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Influence of different-shaped pigments on bisacodyl release from Eudragit L 30 D

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Abstract

Self-prepared bisacodyl pellets were coated in a miniature fluid-bed pan coater with Eudragit L 30 D plasticized with dibutyl phthalate (DBP) or triethyl citrate (TEC) and containing different types of pigments, e.g., titanium dioxide, red iron oxide, talc, mica and platelet-shaped pearl luster pigments with titanium dioxide or iron oxide surfaces, respectively. The pigment volume concentration within all coatings was the same. Dissolution tests in artificial gastric fluid showed that platelet-shaped pigments or fillers, independent of their chemical constitution and polarity of their surfaces, reduce drug release from Eudragit L 30 D. Coarse platelets have a greater effect than finer ones. Coatings with spherical titanium dioxide and red iron oxide needles have no barrier effect or even lead to an increase in permeability depending on their concentration within the coating. Drug release from films plasticized with DBP was slower than from films with TEC. DBP therefore is more suitable for Eudragit L 30 D than TEC.

Keywords: Eudragit L 30 D; Bisacodyl; Pigment; Plasticizer; Film coating; Drug release; Enteric coating

1. Introduction

Many solid dosage forms for oral application are colored to avoid undermixing during manufacturing, to simplify the identification of a preparation, and thus to ensure good compliance. In most of the cases, color is applied within a functional or non-functional film coating containing soluble dyes or insoluble pigments (e.g., iron oxides). Additionally, insoluble solids may be incorporated in film coatings serving as opacifiers (e.g., titanium dioxide) or to reduce tackiness (e.g., talc). By the incorporation of pigments and insoluble fillers, permeability and drug release of a film coating may be affected to varying degrees depending on the volume concentration of the particles, their size and size distribution as well as their chemical constitution and surface charge, and the extent of polymer-particle interaction (Okhamafe and York, 1984).

Studies on the permeability of pigmented pharmaceutical coating systems are sparse. Delporte and Jaminet (1978a,b) found an increase in water vapour permeability of free cellulose acetate phthalate and methyl-/ethylcellulose films loaded with titanium dioxide and a decrease when the films were loaded with talc. List and Kassis

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(1982) observed a similar permeability pattern with both solids in Eudragit L 30 D and explained the results by the ability of the hydrophilic surfaces of titanium dioxide to bind water molecules chemically and to lead to wick-like structures within the coating. Porter and Ridgway (1982) reported that water vapour permeability and the behaviour towards artificial gastric fluid of cellulose acetate phthalate films containing red iron oxide was in accordance with the principle of Chatfield (1962). However, the latter could not be confirmed with polyvinyl acetate phthalate films containing red iron oxide. Chang and Hsiao (1989) observed an increase in theophylline release when Eudragit RS 30 D was filled with talc as well as with silica. Wan and Lai (1993) added both solids to methylcellulose coatings and explained the increase in drug release according to Chatfield (1962). The incorporation of platelet-shaped fillers into organic coatings is well known in the steel industry to protect steel against corrosion (Salensky, 1986; Bieganska et al., 1988). The particles show a tendency to align parallel to the substrate surface and thus build a rooftile-like barrier, rendering the penetration of water as well as of aggressive media difficult. With talc, similar effects have been reported (Heine et al., 1992). Therefore, filling of pharmaceutical film coatings with talc may lead to a decrease in drug release, depending on its lipophilic surface as well as on the barrier effect of overlapping platelets. Spherical titanium dioxide particles may increase permeability because of their hydrophilic surfaces as well as the missing barrier effect. It would be of interest to prove whether the chemical constitution or the platelet shape is the more important parameter when drug release changes by incorporating solids into film coatings.

For pharmaceutical purposes, there are no platelet-shaped pigments with titanium dioxide or iron oxide surfaces available. In the present investigation, a further type of pigments is used which finds application in cosmetics and offers platelet-shaped titanium dioxide as well as red iron oxide surfaces: pearl luster pigments. They consist of mica platelets coated with these oxides so that the surfaces show the oxides' chemical properties. As a contrast to lipophilic talc, pure mica with hydrophilic surface is used as well.

