ELSEVIER

International Journal of Pharmaceutics 143 (1996) 13–23

international journal of pharmaceutics

Compression of enteric-coated pellets to disintegrating tablets

Thomas E. Beckert[a], Klaus Lehmann[b], Peter C. Schmidt[a,*]

[a]*Department of Pharmaceutical Technology, Eberhard-Karls-University Tübingen, Auf der Morgenstelle 8, D-72076 Tübingen, Germany*

[b]*Röhm GmbH, Darmstadt, 64275, Germany*

Received 4 April 1996; revised 3 June 1996; accepted 5 June 1996

Abstract

Enteric-coated sucrose pellets containing a layer of bisacodyl beneath the coating were compressed into tablets on an instrumented single-punch machine using four different filler-binders for direct compression. Different copolymers based on polymethacrylates were applied as coatings. Pellets of two different crushing strengths were used. The quality of the films before and after tableting was evaluated by determining the amount of bisacodyl liberated after treatment for 2 h in 0.1 M HCl according to the requirements of USP 23 for enteric-coated preparations. Results indicate that the most important parameters are the coating agent itself and the amount of coating applied to the pellets. Higher coating weights and coatings with better elastic properties lead to formulations, which liberate less bisacodyl after compression. Formulations are available that fulfil all requirements of USP 23 regarding enteric-coated preparations.

Keywords: Pellet; Coating; Gastrointestinal stability; Acrylic polymer; Tableting; Dissolution behavior

1. Introduction

The compression of coated pellets into rapidly disintegrating tablets is becoming increasingly important. It is possible to produce divisible multiple-unit dosage forms with modified release at low cost. Sandberg et al. (1988) reported that multiple-unit products also enable ready distribution over a large surface area in the intestine and thus less variation in drug release. If applied at a particle size below 2 mm, pellets or microcapsules behave like liquids, leaving the stomach within a short period of time (Clarke et al., 1995). Multiple-unit dosage forms are usually produced by filling pellets into hard gelatine capsules, which unfortunately have the disadvantage of high production cost. Moreover, capsules can not be divided into two or more parts.

In order to establish general guidelines for the preparation of tablets made from coated pellets, it

* Corresponding author.

PII S0378-5173(96)04631-5

is important to know the influences that may cause changes in drug liberation. Needless to say, enteric-coated pellets, in particular, must withstand the applied compaction pressures without being damaged, since cracks, for example, will cause adverse effects to the gastric mucosa by liberating the enteric-coated drug. Lehmann et al. (1990, 1993) developed disintegrating tablets containing enteric-coated acetylsalicylic acid or indometacin pellets, both coated with Eudragit L and liberating less than 10% w/w of the active ingredient within 2 h in 0.1 M HCl. These tablets conformed to the requirements of USP 23 (1994) for enteric-coated preparations. Disintegrating tablets from sulfametoxazole pellets coated with cellulose acetate phthalate were described by Takenaka et al. (1980), but liberated more than 10% of the drug within 2 h in artificial gastric fluid and thus did not conform to the requirements of USP 23.

While only few articles can be found which deal with disintegrating tablets made from enteric-coated pellets, many more have been published describing the compaction of pellets into sustained release tablets, which either disintegrate rapidly (Lehmann et al., 1990, 1993; Lehmann, 1984; Béchard and Leroux, 1992; Maganti and Celik, 1993, 1994; Tirkkonen and Paronen, 1993; Flament et al., 1994; Torrado and Augsburger, 1994) or form a matrix (Nixon et al., 1978; Nixon and Hassan, 1980; Nixon and Agyilirah, 1984; Agyilirah and Nixon, 1980; Chemtob et al., 1986; Dubernet et al., 1987; Sveinsson et al., 1993). In most cases ethylcellulose is used as the film coating.

Béchard and Leroux (1992), Tirkkonen and Paronen (1993) and Torrado and Augsburger (1994) found that polyethylene glycol 3350 and microcrystalline cellulose used as excipients to produce rapidly disintegrating tablets containing pellets cause the lowest increase in drug liberation after tableting. The influence of compaction force on drug liberation after disintegration of tableted pellets is reported controversially, ranging from no influence to a significant increase in liberation with increasing compaction forces (Ly et al., 1993; Prapaitrakul and Whitworth, 1989, 1990). When compared with uncompressed pellets, the compaction of pellets to non disintegrating tablets always leads to a prolongation of drug liberation, while the liberation is always faster from disintegrating tablets (López-Rodríguez et al., 1993). Comparing different pellet sizes, larger pellets were found to liberate more (Ragnarsson et al., 1987, Ragnarsson and Johansson, 1988) or less (Chiao and Price, 1994) drug after compaction than smaller ones. When higher amounts of pellets are incorporated into a tablet, an increase in drug liberation was observed by Aulton et al. (1994). Lehmann et al. (1993) claimed that a certain elongation at break of the film coating needs to be guaranteed to avoid cracks during compaction. Drug liberation decreases when thicker film coatings are used (Flament et al., 1994).

