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RESEARCH PAPER

Factors Influencing Capping and Cracking of Mefenamic Acid Tablets

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ABSTRACT

The tendency of capping and longitudinal cracks of mefenamic acid tablets was evaluated in relation to the amount of the binder, the influence of the granulation technique, and the relative humidity of the granules. Tablets made from fluidized bed granules using methylcellulose in the granulating liquid showed significantly lower capping and longitudinal cracks than tablets from conventional granules prepared by wet granulation using methylcellulose as a dry binder.
Key Words: *Capping; Conventional granulation; Fluidized bed granulation; Longitudinal cracks; Mefenamic acid.*

INTRODUCTION

Mefenamic acid tablets are high-dose (500 mg drug content), immediate-release formulations. Therefore, the drug has a major influence on the compression characteristics of its granules and the resulting tablet properties. The physicochemical properties of mefenamic acid were evaluated in another study (1). In this paper, the tableting behavior is described. Convex mefenamic acid tablets often show capping and longitudinal cracks on the upper side (Fig. 1), which lead to coating problems.

Capping is an often discussed and frequently appearing phenomenon. Hiestand et al. (2) dealt with the internal shear stresses during compression and decompression; these stresses cause fragmentation in some materials. Hiestand et al. designed a test that determines the brittle fracture propensity of the material. This value indicates whether capping may be a problem in tableting of

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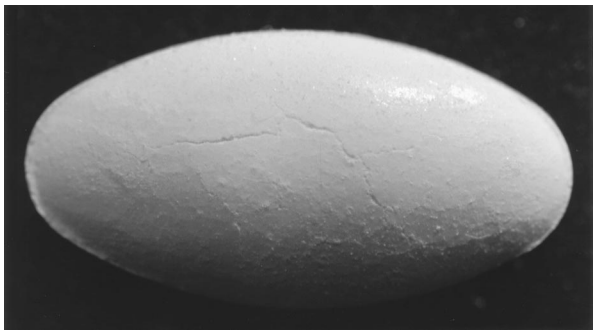

Figure 1. Longitudinal crack on the upper side of a mefenamic acid tablet.

the material. Parmentier (3) gave a summary of the mechanisms that lead to capping of tablets. Capping is caused by an inhomogeneous density and low binding forces in the capping zone. During compression, there are some parameters (like inner die wall friction, compression force, and speed) that affect the capping tendency. Also, the properties of the powder mixture, like moisture content, type and amount of the binder, particle size, and elastic behavior, are important. Van der Voort Maarschalk et al. (4) investigated the influence of viscoelasticity on the capping tendency. Furthermore, the intragranular porosity and the insufficient air escape during compaction are discussed as the main factors that lead to capped tablets (5).

The aim of this study was to improve tablet properties, that is, no capping and cracking would occur while tablets would show acceptable disintegration times and dissolution rates. Thus, the effects of binder amount and mode of application, moisture content of the granules, and compression force and speed on the capping and cracking tendency of mefenamic acid tablets were evaluated. Other tablet properties affected by the granulation technique and binder application as described by Symecko and Rhodes (6) also were determined.

EXPERIMENTAL

Materials

Mefenamic acid, lot 1069015 (Il Yang Metha Pharm. Co., Ltd., Seoul, Korea), was used as the active ingredient. As filler-binders, a mixture of maize starch (Roquette GmbH, Frankfurt, Germany) and pregelatinized maize starch (Cerestar C Top 12018, F. Kreutzer, Sabamühle, Nürnberg, Germany), microcrystalline cellulose (MCC; Avicel PH-101, Lehmann and Voss, Hamburg, Germany), and modified maize starch (Starch 1500®, Colorcon GmbH, Königstein, Germany) were used. Colloidal silicon dioxide (Aerosil 200, Degussa AG, Frankfurt, Germany) was employed as a glidant, and magnesium stearate (Peter Greven, Fett-Chemie GmbH and Co. KG, Bad Münstereifel, Germany) was used as a lubricant. Methylcellulose (Methocel A 15, Dow Deutschland, Inc., Eschborn, Germany) was used as a dry binder or granulating solution. Sodium dodecyl sulfate (SDS) (Krämer and Martin GmbH, Siegburg, Germany) was used as an aqueous solution to effect wetting or binding. All excipients were EP quality.