Drug release from enteric-coated formulations is usually assessed according to the USP XXII recommendations, e.g., after 2 h testing in 0.1 N hydrochloric acid not more than 10% of the drug must be released. The mean gastric residence time of multiple dosage forms, however, is more than 2 h depending on the density of the particles and the presence or absence of food (Devereux et al., 1990; Sugito et al., 1990; Coupe et al., 1993). The dissolution testing time of USP XXII in gastric fluid, therefore, may be insufficient. For this reason all tests were run for 6 h according to comparable studies (Agyilirah and Banker, 1991; Niemann, 1991). Additionally, the prolonged testing time facilitates the differentiation between the release rates of the formulations tested and the results may be compared to similar evaluations made with coatings for controlled release which will be published later.

To evaluate the influence of pigments and plasticizers on drug release of film-coated pellets, a sensitive testing model was selected: bisacodyl, a commonly used drug for enteric coated preparations with good solubility in simulated gastric fluid, easy to analyze spectrophotometrically, was applied onto placebo pellets which afterwards were coated with Eudragit L 30 D. The drug is localized between the pellet core and the coating and is, therefore, dissolved immediately when the simulated gastric fluid has permeated the film. There is no delay in drug permeation through the coating because additives within the pellets may not dissolve at the same time or even before the drug is in solution. Therefore, this model is more sensitive to dissolution testing than a model containing the drug incorporated into the pellets, which may meet the requirements of the USP XXII more easily.

The objective of this study was to gain further insight into the effect of pigmentation with platelet and non-platelet-shaped particles possessing chemically different surfaces on drug release in simulated gastric fluid by coating drug-loaded pellets with an enteric coating. Additionally, the influence of a hydrophilic and a lipophilic plasticizer was investigated.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: methylene chloride (analytical grade, Riedel-de Haen, Seelze, Germany), bisacodyl (Merckle, Blaubeuren, Germany), polyvinyl pyrrolidone, PVP (Kollidon 25, BASF, Ludwigshafen, Germany), placebo pellets (Neutralpellets 833, Werner, Tornesch, Germany), Eudragit L 30 D (Röhm, Weiterstadt, Germany), triethyl citrate, TEC (Morflex, Greensboro, NC, USA), dibutyl phthalate, DBP (Fluka, Buchs, Switzerland), sodium carboxymethylcellulose, NaCMC (Tylose C 30, Hoechst AG, Frankfurt/Main, Germany), antifoaming emulsion (Silicon-Entschäumer, Merck, Darmstadt, Germany), titanium dioxide (Kronos A, Kronos, Leverkusen, Germany), talc (Talkum IT extra, Norwegian Talk Deutschland GmbH, Bad Soden, Germany), red iron oxide (Sicopharm rot 30, BASF, Ludwigshafen, Germany), pearl luster pigments Iriodin 100, Iriodin 110, Iriodin 502, EM 140662 and Mica M (Merck, Darmstadt, Germany), and hydrochloric acid (37%, analytical grade, Merck, Darmstadt, Germany).

2.2. Methods

2.2.1. Characterization of the pigments

Table 1 summarizes the results of various evaluations characterizing the pigments. The density was determined in a gas comparison pycnometer (Model 930 Air, Beckman, Fullerton, USA, $n = 3$) at 20.5°C after drying the substances for 24 h at 105°C. The surface area was determined in a FlowSorb II 2300 (Micromeritics, USA) according to the BET method (gas, nitrogen/helium = 30:70 (% v/v); probe volume according to an absolute measured surface of 15 m^2; $n = 2$) after drying the substances for 3 h at 200°C. The pH was measured in suspension containing 10% (w/w) pigment (dispersing agent, distilled water; probe volume, 2.00 g; $n = 3$) using a pH-Meter 761 (Calimatic, Knick, Berlin, Germany). After centrifugation (4000 rpm, 15 min), the conductivity of the supernatant was determined (Konduktometer 702 with 4-pole measuring unit and temperature detector, Knick, Berlin, Germany; temperature compensation 2.1%/K at 20.0°C). Sicopharm rot 30 showed an excessively high conductivity because of adhering electrolytes. Therefore, Eudragit L 30 D coagulated during the preparation of the mixture containing the higher pigment concentration. To avoid this, Sicopharm rot 30

