DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(15), 1807-1814 (1995)

EFFECT OF CROSPOVIDONE ON THE PHYSICAL PROPERTIES OF ACETAMINOPHEN TABLETS

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ABSTRACT

Acetaminophen tablets containing minimum amount of excipients and varying amounts of cross linked polyvinyl pyrrolidone were prepared under accurately controlled conditions of compression speed and pressure. The disintegration time, dissolution rate, crushing force, friability as well as effect of temperature and humidity on these parameters during storage were determined. Increasing proportions of the cross linked polymer (1-10%) did not influence crushing force or friability but significantly decreased disintegration and dissolution time. Satisfactory tablets with desired properties were obtained by incorporation of optimum quantity of crospovidone. Storage of acetaminophen tablets at room temperature and humidity for a period of 4 weeks did not alter any of the physical properties tested weekly. However the combined effect of elevated temperature and humidity on tablet properties, especially on the dissolution time was significant. The influence of incorporation of equal amounts of crospovidone intragranularly and intra-plus extragranularly on the properties of granules and tablets were also evaluated with scaled-up formulations.

INTRODUCTION

It is well known that suitable excipients are required to form satisfactory tablets of acetaminophen which modify its plastic and elastic characteristics[1]. The problem of capping and lamination is shown to be minimised by incorporation of relatively large amount of Avicel[2], the proportion of which also influence the tensile strength and plastoelasticity[3]. Methocel E-50 was recently reported to produce satisfactory tablets in a comparative study with starch, PVP, methocell E-50, Ethocel E-50, gelatin and sod. CMC. Tablet disintegration time, hardness and friability were unaffected by storage at different conditions of temperature and humidity[4]. In another study of the effect of temperature, humidity and aging on disintegration & dissolution it was observed that acetaminophen tablets prepared with pregelatinised starch were less affected by high humidity than those prepared with providone[5]. Factors influencing properties and compression of acetaminophen tablets are numerous and have been the subject of several studies[6-10].

The aim of the present study was to investigate the combined influence of providone and crospovidone on properties of acetaminophen tablets prepared without the incorporation of the usual bulk additives and to test the assumption that the avoidance of the bulk additives would minimise the variables influencing compression. The use of only two essential agents, PVP as a binder and crospovidone as disintegrant would permit the study of the influence of this pair with similar chemical structures but different physical properties on general properties of tablets.

MATERIALS AND METHODS

A pilot experiment was designed to determine the optimum quantitiy of povidone and crospovidone that would result in satisfactory tablets which was then scaled-up to a production batch utilising the determined optimum proportions.

Preparation of granules: Granules of acetaminophen were prepared by the wet granulation method using an alcoholic solution (10%) of polyvinyl pyrrolidone (Kollidon 30, BASF, Germany) as a binder. The wet mass was passed through a 2.5 mm seive and dried in trays in an oven at 50°C for 24 hrs.

The dry granules were screened through a 1 mm seive and were mixed with varying proportions (1-10% w/w) of cross-linked polyvinyl pyrrolidone

(Kollidon CL, BASF, Germany) and 0.4% w/w magnesium stearate in a Turbula mixer for 15 minutes.

Scaled-up formulations

Formulation1. Acetaminophen powder (1.5 kg) was granulated with povidone (PVP, 10% alcoholic solution). The wet mass was passed through a mesh and was dried in trays in an oven at 50°C for 3 hours. The dried granules were crushed on mesh # 14 and the screened granules were dry-mixed with crospovidone (4% w/w) and magnesium stearate (0.7% w/w).

Formulation 2. Acetaminophen powder (1.5 kg) was mixed with crospovidone (4% w/w) for 5 minutes and was granulated with PVP as described for formulation1. The screened granules were then dry-mixed with crospovidone (4% w/w) and magnesium stearate (0.7% w/w).

Particle size analysis sieve analysis was carried out using a vibratory sieve shaker (Analysette 3 Fritsch, Germany). Weighed amount of acetaminophen granules (200 gms) was placed on the top sieve and shaken for 10 minutes. (at 3000 oscillations per minute). The fractions retained on each screen was determined.

