablet disintegrants, while other mechanisms, such as deformation recovery, particle repulsion theory, heat of wetting and evolution of a gas etc., may play a role in particular cases of tablet disintegration (Kanig and Rudnic, 1984). DMP 504 is an experimental crosslinked polyakylammonium polymer, synthesized from hexamethylene diamine and 1,10-dibromodecane. The polymer contains randomly distributed primary,

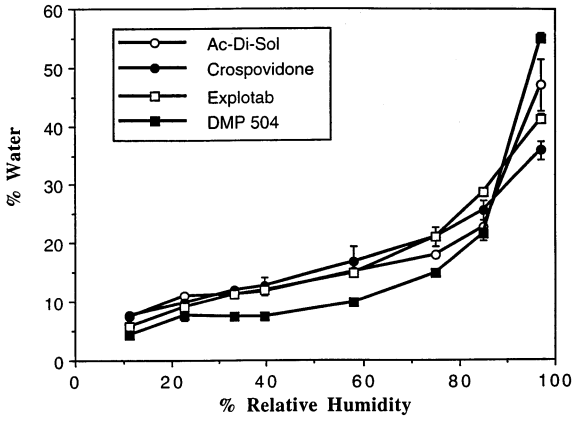

Fig. 1. Equilibrium water vapor uptake by Ac-Di-Sol®, Polyplasdone XL®, Explotab®, and DMP 504 as a function of RH. The percent water values are 3-week values. The data points and error bars represent the mean ± S.D. of three replicates.

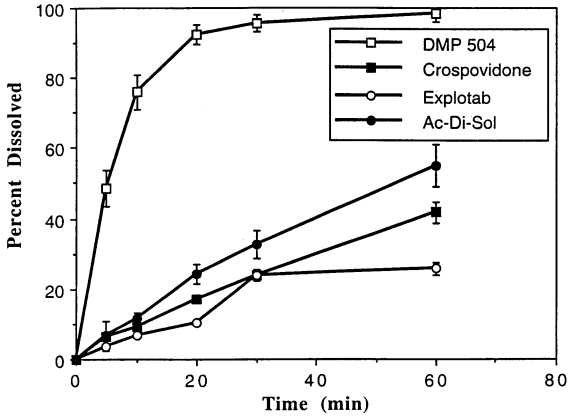

Fig. 2. Dissolution profiles for HCTZ tablets containing 0.25% disintegrant.

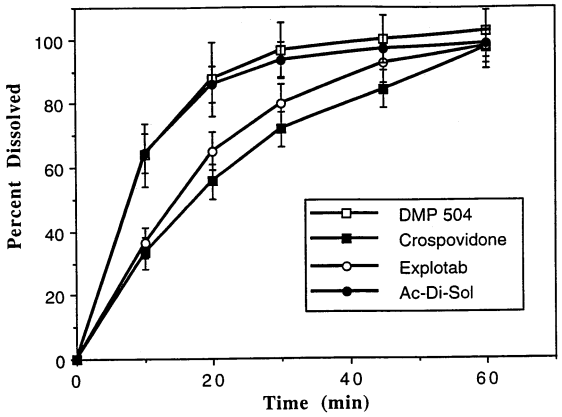

Fig. 3. Dissolution profiles for ASA tablets containing 1.0% disintegrant.

Table 2
Liquid water uptake data for DMP 504 generated by using an automated gravimetr liquid uptake apparatus

Run No.	Initial liquid uptake (g)				Mean maximum liquid uptake (g)	Initial liquid uptake rate (g s^{-1})	Time to 50% maximum uptake (s)
	Elapsed time (s)						
	10	20	30	50			
1	1.60	2.55	3.15	4.00	4.15	0.0800	15
2	2.05	2.95	3.54	4.25	4.65	0.0850	12

The water uptake data were generated by using a published method (Shah et al., 1994; Shah, 1996).

secondary, tertiary, and quaternary amine groups in their hydrochloride salt form. The alkylammonium groups which comprise this polymer form a random network containing a high level of branching and a low level of cross-linking (Figuly, 1994; Royce et al., 1996). DMP 504 has excellent water uptake and swelling properties (Raghavan et al., 1997). The purpose of the current study was to evaluate DMP 504 as a tablet disintegrant in direct compression formulations in comparison with three so-called super disintegrants, i.e. croscarmellose sodium, crospovidone, and sodium starch glycolate.

2. Materials and methods

2.1. Materials

DMP 504 was prepared by the Chemical Processing Division of the DuPont Merck Pharmaceutical Company. The physicochemical properties of DMP 504 have been well characterized in separate studies (Raghavan et al., 1997). Three commercially available disintegrants, i.e. croscarmellose sodium (lot # MS-012-91, Ac-Di-Sol®, FMC), crospovidone (lot # 96-pH-36, Polyplasdone XL®, International Specialty Products), and sodium starch glycolate (lot # 9502000029, Explotab®, Edward Mendell), were used as received.