Table 1
Characterization of the pigments

Pigment	Particle size	Morphology	Chemical composition	Density (g/cm^3)	Surface area (m^2/cm^3)	pH of suspension	Conductivity of supernatant (μS)
Titanium dioxide Kronos A	$\ll 15\ \mu m$	spherical	titanium dioxide	4.02	36.98	8.29	380
Iriodin 110	$< 15\ \mu m$	platelets	titanium dioxide-coated mica	2.85	34.20	9.57	75.4
Iriodin 100	$10–60\ \mu m$	platelets	titanium dioxide-coated mica	3.01	22.73	9.97	87.6
Mica M	$< 15\ \mu m$	platelets	mica	2.49	16.48	8.29	32.2
Talkum IT extra	$< 15\ \mu m$	platelets	talc	2.76	22.35	9.66	77.5
Sicopharm rot 30	$\ll 15\ \mu m$	needles	hematite (red iron oxide)	5.08	49.28	5.31	34.6 [a]
EM 140662	$< 15\ \mu m$	platelets	hematite-coated mica	3.90	30.58	4.30	343
Iriodin 502	$10–60\ \mu m$	platelets	hematite-coated mica	3.49	17.80	5.06	204

Characterization of the pigments: coarse classification of their particle size, description of the particles' morphology and chemical composition and results of physicochemical examinations, e.g., density determined in a gas comparison pycnometer, surface area determined by BET method, pH of suspension measured with a pH-meter and conductivity of the suspensions' supernatant, determined using a conductometer

[a] Soxhlet-extracted.

was extracted in a Soxhlet apparatus with distilled water (extraction time, 3 h) and dried before use (100°C, 12 h). Fig. 1 shows SEM photographs of the four pigments, red iron oxide, titanium dioxide, a fine and a coarse pearl luster pigment, giving an impression of their different particle size and morphology.

2.2.2. Preparation of the bisacodyl-loaded pellets

Bisacodyl (6.3 g) and PVP (5.0 g) were dissolved in methylene chloride (88.7 g) and sprayed onto the placebo pellets in a miniature fluid-bed pan coater (MiniWiD, Niemann, 1991; drug solution, 50.0 ml; batch size, 100 g; core temperature, 27°C; spraying rate, 0.78 ml/min; post-drying time, 2 min). The drug content of the pellets was 3.94% (w/w) bisacodyl (determined spectophotometrically, three batches, $n = 30$, relative standard deviation 1.55%).

2.2.3. Film coating of the bisacodyl-loaded pellets

According to Table 2, coating suspensions with different content and types of pigment were prepared so that the pigment volume concentration within the four series was the same. NaCMC (6.0 g) was dissolved in water (144.0 g). The plasticizer was emulsified into the latex and allowed to stand with stirring overnight. In a separate bottle the