The compositions of granule formulations are summarized in Table 1.

Fluidized Bed Granulation

Mefenamic acid and an appropriate amount of filler were mixed in a tumbling mixer (Turbula model T2C, W. A. Bachofen, Basle, Switzerland) for 5 min and transferred into the fluidized bed granulator (HKC 05 TJ, BWI Hüttlin GmbH, Steinen, Germany). The batch size of each granulation was 330 g. Aqueous solutions of methylcellulose and SDS were sprayed onto the powder mixture at a spray rate of 14.5 g/min and an inlet air temperature of 60°C. After spraying, the granules were dried in the HKC 05 TJ until the outlet air temperature reached 30°C, resulting in a relative humidity of about 75% for the dried granules at room temperature.

Conventional Wet Granulation

Mefenamic acid, the maize starch mixture, and methylcellulose were mixed for 5 min in a ploughshare mixer (SW1/S, Erweka, Heusenstamm, Germany). The batch size was 560 g. The mixture was then moistened using an aqueous solution of SDS and was granulated using a Frewitt granulator equipped with a 1.0-mm sieve. The granules were dried at 55°C in a tray dryer (model 700, Memmert, Schwabach, Germany) to 75% relative humidity. A portion of the granules was dried for 24 hr to a relative humidity of 0.5%, divided into four parts, and stored in desiccators for 12 days at relative humidities of 0% (silica gel) and 12%, 33%, and 59% over saturated salt solutions until the equilibrium water uptake was reached. The water content was determined by Karl-Fischer titration.

Wet Granulation Using a High-Shear Mixer

The powder mixture was prepared as described above and mixed using the MGT 70 (Lödige Fördertechnik

Table 1

Composition of Mixtures Prepared for Fluidized Bed and Conventional Granulation (%)

	Granules Prepared by Fluidized Bed Technique, HKC 05TJ							
	A	B	C	D	E	F	G	H
Mefenamic acid	89.15	86.07	82.64	89.82	86.07	86.07	82.64	89.82
Maize starch mixture	8.63	8.33	11.99	4.34				
Cerestar C Top					8.33			
Starch 1500						8.33		
MCC							11.99	4.34
Methylcellulose	1.78	5.17	4.96	5.39	5.17	5.17	4.96	5.39
SDS	0.44	0.43	0.41	0.45	0.43	0.43	0.41	0.45

Granules Prepared by Wet Granulation Using a High-Shear Mixer				
Erweka SW1/S	I	Lödige MGT 70	J	K
Mefenamic acid	86.07	Mefenamic acid	89.15	86.07
Maize starch mixture	8.33	Maize starch mixture	8.63	8.33
Methylcellulose	5.17	Methylcellulose	1.78	5.17
SDS	0.43	SDS	0.44	0.43

GmbH, Scherfede, Germany) for 5 min. The batch size was 15 kg. An aqueous solution of SDS was added during a mixing time of 7 min at an impeller speed of 200 rpm and chopper speed level 1. The power consumption was constant at 1.6 kW. The mixture was granulated using an FSG granulator (Erweka, Heusenstamm, Germany) with a 3.15-mm sieve and was dried in a fluidized bed dryer (GPCG 15/25, Glatt GmbH, Binzen, Germany) at an inlet air temperature of 60°C until the exhaust air temperature reached 30°C. After drying, the granules were sieved using the FSG granulator equipped with a 1.00-mm sieve.

Blending and Tableting

Table 2 shows the full range of mixtures prepared for tableting. The appropriate quantities of filler, colloidal silicon dioxide, and magnesium stearate were added to the granules and mixed using a gyro-wheel mixer (Erweka). The resulting binder contents were either 1.4% or 4.1% (w/w). Tableting was performed using an instrumented rotary tablet press (Korsch PH 230/17, Korsch Pressen GmbH, Berlin, Germany) with special oblong tooling at machine speeds of 26, 50, or 75 rpm and compression force levels of 10 to 30 kN.