Our intention was to give reasonable hints for the development of rapidly disintegrating tablets containing coated pellets. A model has been developed that allows to describe various influences on crack formation during tableting. As the effect of time on drug dissolution is to be reduced to a minimum, the model drug is to dissolve quickly and easily in the test medium 0.1 M HCl. Therefore bisacodyl has been chosen as a model drug because it is usually applied as an enteric-coated formulation. It shows very good solubility in acidic media and can easily be assayed via UV spectroscopy (Hoffmann and Petersen, 1993). The model consisted of sucrose pellets coated with approximately 4% w/w bisacodyl. Different enteric coatings were applied directly onto the bisacodyl layer, so that cracks within the film caused by the compression force of a tableting machine would lead to dissolution of the drug. This model is more sensitive than those employed in earlier studies (Lehmann et al., 1993), where highly dosed and sparingly soluble drugs like ASA and indometacin were used. Pellets of two different crushing strengths were coated using a fluidized bed apparatus. The influences of compression force, type and amount of excipient, pellet hardness, film elasticity and film thickness on the liberation of bisacodyl after compaction of the pellets with various amounts of different excipients were studied. A gastroresistant formulation with a new polymer showing good tableting properties is presented.

2. Materials and methods

2.1. Materials

Avicel PH101 and Avicel PH200 were supplied by Lehmann and Voss (Hamburg, Germany), Eudragit L 30 D-55 (methacrylic acid copolymer type C USP), Eudragit NE 30 D (polyacrylate dispersion 30% German Pharmacopeia (1996b)), two new polymers based on polymethacrylates, crystalline sucrose and triethyl citrate by Röhm (Darmstadt, Germany), Kollidon 25 (povidone) and Kollidon CL (crosslinked povidone) by BASF (Ludwigshafen, Germany). Bekapress D2 (dicalcium phosphate anhydrous USP 23) was delivered by Benckiser-Knapsack (Ladenburg, Germany), Cellactose (excipient for direct compression made of 75% w/w lactose and 25% w/w cellulose) and Lactose D 80 by Meggle (Wasserburg, Germany), polyethylene glycol 6000 by Hoechst (Frankfurt, Germany). Bisacodyl was purchased from MS Chemicals (Milan, Italy), magnesium stearate from Bärlocher (Munich, Germany), glycerol monostearate from Hüls (Troisdorf, Germany), citric acid, trisodium phosphate, hydrochloric acid fuming, sodium hydroxide and talc from Merck (Darmstadt, Germany), placebo pellets type 841 from Werner (Tornesch, Germany), polysorbate 80 from ICI (Essen, Germany).

2.2. Preparation of pellets

A variation of the technique used by Lehmann et al. (1989) was applied to produce *soft* pellets. These were prepared by a powder layering method using sucrose crystals as seed and a mixture of Lactose D80, Aerosil 200 and Kollidon 25 as adherent (Table 1). An aqueous binder solution containing Eudragit NE 30 D and sucrose was sprayed onto the crystals with a spray nozzle (WAINBA, Walther, Cologne, Germany) in a 10 l coating pan (Erweka, Heusenstamm, Germany). Adherent powder was poured into the coating pan every 30 s. Growing pellets were dried using an airstream of 25°C. After completion of the process the pellets were dried for an additional 24 h in a tray drier at 40°C. The shape of these pellets was almost spherical, but not as perfect as that of the hard pellets. Well-rounded hard pellets containing mainly sucrose were purchased as cited above. Size fractions of both kinds of pellets between 0.5 and 1.25 mm in diameter were obtained by sieving and used for further processing. Both kinds of sucrose pellets were coated with approximately 4% w/w bisacodyl in a fluidized bed processor (GPCG1 and WSG5, Glatt, Binzen, Germany), using a binder consisting of 33.3% w/w Eudragit L 30 D-55 dry substance calculated on bisacodyl content, plasticized with 10% w/w triethyl citrate and 50% w/w talc as a glidant. The mixture was sprayed onto the pellets from a 20% w/v aqueous dispersion. The dispersion was stirred with a magnetic stirrer during the coating process. The inlet temperature was kept constant at 45°C. When the coating was finished the pellets were dried in the fluidized bed processor for an additional 5 min. Between 77 and 100% of the theoretical amount of bisacodyl was found on the pellets.