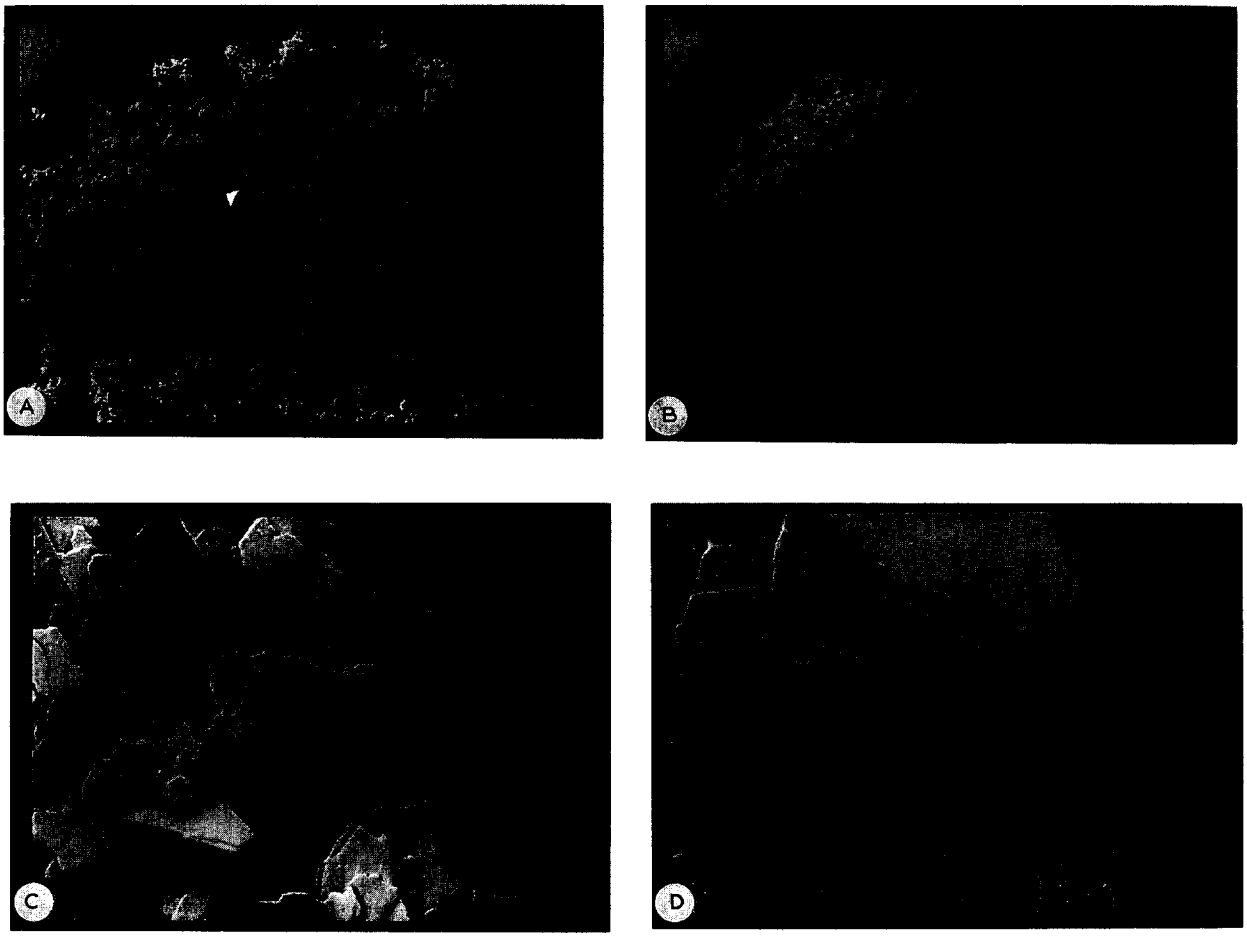

Fig. 1. SEM photographs of spherical titanium dioxide particles (top left), a red iron oxide particle (top right), fine (bottom left) and coarse (bottom right) pearl luster pigments. Length of bar: 5 μm.

Table 2
Formulations with Eudragit L 30 D

Series number, plasticizer and coating level	Type of pigment	Amount of pigment (g)	Amount of additives (g)	Total amount (g)	Content of dry polymer (% w/w)	Content of solids (% w/w)	Content of pigment (% w/w related on dry polymer)
1, 2	without	–	98.05	98.05	15.30	19.02	–
	spherical TiO_2	4.02	98.05	102.07	14.70	22.21	26.80
TEC or DBP	fine TiO_2 platelets	2.85	98.05	100.90	14.87	21.31	19.00
	coarse TiO_2 platelets	3.01	98.05	101.06	14.84	21.43	20.07
5.05 g dry	mica	2.49	98.05	100.54	14.92	21.03	16.60
polymer/50 g	talc	2.76	98.05	100.81	14.88	21.24	18.40
pellets = 10%	red iron oxide (needles)	5.08	98.05	103.13	14.54	23.01	33.87
	fine iron oxide platelets	3.90	98.05	101.95	14.71	22.12	26.00
	coarse iron oxide platelets	3.49	98.05	101.54	14.77	21.80	22.27
3	spherical TiO_2	8.04	98.05	106.09	14.14	25.16	53.60
TEC	fine TiO_2 platelets	5.70	98.05	103.75	14.46	23.47	38.00
10%	coarse TiO_2 platelets	6.02	98.05	104.07	14.41	23.71	40.13
4	spherical TiO_2	4.02	98.05	102.07	14.70	22.21	26.80
TEC	fine TiO_2 platelets	2.85	98.05	100.90	14.87	21.31	19.00
20%	coarse TiO_2 platelets	3.01	98.05	101.06	14.84	21.43	20.07