Water Uptake of Dry Granules

The water uptake of granules dried for 24 hr at 55°C and with a relative humidity of 0.5% was determined using a processor tensiometer (K12, Krüss Laborgeräte GmbH, Hamburg, Germany). About 2 g each of the samples were filled into a special polypropylene disk. The

Table 2

Composition of Mixtures Prepared for Tableting (%)

	A and J	B, I, and K	C	D	E	F	G	H
Granules	78.72	79.30	82.61	76.00	79.30	79.30	82.61	76.00
Maize starch mixture	6.79	6.61	3.30	9.91				
Maize starch					6.61			
Starch 1500						6.61		
MCC	14.04	13.65	13.65	13.65	13.65	13.65	16.95	23.56
Colloidal silicon dioxide	0.28	0.27	0.27	0.27	0.27	0.27	0.27	0.27
Magnesium stearate	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Binder content	1.4	4.1	4.1	4.1	4.1	4.1	4.1	4.1

disk containing the test sample was then linked to the balance of the tensiometer and kept over the specified saturated salt solution in a closed chamber. The weight increase of the sample was registered by the tensiometer until a plateau was reached. To compare the water uptake of the granules stored in desiccators at the same humidity levels, the water content of the granules was also determined by Karl-Fischer titration.

Crushing Strength

The crushing strength was determined using a Schleuniger 6D tester (Dr. Schleuniger, Solothurn, Switzerland). The mean value of 10 tablets was calculated, and the capping tendency of each tablet was noted.

Disintegration

The disintegration times of the tablets were determined according to USP 23 in 0.1 N HCl at 37°C using a PTZ 1 (Pharmatest Apparatebau GmbH, Hainburg, Germany). Six tablets from each batch were used for the determinations.

Dissolution Rates

The dissolution rates of mefenamic acid tablets were determined according to the USP 23 paddle method using a PTW dissolution tester (Pharmatest Apparatebau GmbH) at a paddle speed of 100 rpm. The dissolution medium consisted of 900 ml Tris buffer at pH 9 (Merck KGaA, Darmstadt, Germany) maintained at a temperature of 37°C. At suitable intervals, samples of 5 ml were taken without replacing the volume. The samples were measured after dilution at a wavelength of 332 nm using a spectrophotometer (S550, Perkin-Elmer, Stuttgart, Germany). All measurements were done in triplicate.

Determination of Capping and Cracking

Tablets were inspected by magnifying glass for surface roughness, longitudinal cracks, and capping.

RESULTS AND DISCUSSION

Influence of Binder Amount and Mode of Application on Tablet Properties

Tablets with a binder content of 1.4% showed crushing strengths of 40 to 60 N. Tablets produced from granules prepared in a fluidized bed (tablets A) showed slightly higher crushing strength values than those tablets produced from granules prepared by the wet granulation method (tablets J) (Fig. 2). In all cases, however, the capping tendency was high, and almost every tablet laminated during the determination of the crushing strength. The surface was rough, and longitudinal cracks appeared at the upper side of the tablets. An increase of the binder content to 4.1% resulted in higher crushing strength values and lower capping tendencies (tablets I and K). The surface of the tablets became smoother, and no longitudinal cracks occurred. The best results regarding capping