2.3. Preparation of coating dispersions

For details of the formulations see Table 2. In general, the adjuvants were homogenized in demineralized water, using an Ultra-Turrax (Jahnke and Kunkel, Staufen, Germany). Polymer dispersions were added after homogenization. Stirring was necessary when talc was among the excipients. When glycerol monostearate was used, it was dispersed in water together with polysorbate 80 and heated to approximately 70°C until it melted. The emulsion was cooled down to 30°C before further processing was undertaken. During

Table 1
Formulation for the production of 1 kg of pellets in a coating pan

Cores	Sucrose, sieved 0.5–0.8 mm	317.6 g
Powder	Lactose D 80	613.1 g
	Kollidon 25	19.1 g
	Aerosil 200	3.2 g
Binder solution	Eudragit NE 30 D (dry polymer substance)	39.2 g
	Sucrose	7.8 g
	Water (evaporated)	110.0 g

Table 2
Formulations used for enteric coatings, calculated as coatings for 1 kg bisacodyl pellets

Formulation	1	2	3	4	5	6	7	8	9
Eudragit L 30 D-55 (g)	416.7	833.3	208.3	416.7	208.3				
Sodium hydroxide (2% w/v solution) (g)			1.5	3.0	1.5				
Eudragit NE 30 D (g)			208.3	416.7	208.3				
Citric acid (20% w/v solution) (g)			5.7	11.4	5.7				
Experimental polymer I (g)						416.7	833.3		
Experimental polymer II (g)								416.7	833.3
Triethyl citrate (g)	12.5	25.0	12.5	25.0				6.25	12.5
Dibutyl phthalate (g)					25.0				
Glycerol monostearate (g)			3.8	7.5	3.8	3.8	7.5	3.8	7.5
Polysorbate 80 (33.3% w/v solution) (g)			2.0	2.0	2.0	2.0	2.0	2.0	2.0
Talc (g)	62.5	125.0							
Demineralized water (g)	508.5	1017.0	505.0	1015.0	360.0	223.5	447.0	256.5	504.7
Simeticon emulsion (g)	q.s	q.s.	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	
Dry coating substance (% w/w)	12.5	25	12.5	25	12.5	12.5	25	12.5	25
Coating conditions									
Inlet temperature (°C)	42	42	47	47	35	36	40	36	38
Outlet temperature (°C)	32	32	35	35	28	28	25	26	25
Aperture of nozzle (mm)	1.0	1.0	1.0	1.0	1.2	1.0	1.0	1.0	1.0
Pressure of coating air (bar)	1.2	1.2	2.0	2.0	1.2	2.0	1.7	1.6	1.5
Preheating (min)	5	5	5	5	5	5	5	5	5
Time of coating (min)	48	96	47	98	62	72	76	88	106
Liberation of bisacodyl									
After 2 h at pH 1.0 (%)	1.6	0.1	1.4	0.0	1.3	2.9	2.5	0.0	0.0
After 45 min at pH 6.8 (%)	97.9	95.6	83.7	47.2	60.9	99.9	99.1	99.1	82.4[a]

[a] at pH 7.0

the melting process, the mixture was stirred with a magnetic stirrer (IKA, Staufen, Germany) at high speeds. Before mixing, the dispersions of Eudragit L and Eudragit NE had to be adjusted to pH 3.0. At lower pH values agglomeration of the polymers occurred. For technical conditions of coating also see Table 2.

2.4. Blending and tableting

Different amounts of pellets were blended for 10 min with 4% w/w Kollidon CL as a disintegrant, using a Turbula T2C mixer (Bachofen, Basel, Switzerland) at 42 rpm. Excipients were then added in corresponding amounts and blended for 20 min. Finally, 0.25% w/w magnesium stearate was passed through a 315 mm sieve onto the mixture and blended for 5 min in the Turbula. Batches of 400 g each were prepared. The degree of filling of the mixing vessels used was between 40 and 70% by volume to ensure proper mixing. Tablets of 400 ± 20 mg, 10 mm in diameter and with bevelled edges, were compressed on an instrumented single-punch machine type Korsch EK0 (Korsch, Berlin, Germany). The machine speed was set to 35 rpm. Tablets were compressed at five different force levels (5, 10, 15, 20, 25 kN). The lower punch holder was instrumented with four strain gauges (3/120 LY11, Hottinger Baldwin Meßtechnik, Darmstadt, Germany) in a temperature-compensated full bridge. Data acquisition was achieved by a DASH16 A/D converter board (Keithley, Munich, Germany) on an IBM AT03 personal computer (IBM, Stuttgart, Germany). Data analysis was performed using Meßfix, which was programmed by Herzog (1991). Calibration of the system against piezoelectric load washers (9021, Kistler, Winterthur, Switzerland) proved linearity of the system from 0 to 35 kN with a correlation coefficient of 0.9998.