All formulations contain 15.0 g NaCMC solution (4% w/w), 3.0 g plasticizer, 0.05 g antifoaming emulsion, 30.0 g distilled water (pH 3.0) and 50.0 g Eudragit L 30 D, summarized above as the amount of additives.

pigment suspensions were prepared as follows: water, NaCMC solution and antifoaming emulsion were mixed. Iriodin pigments, EM 140662 or Mica M were added and stirred for 15 min (magnetic stirrer). After adding the latex-plasticizer emulsion, the mixture was stirred again for 15 min prior to coating. Iron oxide, talc and titanium dioxide were ultrasonically dispersed in water containing the antifoaming emulsion (15 min, Bransonic 12, Knauer, Berlin, Germany). After adding the NaCMC solution by stirring (15 min), the pigment suspension and the latex/plasticizer emulsion were mixed for 15 min prior to use. All coating mixtures were sprayed onto the bisacodyl pellets in the MiniWiD-Coater (batch size, 50.0 g; core temperature, 35°C; spray rate, 0.15 ml/min for the first 4 ml, then 0.5 ml/min; post-drying time, 5 min; post-drying temperature, 35°C) so that the level of dry polymer applied within the four series was the same. The loss of coating was found to lie between 2 and 5%. The coated pellets were tempered at 50°C for 24 h and stored for 7 days at room temperature prior to dissolution testing.

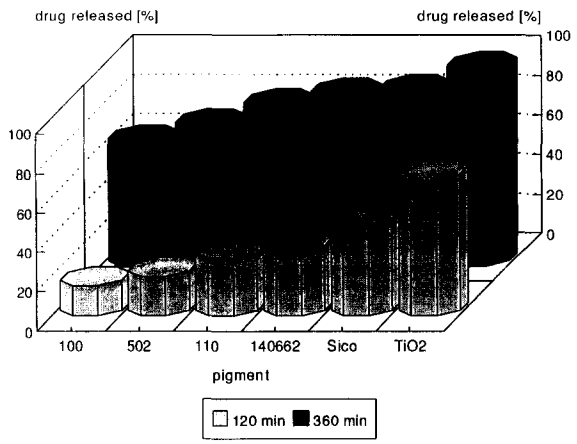

Fig. 2. Influence of particle form and size on drug release from bisacodyl pellets coated with Eudragit L 30 D after 3 and 6 h dissolution testing. The coatings contain different-shaped and -sized iron oxide (Iriodin, 502, 140662 and Sicopharm rot 30) and titanium dioxide (Iriodin 100, 110 and titanium dioxide Kronos A) pigments all in a high pigment concentration, which are depicted according to decreasing particle size from left to right.

2.24. Drug release

The USP XXII rotating paddle method (2.5 g pellets, 37°C, 100 rpm, 800 ml 0.1 N HCl prepared by dilution and used as simulated gastric juice) was used to study bisacodyl release from

the coated pellets. The samples (10 ml, replaced by dissolution medium) were withdrawn after 15, 30, 60, 90, 120, 150, 180, 240, 300 and 360 min and assayed spectrophotometrically at $\lambda = 263$ nm. Each data point was obtained as a mean of three runs ($n = 3$).

2.2.5. SEM photographs

All samples were fixed onto aluminum pins by double-sided adhesive tape and sputtered with gold (sputter coater, type E 5100, BioRad, München, Germany; vacuum, 0.02–0.03 mbar; strength of the electric current, 20 mA; voltage, 2.1 kV; sputtering time, 150–165 s). The pigment powders were dusted onto the pins, and the coated pellets were cross-sectioned with a razor blade. SEM photographs were taken with a scanning electron microscope (DSM 940 A, Zeiss, Oberkochen, Germany; voltage, 5 kV; working distance, 6–8 mm) fitted with a Contax 167 MT (Yashica Kyocera, Hamburg, Germany; film, Ilford pan F).