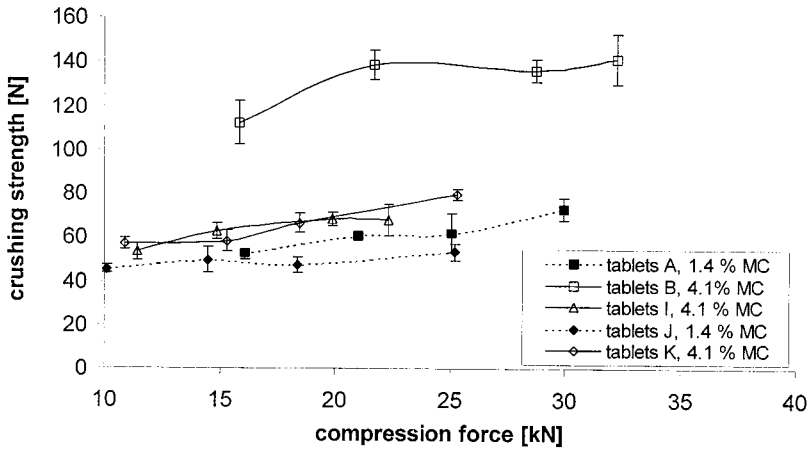

Figure 2. Tablet hardness versus compression force of tablets with different amounts and modes of application of binder (MC = methylcellulose). Tablets A and B, fluidized bed granulation; tablets I, conventional wet granulation using an Erweka SW/1; tablets J and K, conventional wet granulation using a Lödige MGT 70.

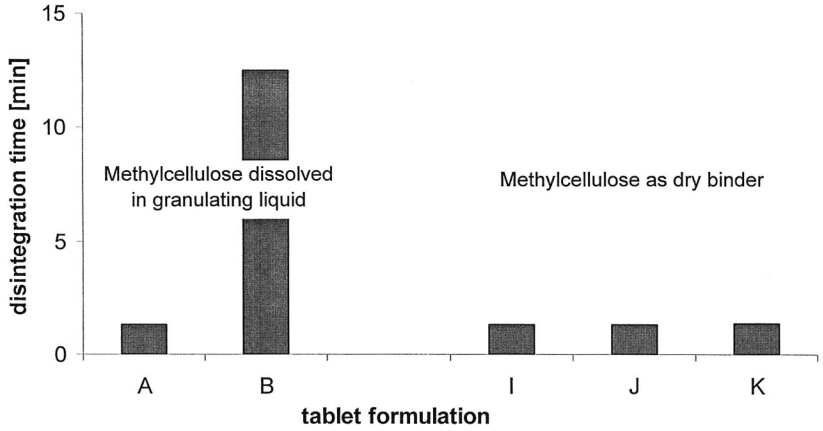

Figure 3. Disintegration times of tablets with different amounts and application modes of binder. Tablets A and B, fluidized bed granulation; tablets I, conventional wet granulation using an Erweka SW/1; tablets J and K, conventional wet granulation using a Lödige MGT 70.

and cracking were obtained with tablets containing fluidized bed granules at a binder content of 4.1% (tablets B). The lamination in the hardness tester was eliminated completely, and the surface appeared to be polished without any cracks.

As described by Sunada et al. (7) for a standard tablet formulation based on fluidized bed granulation, the tablets with the best surface properties showed longer disintegration times and delayed dissolution rates due to the higher binder content. In this study, all tablets except formulation B disintegrated within 2 min (Fig. 3). This formulation contained dissolved methylcellulose, and therefore the disintegration time increased to more than 10 min.

The dissolution rates of all tablet formulations are shown in Fig. 4. Tablets containing 1.4% binder reached the 75% level after 15 min, and after 45 min, 100% was released. Tablets containing 4.1% binder did not reach the 100% level, and after 45 min, only 75% of the drug was released. The application of methylcellulose as a dry binder had less effect on release rates. Kokubo et al. (8,9) found similar results for methylcellulose in their studies of different cellulose-based binders used for fluidized bed or high-speed mixer granulation. The dissolution of the binder in the dry mixing method was insufficient, and hence the binding force of methylcellulose was reduced. The granules were soft compared to granules prepared with a binder solution.

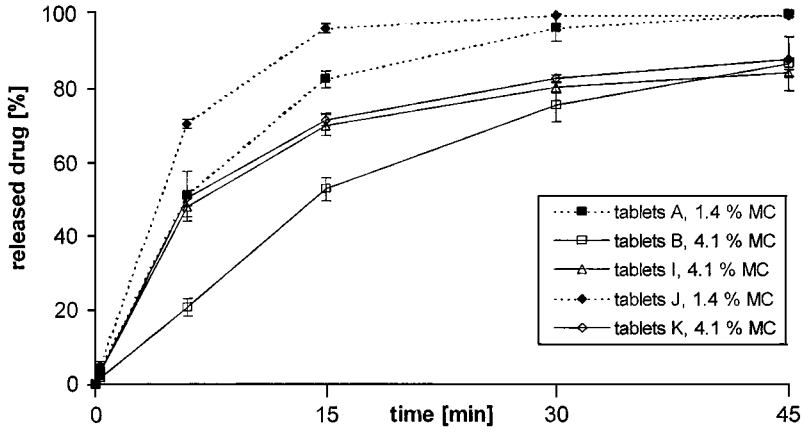

Figure 4. Dissolution rates of tablets with different amounts and modes of application of binder. Tablets A and B, fluidized bed granulation; tablets I, conventional wet granulation using an Erweka SW/1; tablets J and K, conventional wet granulation using a Lödige MGT 70.