2.5. Crushing strength of pellets

The crushing strength of the pellets was measured using an apparatus described by Kopp (1986). The measuring device of this instrument is based on a piezoelectric load washer. It is possible to obtain force-time curves showing the maximum crushing strength and the shape of the breaking curve. Recording of force-time curves was performed using Signalys software (Ziegler Instruments, Mönchengladbach, Germany) on an IBM AT03 personal computer with a Bakker BE 435 A/D converter board (Ziegler Instruments).

2.6. Tablet testing

Radial crushing strength of the tablets was determined 24 h after compaction, using a Schleuniger 6 D hardness tester (Schleuniger, Solothurn, Switzerland). Friability was evaluated by the weight loss of 20 tablets in a Roche friability tester (Erweka, Heusenstamm, Germany) after tumbling for 5 min at 25 rpm. Disintegration was determined according to German Pharmacopeia (1996a), using a type PTZ 1 disintegration tester (Pharmatest, Hainburg, Germany).

2.7. Dissolution studies

All preparations, pellets and tableted pellets, were tested for intact films according to USP 23, drug release, enteric-coated articles, method A (1994). The dissolution medium for the investigation consisted of 750 ml of 0.1 M HCl prepared with demineralized water and fuming HCl. It was adjusted to pH 1.0 in a 1000 ml dissolution vessel. A stirring rate of 100 rpm was applied, temperature was set to 37°C. Tablets containing between 200 and 400 mg of pellets or 400 mg of pellets were analyzed in triplicate. After 30, 60 and 120 min, 10-ml aliquots were removed and filtered through a cellulose acetate membrane filter (order no. 11107-25-N, pore size 0.2 mm, Sartorius, Göttingen, Germany). After treatment in 0.1 M HCl the pellets were homogenized using an Ultra-Turrax to quantify the total bisacodyl content in the vessels. For determination of the liberation of bisacodyl at pH 6.8, 250 ml of 0.2 M trisodium phosphate solution were added and adjusted to pH 6.8 with 1 M sodium hydroxide solution. After 45 min the solution was adjusted to pH 1.0 with approximately 100 ml of 2 M HCl. Three 10-ml aliquots were removed from that solution before homogenization. All samples were assayed three times, using UV spectrophotometric analysis.

2.8. Spectrophotometric analysis

A Lambda 16 UV-vis spectrophotometer (Perkin-Elmer, Überlingen, Germany) was used for the determination of bisacodyl content. Bisacodyl content was measured against 0.1 M HCl at 264 nm. Calibration proved that the system was linear from 0.57 mg/ml to 56.5 mg/ml with a correlation coefficient of 0.9997. The regression equation according to Lambert-Beer's law was $A = 231.8 \times C + 5.2$ (A, absorption; C, concentration) when a cuvette of 1 cm in diameter was used.

3. Results and discussion

3.1. Pellets

The deformation behavior and cracking of hard and soft pellets under mechanical load is shown in

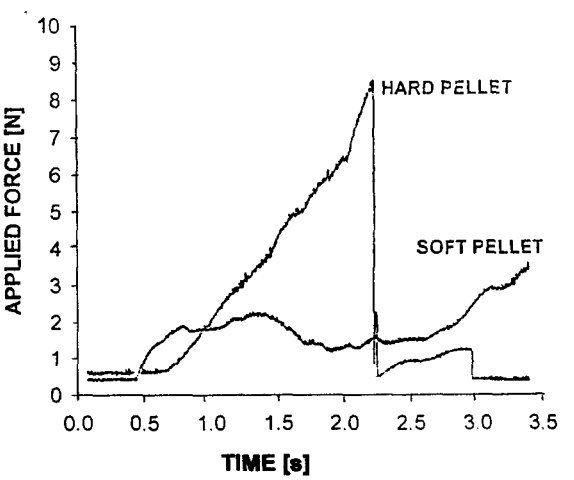

Fig. 1. Deformation behavior and cracking of hard and soft pellets under mechanical load.