3. Results and discussion

The incorporation of pigments with their chemically active surfaces into latex dispersions sometimes leads to incompatibilities such as coagulation of the latex or flocculation of the pigments (Bauer and Osterwald, 1979; List and Kassis, 1982; Lehmann, 1989, p. 178; Bauer et al., 1988). The latter occurred when red oxide and iron oxide-pearl luster pigment in low concentration were used. To stabilize the pigmented latex dispersions, it is useful to add either surfactants or supporting polymers to the pigment suspension before mixing it with the latex. Because of the low viscosity of the mixtures ready for use, the coating mixtures were stabilized by adding a sodium carboxymethylcellulose solution (4% w/w). The polymer chains of this anionic cellulose ether led to sterical stabilization of the pigments and prevented settling and flocculation by increasing the viscosity of the mixture. NaCMC is readily soluble in water. The added amount of 4% (w/w, related to dry L 30 D), however, had no influence on the permeability of the coatings. If the applied coating volume was 20% (= 4.8 mg dry L 30 D/cm^2 surface of the pellets) according to the supplier's recommendations (3–6 mg/cm^2; Eudragit Handbook, 1991), drug release was below 10% in simulated gastric fluid for 2 h and the films met the USP XXII requirements. All films dissolved within 15–25 min, after neutralizing the dissolution medium by adding an appropriate amount of sodium hydroxide.

The reproducibility of the coating process was demonstrated using an Eudragit L 30 D film containing EM 140662 and plasticized with TEC. Two batches were separately coated within 4 weeks and tested for dissolution ($n = 3$). The

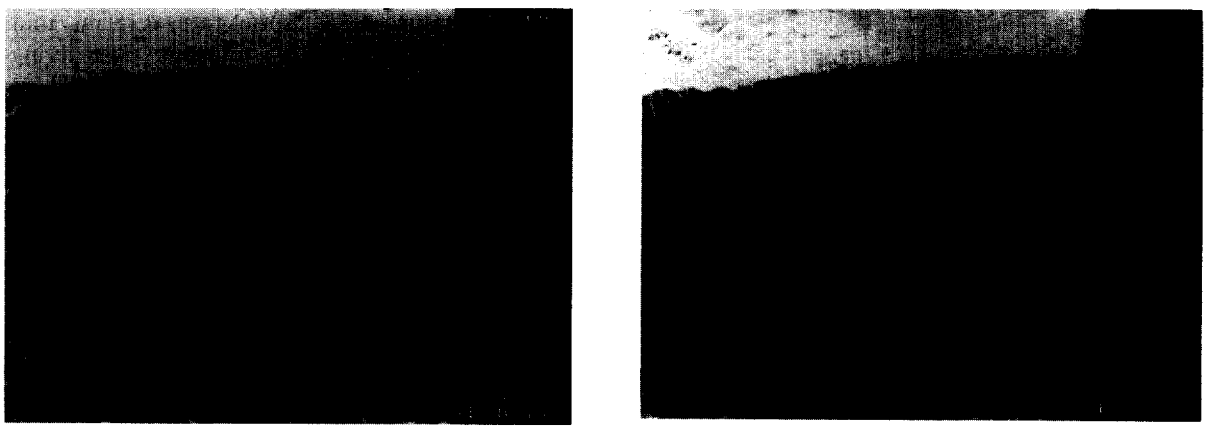

Fig. 3. SEM photograph of the cross-sectioned coating layer of a bisacodyl pellet coated with Eudragit L 30 D, plasticized with TEC and pigmented with spherical titanium dioxide (right) and red iron oxide needles (left). Length of bar: 2 μm.