2.2. Water vapor uptake isotherms

The water sorption isotherms for DMP 504 along with the three other super disintegrants were generated by storing the materials (20 g of each) in desiccators containing various saturated salt solutions (lithium chloride for 11, potassium acetate for 22, magnesium chloride for 33, sodium iodide for 39.5, sodium bromide for 58, sodium chloride for 75, potassium chloride for 85, and potassium sulfate for 97% relative humidity (RH)). After equilibrium, the moisture content corresponding to individual isotherm points was measured by thermogravimetric analysis (TGA 2950, TA Instruments). The sample weight for thermogravimetric analysis was 10–15 mg. A heating rate of 20°C min^{-1} over a temperature range of 25–500°C was used. The TGA data were analyzed on a data analysis program (TA Instruments 2100).

2.3. Liquid water uptake kinetics

The liquid water uptake of DMP 504 was measured by using an automated gravimetric liquid uptake apparatus (Shah et al., 1994; Shah, 1996). A 200 mg powder sample was used to determine the water uptake.

2.4. Dry and wet particle size measurement

The dry particle size of all the disintegrants was measured by using an aerosizer (model Mach 2, Amherst Process Instruments, Hardley, MA). For the wet particle size, the material was dispersed in water for 5 min. The swelling equilibrium for DMP 504 and the other super disintegrants was established within a very short period of time (i.e.

Table 3
Dry and wet particle sizes for DMP 504, Ac-Di-Sol®, Polyplasdone XL®, and Explotab®

	10% Particle size			50% Particle size			90% Particle size		
	Wet	Dry	Ratio	Wet	Dry	Ratio	Wet	Dry	Ratio
Ac-Di-Sol®	23	16	1.44	89	26	3.42	170	39	4.36
Polyplasdone XL®	40	16	2.50	125	30	4.17	261	46	5.67
Explotab®	61	26	2.35	132	42	3.14	227	58	3.91
DMP 504	18	11	1.64	82	19	4.32	221	31	6.81

The wet and dry particle sizes are in μ. The ratio presented was the ratio between wet particle size and dry particle size.

less than 5 min). Subsequently, the particle size of DMP 504 and the other super disintegrants in the swollen state was measured by using a Malvern droplet and particle size analyzer (Malvern Instruments, Southborough, MA).

2.5. Tablet preparation and testing

Aspirin (ASA, Rhone Poulenc) and hydrochlorothiazide (HCTZ, Merck) were selected as the model drugs and the tablet compositions used in this study are shown in Table 1. All the components of any given formulation except the lubricant were mixed in a Turbula mixer (Glenmills, Clifton, NJ) at 30 rpm for 5 min. The powder blends were screened through a US 20 mesh screen and the screened powder blends were lubricated with magnesium stearate for HCTZ formulations or stearic acid for ASA formulations in a Turbula mixer at 30 rpm for 5 min. The tablets were compressed on an automated Manesty model F-3 single punch tablet press with 11/32 in. standard concave punches at the tablet weight and hardness specifications of 300.0 ± 9.0 mg and 10 ± 3.0 Strong-Cobb units, respectively. The tablet weights of 20 randomly selected tablets were measured using a Mettler AC 100 analytical balance. The tablet thickness was determined with a micrometer and the tablet hardness with an Erweka TBS-28 hardness tester. The results are reported as the mean of 10 individual measurements. The friability of all the tablets studied was determined using a Roche friabilator. An Erweka disintegration apparatus (model ZT6-1-D) was used to evaluate the disintegrants following the USP 23 disintegration test procedure for uncoated tablets. The dissolution profiles were determined using the USP basket apparatus. A volume of 900 ml deionized water was used as the dissolution medium, and a stirring speed of 100 rpm was maintained. Serial sampling of the medium at appropriate time intervals, with subsequent UV analysis for drug content were performed to generate a cumulative percent released-time profile.

3. Results and discussion

Fig. 1 shows the moisture sorption isotherms for DMP 504 and three super disintegrants. DMP 504 sorbed significant amounts of moisture (i.e. $> 20\%$ water at 85% RH), but sorbed less moisture than the commercially available disintegrants at an RH less than 85%. DMP 504, however, picked up more moisture than the other disintegrants at 97% RH. Under these equilibrium conditions, DMP 504 demonstrated its water uptake ability as a disintegrant. The liquid water uptake data for DMP 504 powder are reported in Table 2. The data further indicate that DMP 504 possesses excellent water uptake property (i.e. DMP 504 sorbed more than 20-fold of its weight in water). It has been demonstrated that the dissolution profiles of tablets do not correlate with the water uptake profile, which suggests that other factors also play an important role in the disintegration process (Shah et al., 1994; Shah, 1996). The extent of swelling in water for DMP 504 and the three other super disintegrants was evaluated by dry and wet particle sizes at 10, 50, and 90 percentile and the data for this swelling potential measurement are shown in Table 3. DMP 504 powder is similar to croscarmellose sodium in

Table 4
Characteristics of HCTZ and ASA tablets using 0.25% of various disintegrants