Table 3
Elongation at break of film coatings as determined by Lehmann and Süfke (1995)

Formulation	Film-forming components	Elongation at break (%)
1 and 2	Eudragit L 30 D-55	<5
3 and 4	Eudragit L 30 D-55 and Eudragit NE 30 D (1:1)	112
5	Eudragit L 30 D-55 and Eudragit NE 30 D (1:1)	198
6 and 7	New polymer type 1	56
8 and 9	New polymer type 2	50
Not applied	Eudragit NE 30 D	600

Fig. 1. The hard pellets, which are manufactured by the extrusion–spheronisation method, show a straight force increase until a maximum is reached where the pellet is abruptly crushed. The crushing strength varies from 6 to 8 N. No maximum crushing strength can be measured with most of the soft pellets manufactured in the coating pan. The applied force increases, but no precise maximum can be observed, as the pellet is slowly deformed. The maximum applied force varies from 2 to 6 N. The relative standard deviation of these measurements was at approximately 20%, which is very high and due to the fact that the pellets themselves differ in size. Coatings seem to increase the crushing strength, but this is not statistically significant. The coated pellets conform to the requirements of USP 23 for enteric-coated preparations, liberating less than 10% of bisacodyl within 2 h in 0.1 M HCl and more than 80% within 45 min at pH 6.8. For bisacodyl liberation from pellets, also see Table 2. Only pellets coated with 25% w/w of a 1:1 mixture of Eudragit L 30 D-55 and Eudragit NE 30 D do not release sufficient bisacodyl at pH 6.8. Although these formulations do not comply with the requirements of USP 23, they were not excluded from the tableting experiments, because we wanted to study the influence of different elongations at break of films. If Eudragit NE 30 D is added to a coating formulation, the elongation at break is improved, as is shown in Table 3.

3.2. Tablets

The influence of the mixing sequence on the disintegration behavior of tablets prepared from pellets coated with a 1:1 mixture of Eudragit L 30 D-55 and Eudragit NE 30 D in comparison with those coated with Eudragit L 30 D-55 is shown in Fig. 2. Preblending of pellets containing Eudragit NE 30 D with magnesium stearate reduces the tendency of the pellets to form a matrix after compression. Tablets compressed with forces up to 15 kN show disintegration times below 15 min in demineralized water and 0.1 M HCl, whereas tablets from mixtures blended in the way given in the methods section of this article disintegrate only in 0.1 M HCl. All other tablets disintegrate within 15 min. Radial crushing strength of tablets containing up to 70% w/w pellets is above 50 N if they are

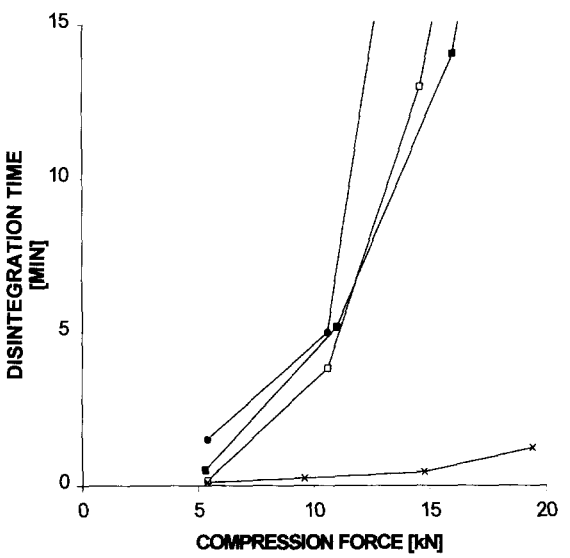

Fig. 2. Influence of different blending sequences on the disintegration time of tablets containing pellets with coatings from Eudragit L (formulation 1, symbol (x)) or 1:1 mixtures of Eudragit L and Eudragit NE (formulation 3) and Cellactose as excipient. Magnesium stearate was added in the first step of mixing, disintegration test carried out in demineralized water (o), or 0.1 M HCl (n), magnesium stearate was added in the last step of mixing, disintegration test carried out in 0.1 M HCl (l).