Bulk density. The granules were poured through a funnel into a tared 100 ml graduated cylinder to determine the volume and weight. The bulk density was calculated as the ratio of the sample weight to sample volume.

Water content Water content in the granules was determined by heating a weighed quantity in an infrared heater Balance (Mettler) until no further decrease in weight was observed. Water content was computed as the difference between the initial and final weight of the granules.

Tablet compression

An Instron physical testing intrument, (Instron Corporation, High Wycombe, U.K.) adapted for tablet compression, was employed to prepare tablets from 500 mg of the granules. Granules were compressed at a crosshead speed of 1 cm/min with 12.5 mm, flat-faced punch and die system. The compression pressure ranged from 10-30 KN. The tablet was held at the indicated pressure for 30 seconds and then ejected over 30 seconds. Tablets were stored over silica gel for 24 hrs before testing for friability, hardness, disintegration and dissolution time. Tablets from formulation 1 and 2 were prepared by a rotary tablet machine.

Hardness determination. The Instron physical testing instrument was used to determine the diametral crushing force.

Friability determination. Tablet friability was determined using the Erweka friability tester. Ten tablets, randomly selected, were rotated at 40 r.p.m, for 10 min and the percent weight loss was calculated.

Disintegration time. Disintegration time was determined by the USP method (Erweka ZT4, Germany) for individual tablets and the mean disintegration time of six tablets was calculated.

Dissolution time. Dissolution rate of the tablet was measured in 0.1 N HCl at 37°C + 0.5°C at 50 r.p.m by the USP method. Samples withdrawn at different time intervals were assayed for acetaminophen by measurement of absorbance at 249 nm. The mean dissolution rate for six tablet was calculated.

Storage The tablets contained in open glass bottles were placed in controlled environmental chambers at 44% and 75% relative humidity, at 60°C and at 60°C/75% relative humidity. Physical properties of the tablets were tested weekly for a period of 4 weeks.

RESULTS AND DISCUSSION

Acetaminophen tablets containing 10% (w/w) cross-linked polyvinyl pyrrolidone (crospovidone) as disintegrant were prepared under controlled compression speed and pressure. Amount of crospovidone in the range of 1-10% (w/w) were incorporated into dried granules prior to compression. The influence of crospovidone on tablet properties in shown in table 1. The disintegration time decreased 20 fold as proportion of crospovidone was increased from 1-10% (w/w). The time required for 100% dissolution was also reduced with increasing proportion of crospovidone. Since 4% (w/w) crospovidone resulted in 100% dissolution in 30 minutes this proportion was considered adequate for further studies of the effect of ageing at elevated temperatures and humidity. The superior disintegrating action of crospovidone is attributed to its wicking and swelling property in presence of water[10].

The sponge-like structure of the polymer is believed to contribute to its wicking action with subsequent swelling to aid disintegration.

The effect of storage of acetaminophen tablets at room temperature, 60°C, room temperature\44% RH, room temperature\75% RH and at 60°C\75% RH over a period of 4 weeks on tablet characteristics are shown in table 2. Storage at room temperature did not alter tablet properties. The influence of 44% humidity was an increase in crushing force, which, by the

TABLE 1.

Effect of Varying proportions of Crospovidone on Acetaminophen Tablet Hardness, Friability, disintegration Time and Dissolution Rate (Compression force = 30 KN).

% Crospovidone	Crushing Force (kg)	Friability (% loss)	Disintegration Time (mins.) With mag. Stearate	Disintegration Time (mins.) Without mag. Stearate	Dissolution Time (T 100%, mins.) With mag. Stearate	Dissolution Time (T 100%, mins.) Without mag. Stearate
0%	8.18	2.45	120	50	*	+
1%	8.10	2.45	20	12	**	++
2%	8.20	2.41	6	3	50	25
4%	8.10	2.15	4	2	30	25
8%	7.8	2.34	2	0.75	15	15
10%	7.9	2.15	1	0.5	15	15

* 45% Dissolved in 60 min.
** 53% Dissolved in 60 min.
\+ 35% Dissolved in 60 min.
++ 65% Dissolved in 60 min.