Disintegrant	Model drug	Tablet weight (mg)	Tablet thickness (mm)	Tablet hardness (SCAU)	Disintegration time (min:s)
Ac-Di-Sol®	HCTZ	302.0 ± 1.0	3.44 ± 0.01	11.19 ± 0.81	0:19 ± 0:04
Polyplasdone XL®	HCTZ	301.0 ± 1.0	3.46 ± 0.00	11.95 ± 0.87	3:30 ± 1:39
Explotab®	HCTZ	299.0 ± 3.0	3.43 ± 0.02	11.07 ± 0.82	4:37 ± 2:25
DMP 504	HCTZ	300.0 ± 1.0	3.48 ± 0.01	11.01 ± 0.80	0:06 ± 0:02
Ac-Di-Sol®	ASA	301.0 ± 1.0	3.71 ± 0.01	12.57 ± 1.03	48:22 ± 26:41
Polyplasdone XL®	ASA	302.0 ± 1.0	3.74 ± 0.02	11.93 ± 0.78	50:24 ± 29:23
Explotab®	ASA	302.0 ± 1.0	3.75 ± 0.01	10.37 ± 0.72	92:01 ± 54:19
DMP 504	ASA	301.0 ± 1.0	3.75 ± 0.01	10.06 ± 0.65	32:55 ± 12:28

terms of dry and wet particle size distributions. The ratio between the wet and dry particle size for DMP 504 powder is at least comparable to the other super disintegrants.

Tables 4 and 5 shows the physical testing results for batches using 0.25 and 1% disintegrant levels, respectively. All the in-process testing results were well within the in-process limits. It is interesting to note that a low disintegrant level (0.25%) can effectively disintegrate the tablets following the USP 23 disintegration test procedure in the HCTZ cases. On the other hand, a low level of disintegrant resulted in an unacceptably long disintegation time for all ASA batches. The nature of the drug or other factors such as the amount of calcium phosphate and the type of lubricants used in the formulations may have an impact on the wicking and swelling properties of the disintegrant. While at a 1% disintegrant level, all the disintegrants used in the present study effectively broke apart the tablets in less than 2 min. A general trend can be discerned from both the 0.25 and 1% disintegrant data that favor DMP 504 as a disintegrating agent.

Fig. 2 shows the dissolution profiles for HCTZ tablets containing 0.25% disintegrant. DMP 504 effectively disintegrated HCTZ tablets and gave a superior dissolution profile as compared to the other super disintegrants. For HCTZ tablets containing 1% disintegrant, the dissolution of hydrochlothiazide was extremely fast (i.e. $>80\%$ drug dissolved at the 20-min time point). There is no significant difference in the drug release profiles among the disintegrants tested at 1% concentration.

The dissolution profiles for ASA tablets containing 1% disintegrant are presented in Fig. 3. The dissolution profile for ASA tablets using DMP 504 as a disintegrating agent was similar to that for the tablets containing croscarmellose sodium and much faster than that for tablets containing crospovidone or sodium starch glycolate. For ASA tablets containing 0.25% disintegrant, the dissolution of ASA was extremely slow for all the disintrgrants tested (i.e., $<20\%$ drug dissolved at the 60-min time point).

In summary, DMP 504 along with three other super disintegrants were evaluated via water vapor uptake, water uptake, and dry/wet particle size measurements. Direct compression model formulations were prepared to study the effect of the disintegrants on disintegration and dissolution. All the data consistently revealed that the crosslinked polyalkylammonium polymer can be an effective tablet disintegrant. Further experiments and characterization of DMP 504 are needed to prove that it does posses superior disintegration properties.

Acknowledgements

The authors would like to acknowledge the contributions of Dr Umang S. Shah, Dr Krishnaswamy S. Raghavan, and Anthony Gawronsky.

Table 5
Characteristics of HCTZ and ASA tablets using 1.0% of various disintegrants

Disintegrant	Model drug	Tablet weight (mg)	Tablet thickness (mm)	Tablet hardness (SCAU)	Disintegration time (min:s)
Ac-Di-Sol®	HCTZ	300.0 ± 1.0	3.50 ± 0.01	11.00 ± 0.74	0:06 ± 0:02
Polyplasdone XL®	HCTZ	299.0 ± 2.0	3.49 ± 0.02	11.14 ± 0.56	0:09 ± 0:02
Explotab®	HCTZ	301.0 ± 1.0	3.49 ± 0.02	11.24 ± 0.56	0:06 ± 0:03
DMP 504	HCTZ	300.0 ± 1.0	3.52 ± 0.01	11.13 ± 0.90	0:04 ± 0:00
Ac-Di-Sol®	ASA	299.0 ± 1.0	3.77 ± 0.01	9.93 ± 0.89	0:20 ± 0:02
Polyplas-doneXL®	ASA	298.0 ± 2.0	3.85 ± 0.0 2	8.73 ± 0.63	0:27 ± 0:06
Explotab®	ASA	306.0 ± 2.0	3.85 ± 0.02	10.19 ± 0.72	1:20 ± 0:18
DMP 504	ASA	301.0 ± 1.0	3.77 ± 0.05	10.07 ± 0.90	0:17 ± 0:02

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