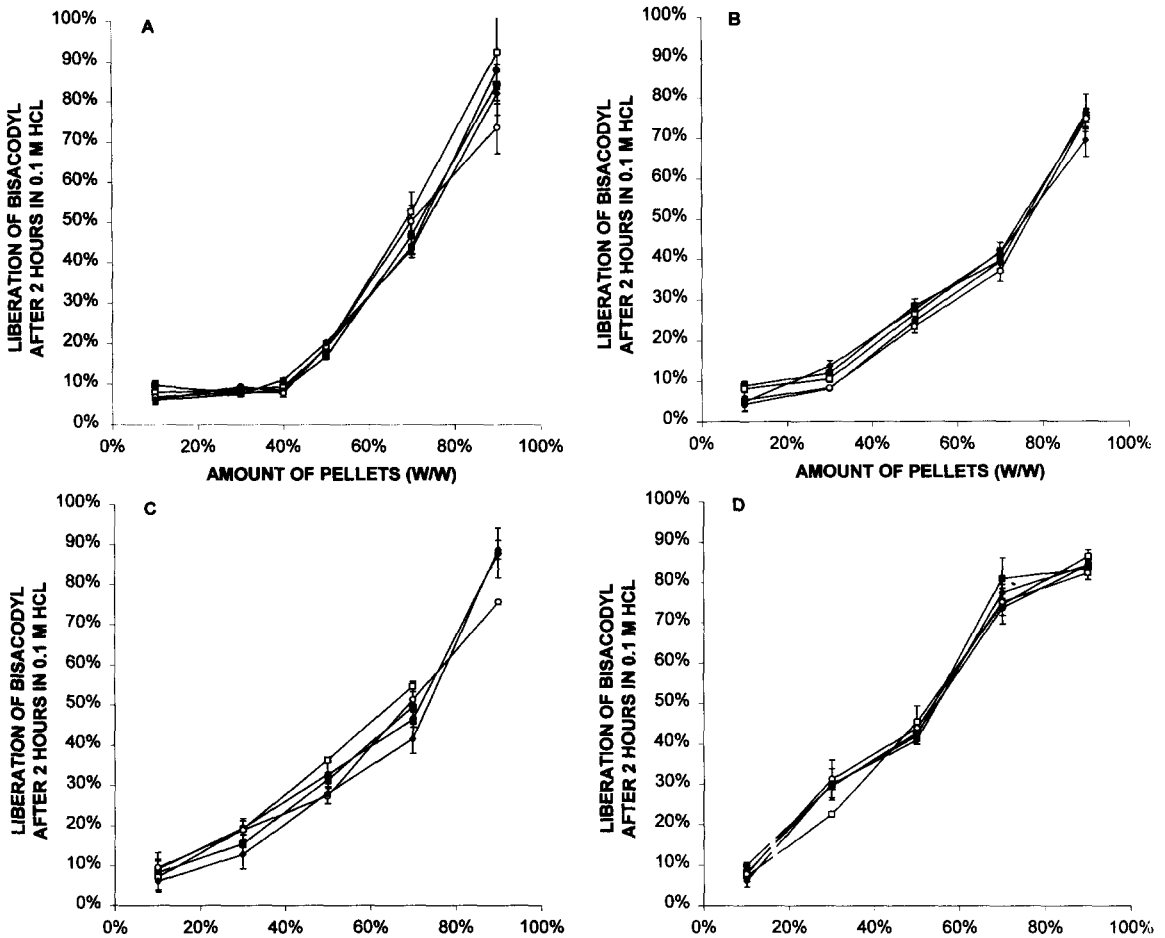

Fig. 3. Liberation of bisacodyl after 2 h in 0.1 M HCl from pellets coated with 12.5% Eudragit L 30 D-55 and compressed with polyethylene glycol (A), Cellactose (B), Avicel PH200 (C) and Bekapress D2 (D) at five different force levels: 5 kN (l), 10 kN (m), 15 kN (n), 20 kN (o), 25 kN (u).

compressed at 10 kN or more. Friability was below 0.5% in these cases. Tablets containing polyethylene glycol form solid compacts with a crushing strength of only 20 N at low friability (< 1%), unless up to 30% of pellets are incorporated in the tablet. Above this concentration these tablets become brittle. Uniformity of dosage form of the tablets is in agreement with the requirements of USP 23 (1994) and German Pharmacopeia (1996c) if excipients with a large particle size, like Avicel PH200 and Cellactose, are used. Additional information on mass and content uniformity is given elsewhere (Beckert et al., 1994).

3.3. Influence of compression force and amount of pellets

The liberation of bisacodyl from compressed pellets after 2 h in 0.1 M HCl is independent of the compression forces applied for all direct compression excipients, as shown in Fig. 3A–D. None of the excipients examined shows a significant impact on the release of bisacodyl attributable to compression force. Damage of the pellets is mainly caused by rupture of the films, resulting from pellet deformation. Deformation of pellets can take place only when the pellets are in contact

with a harder material. This is the case either on the surface of a tablet, where the pellets are in contact with the punches, or inside the tablet, when pellets are in close contact with each other. Up to approximately 30% w/w of pellets, deformations can be observed only at the surface of the tablets. Higher amounts of pellets cause additional pellet deformation within the tablets, because the pellets are in contact with each other. The pellet with the lower crushing strength will deform, and this may lead to ruptures in the film.