TABLE 2.

Effect of Storage at Different Temperatures and Humidity on Tablet Properties

	Hardness (kg)				Friability (% loss)				Disintegration Time (mins))				Dissolution Time T 100% (mins.)			
Weeks:	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Room Temp	8.1	7.8	8.2	7.9	2.1	2.3	2.2	2.0	4	4	4	4	30	30	30	30
Room temp / 44% RH	9.5	10.8	10.5	12.2	1.7	1.8	1.6	1.2	6	8	8	10	50	50	30	40
Room temp / 75% RH	7.5	8.6	8.7	8.5	2.0	4.4	5.9	9.8	13	15	10	10	30	30	30	30
60°C	8.8	9.5	8.8	8.6	2.4	2.1	1.1	1.2	12	16	15	13	60	50	50	50
60°C / 75% RH	9.5	10.9	11.3	14.8	1.1	1.5	1.2	1.3	21	21	17	21	90	90	100	90

TABLE 3

Granule Characteristics and Physical Properties of Acetaminophen Tablets Prepared from Two different Formulations.

Selve (microns)	Formulation 1			Formulation 2		
1000	35			37		
710	16			16		
500	9			10		
355	6			7		
250	7			8		
180	7			7		
90	11			10		
63	7			5		
fines	2			0		
% water content	0.578	1.28	1.98	0.73	1.3	2.0
Friability (% loss)	*	2.1	1.9	*	1.6	1.3
Crushing force (kg)	4.5	8.5	8.5	6.5	9.5	9.5
Bulk density	0.51	0.54	0.6	0.48	0.5	0.52
Disintegration time (minutes)	0.5	0.5	0.5	0.5	0.5	0.5

* Capped

4th week had increased from the base value of 8.1 kg to 12.2 kg. Though there was a reduction in hardness of tablets stored at 75% RH, the disintegration time had increased compared to that of tablets stored at 44% RH. A large increase in both hardness and disintegration time was observed when the tablets were stored in a warm and humid atmosphere (60°C\75% RH). The dissolution time also was three fold higher compared to storage at room temperature. By the fourth week, a small number of tablets did show some visible changes such as an increase in size. This is probably due to swellable structure of the polymer. It is not certain whether the moisture and temperature-induced changes is due to presence of PVP or crospovidone or which one of these would have a greater influence.

Table 3 shows the result of particle size analysis of the two formulations which differ only in the manner in which the disintegrant is

incorporated. In formulation 1, crospovidone was incorporated intragranularly while in formulation 2, crospovidone was added in divided portions before and after granulation process. There was no significant difference in the particle size distribution of the two formulations. The incorporation of crospovidone before granulation, however required more granulating fluid (alcohol) as shown by the increased rinse volume. The crushing force is increased and capping decreased with increase in water content of the granules.

The physical properties of compressed tablets are influenced by several factors, among which the moisture content of granules is probably the most critical. The usual additives such as starch, lactose and cellulose derivatives absorb water in a random manner and each has it own equilibrium water content. In the case of acetaminophen tabletting the most frequently encountered problem is capping and lamination influenced by the moisture content. Since the water uptake by the bulk additives is highly variable and since moisture content is very critical in the production of satisfacotry tablets, it would be logical to avoid or atleast limit the influence of such variables. Avoidance of bulk additives and the use of only povidone and crospovidone (less than 10% of the formulation) would restrict water uptake and allow acetaminophen to absorb the amount needed without competition with other additives.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the permission and assistance received from Mr. Yousef Swaidan, department of Mechanical Engineering in the use of the Instron Physical Testing Instrument and the Jordanian pharmaceutical manufacturing Company, Naor, Jordan for providing the raw materials.

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