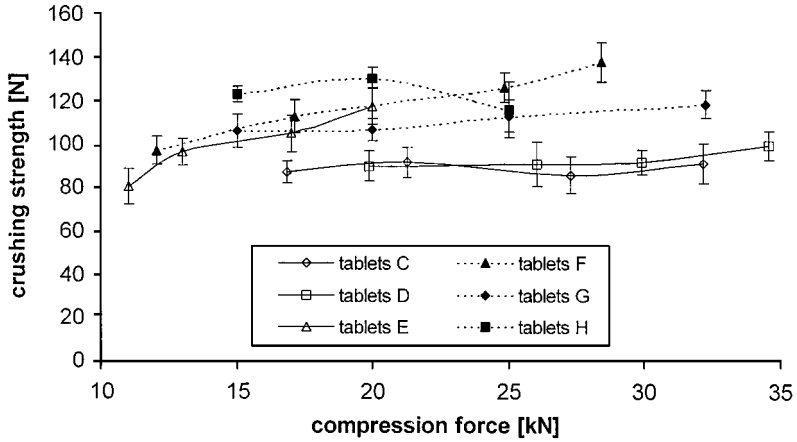

Figure 5. Tablet hardness versus compression force of tablets containing 4.1% methylcellulose as a binder and different filler-binders. The granules were prepared by the fluidized bed technique. Tablets C and D, 75% or 25% maize starch mixture in the granules; tablets E, pregelatinized maize starch (Cerestar C Top) in the granules, normal maize starch in outer phase; tablets F, maize starch mixture replaced by Starch 1500; tablets G and H, maize starch mixture replaced by Avicel PH-101.

Effects of Different Filler-Binders on Crushing Strength, Disintegration Time, and Dissolution Rates

The use of fluidized bed granules with 4.1% binder content (tablets B) reduced capping and cracking significantly, but the tablets showed delayed dissolution rates and prolonged disintegration times. To enhance the dissolution behavior and the disintegration time, the effects of different filler-binders and their mode of distribution between the granules and the outer phase were investigated.

Avicel PH-101 is a well-known substance that produces hard, fast-disintegrating tablets at low compression forces (10). Owuso-Ababio et al. (11) observed higher dissolution rates and faster disintegration times with mefenamic acid tablets containing Avicel PH-101. Despite the normal value of tablet hardness of approximately 100 N (Fig. 5), in this study, when the starch was completely replaced by Avicel PH-101, the tablets (i.e., those containing only MCC as the filler-binder, which were formulations G and H) did not disintegrate within 1 hr, and the drug release was slow (Figs. 6 and 7, respectively). Thus, the presence of maize starch in the formulation is obvi-

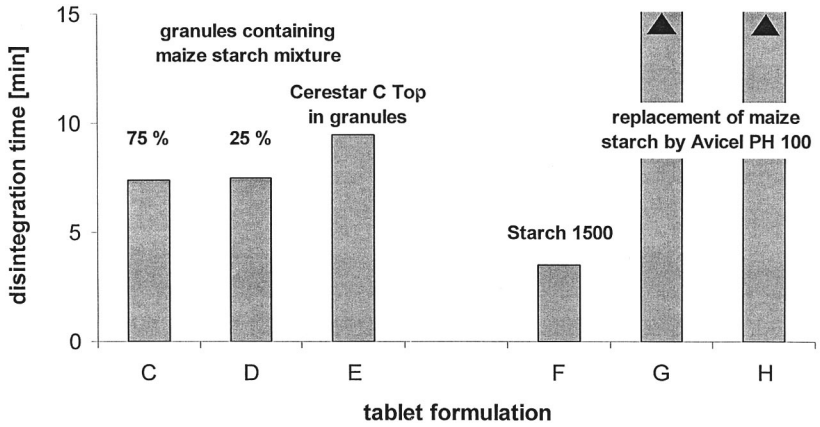

Figure 6. Disintegration times of tablets containing different filler-binders with binder content of 4.1%. The granules were prepared by fluidized bed technique.