3.4. Influence of different excipients

To compare different excipients, a compression force level of 15 kN was chosen. The results are shown in Fig. 4. At a pellet level of 10% w/w there are only marginal differences in bisacodyl liberation between the four excipients. Between 30% w/w and 70% w/w pellets per tablet, the influence on the liberation of bisacodyl in 0.1 M HCl after 2 h is in the order: Cellactose < Avicel PH200 < Bekapress D2. Polyethylene glycol, which has been included in this study because it sinters during compaction, is ranked between Cellactose and Avicel PH200. At 90% w/w pellets the liberation of bisacodyl is high in all cases. This behavior is explained as follows: at lower amounts of pellets, single pellets are isolated and surrounded by the excipients. At intermediate amounts of pellets from 30 to 70% w/w, increasing amounts of pellets are in contact with the punches or with each other, causing increasing bisacodyl liberation due to ruptures in the films as a result of pellet deformation. At amounts of 50% w/w of pellets plastically deforming excipients like polyethylene glycol show the lowest liberation of bisacodyl, followed by Cellactose, which is a loose agglomerate containing 75% α-lactose monohydrate and 25% powdered cellulose. If Avicel PH200, a granulation of microcrystalline cellulose, is used, increased dissolution of bisacodyl is found compared with Cellactose. Bekapress D2, a brittle substance, leads to the highest degree of film damage, which is probably due to its higher hardness and density.

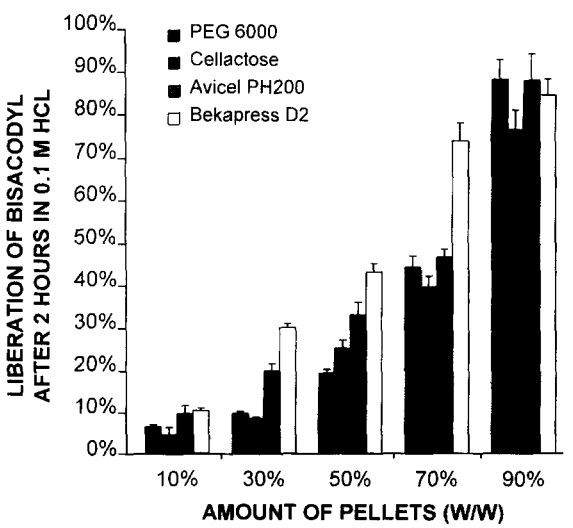

Fig. 4. Influence of different excipients on the liberation of bisacodyl after 2 h in 0.1 M HCl from pellets coated with 12.5% Eudragit L 30 D-55 (formulation 1) and compressed at 15 kN.

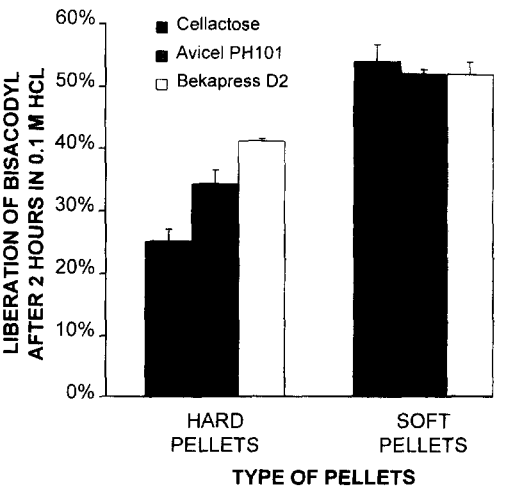

Fig. 5. Influence of pellet crushing strength on the liberation of bisacodyl after 2 h in 0.1 M HCl from tablets containing 50% w/w pellets with a coating according to formulation 1.

3.5. Influence of pellet crushing strength

Fig. 5 shows the influence of soft and hard pellets on the release of bisacodyl after tableting. Three different excipients were tested in order to exclude the influence of the excipient. The libera-

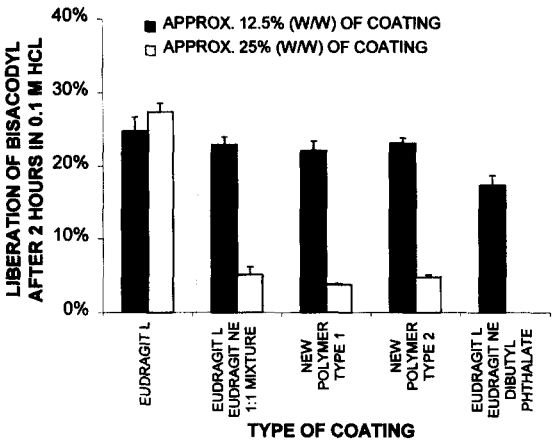

Fig. 6. Influence of film elasticity and thickness on the liberation of bisacodyl after 2 h in 0.1 M HCl from tablets compressed at 15 kN and containing 50% w/w pellets.

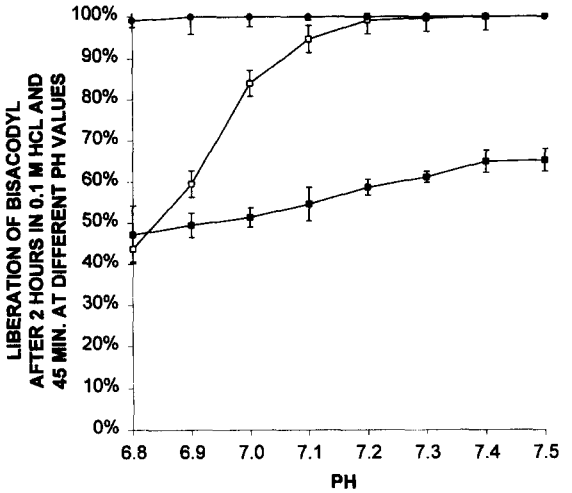

Fig. 7. Influence of pH on the liberation of bisacodyl after 2 h in 0.1 M HCl and 45 min at different pH values from pellets with 25% w/w of different coatings: Eudragit L and Eudragit NE 1:1 mixture (n), new polymer type 1 (o), new polymer type 2 (l).

tion of bisacodyl is enhanced when soft pellets with lower crushing strength are used. Hard pellets are better able to withstand compression forces, so that they are not deformed as much and ruptures in their film coatings which are low.

3.6. Influence of film coatings

Fig. 6 shows the liberation of bisacodyl from tablets containing Cellactose and 50% w/w pellets, coated with films with 12.5% w/w and 25% w/w dry coating substance. The elasticity of the films, measured as elongation at break according to Lehmann and Süfke (1995), is given in Table 3. The reduction in bisacodyl liberation with elastic films is mainly due to the enhanced ability of the coatings to follow the deformation of the pellets during compression. Films made from Eudragit L 30 D-55 are so brittle that even the double amount of coating does not reduce the damage within the coatings. But since rupturing is a time-dependent process at least short-time elasticity improves with the thickness of more elastic coatings. The amount of bisacodyl liberated is reduced with thicker films if coatings containing a mixture of Eudragit L and Eudragit NE are applied. The liberation of bisacodyl in 0.1 M HCl from this film is approximately 4% w/w of the total bisacodyl content. As these coatings do not dissolve and release sufficient bisacodyl between pH 6.8 and 7.5, two new polymers (Table 4) showing high elasticity combined with sufficient dissolution in the pH range 6.8–7.0 (Fig. 7) have been developed by Lehmann and Süfke (1995). Pellets coated with 25% w/w of one of the new polymers liberate only 4–5% w/w bisacodyl in acidic media after tableting. The liberation of bisacodyl in phosphate buffer within 45 min at pH 6.8 is 100% for polymer 1 and 40% for polymer 2 and rises to 100% at pH 7.2. Thus, tablets comprising enteric-coated bisacodyl pellets are available which comply with all recommendations of USP 23.

Table 4
New polymers for enteric coatings

	Type 1	Type 2
Monomers (% of polymer)		
Methacrylate	90	65
Methacrylic acid	10	10
Methyl methacrylate	25	
Glass transition temperature	30°C	48°C
Minimum film-forming temperature	20°C	14°C
Solubility in artificial gastric juice at	pH 6.4	pH 7.2

4. Discussion

The bisacodyl model can be used to optimize formulations for rapidly disintegrating tablets compressed from coated pellets. It is a suitable model for characterizing different influences on film damage during tableting. Liberation of bisacodyl in acid media is mainly caused by deformation of the pellets during tableting and the resultant rupture of films. The relative amount of deformed pellets depends on the amount by volume of pellets in the tablet. Variations in compression force do not influence the amount of pellets damaged. Improvements in gastro-resistance and less film damage can be achieved by using excipients that deform plastically during tableting, pellets with higher crushing strength, coatings made from polymers with higher elongation at break and films of increased thickness. It is necessary to use a system of pellets and excipients which prevents deformation of the pellets. Compaction forces have to be absorbed mainly by the excipients. The remaining deformation of pellets needs to be neutralized by elastic coatings which can follow the deformation without rupturing. The most important parameters are the type and the applied thickness of the film forming polymer. Disintegrating tablets can be obtained from enteric-coated pellets which do not liberate more than 10% bisacodyl after 2 h in 0.1 M HCl, thus complying with USP 23.

Acknowledgements

We gratefully acknowledge technical and material support from Röhm GmbH, Darmstadt, Germany.

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