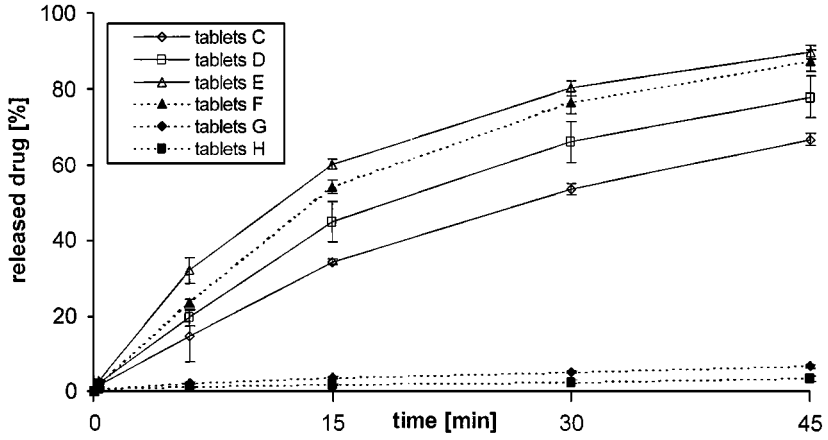

Figure 7. Dissolution rates of tablets containing different filler-binders with binder content of 4.1%.

ously necessary for the disintegration of the tablets. For this reason, some experiments were made keeping the amount of maize starch mixture, but changing the mode of contribution in the granules and the outer tablet phase. The incorporation of either 25% or 75% maize starch mixture in the outer tablet phase (formulations C and D) led to faster disintegration times compared to formulation B (Fig. 6), but the dissolution rates were still slow (Fig. 7). The tablets of formulation E, containing the pregelatinized starch (Cerestar C Top) in the granules and the normal maize starch in the outer phase disintegrated in less than 10 min (Fig. 6), but showed the highest drug release within 45 min (Fig. 7).

The replacement of maize starch mixture by another type of pregelatinized maize starch (Starch 1500) in formulation F showed the best results regarding disintegration times and dissolution. The tablets disintegrated in less than 5 min, which was comparable to tablets containing 1.4% methylcellulose (tablets A and J). The dissolution rates were enhanced compared to tablets with maize starch mixture, but did not reach the 100% level within 45 min.

Influence of Storage Humidity of the Granules Onto Capping and Cracking Tendency

The water uptake of granules occurred fast in the range 20% to 80 % relative humidity (Fig. 8), as described for the sorption characteristics of tablets by Fischer and Schepky (12). The moisture content of granules stored in desiccators over saturated salt solutions for

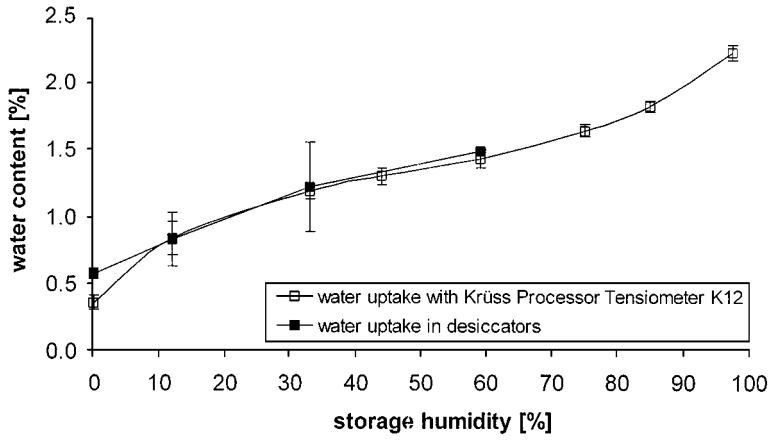

Figure 8. Comparison of water content of mefenamic acid granules after storage over different saturated salt solutions.

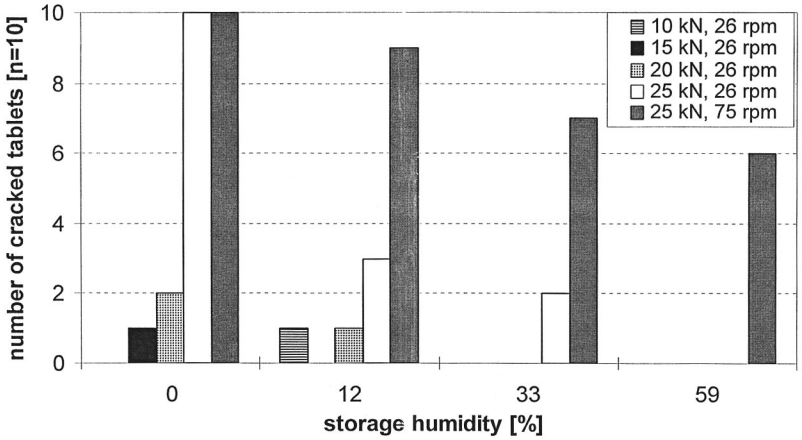

Figure 9. Influence of storage humidity and tableting speed on the cracking tendency of mefenamic acid tablets.

12 days is comparable to the water uptake of granules determined at the same humidity levels using a processor tensiometer. Therefore, it can be assumed that the equilibrium water uptake is reached after 12 days. The inspection of tablets containing granules of different moisture contents revealed that relative humidity of the granules plays a major role in the cracking tendency of mefenamic acid tablets (Fig. 9). An increase in relative humidity resulted in fewer cracked tablets with smaller size cracks. Tablets compressed at higher compression force and speed showed a higher cracking tendency; almost 100% of the inspected tablets were broken. Although the binder content of the tablets was high, the capping tendency was marked (Fig. 10). Higher storage humidities did not lead to lower capping tendencies due to the drying process of the granules and the application of the methylcellulose as a dry binder.

CONCLUSION

The capping and cracking tendencies of mefenamic acid tablets can be reduced by increasing the binder content from 1.4% to 4.1% per tablet. The dissolution rate and the slow disintegration of these tablets can be slightly improved by using Starch 1500. The type of filler-binder did not significantly improve the tablet properties. The replacement of a maize starch mixture by Avicel PH-101 lead to nondisintegrating tablets and reduced dissolution rates. There is a strong effect of storage humidity on the

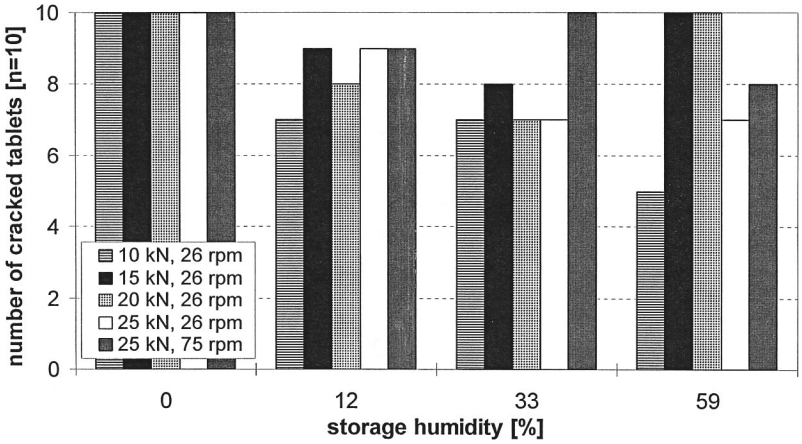

Figure 10. Influence of storage humidity and tableting speed on the capping tendency of mefenamic acid tablets.

cracking phenomenon, but the capping tendency cannot be reduced by only controlling relative humidity. To eliminate the cracking and capping tendencies, it is necessary to use fluidized bed granules prepared using binder solutions.

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