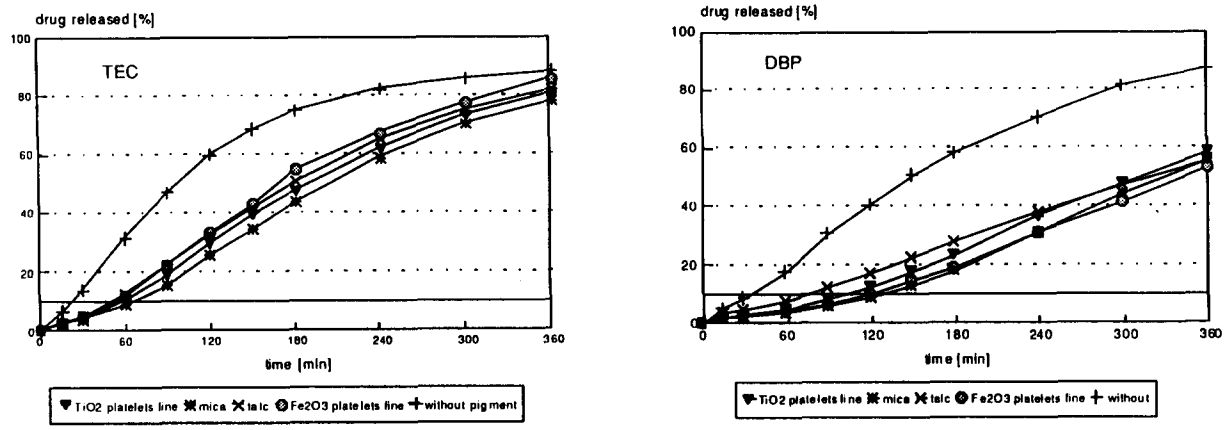

Fig. 4. Influence of the pigments' chemical surfaces on drug release from bisacodyl pellets coated with Eudragit L 30 D, containing four pigments of different surface properties but comparable shape and size at high pigment concentration. (Left) Plasticizer TEC; (right) plasticizer DBP. For comparison, release rates of the unpigmented films are shown as well.

maximum difference in the release rate between the two batches was 5%.

The influence of the pigments' form and size on drug release is given in Fig. 2, showing the release rates with different titanium dioxide and iron oxide pigments after 2 and 6 h testing. The coarse platelets of Iriodin 100 and 502 make the coatings least permeable, followed by the finer types Iriodin 110 and EM 140662. These results confirm the barrier effect of the platelets (Nielsen, 1967). Mostly permeable are the films with iron oxide needles and spherical titanium dioxide, which has also been reported by others (Delporte and Jaminet, 1978a,b; Lippold et al., 1981). The high release rates have been attributed either to a loss of pigment particles during dissolution test-

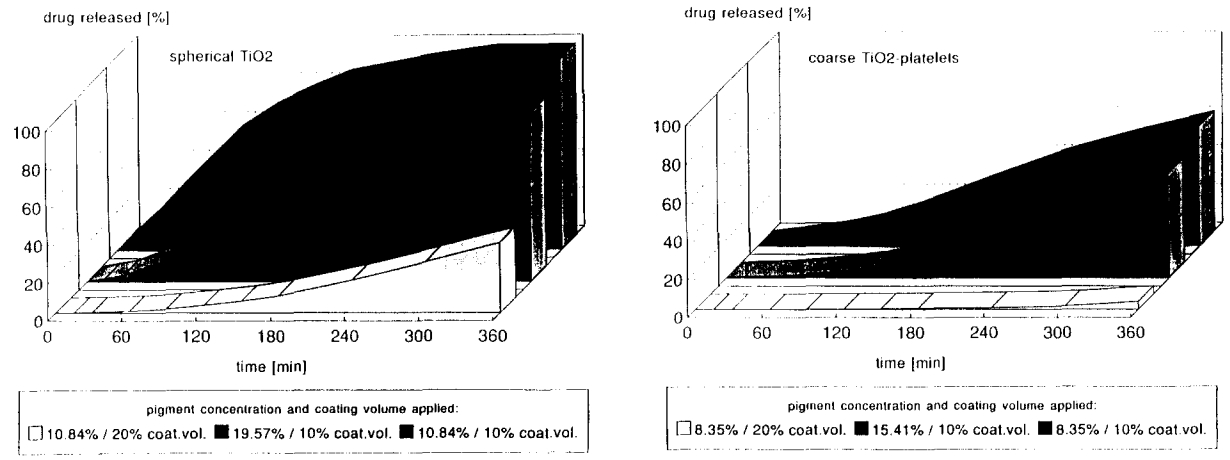

Fig. 5. Influence of pigment concentration on drug release from Eudragit L 30 D plasticized with TEC. (Left) Spherical titanium dioxide; (right) coarse titanium dioxide platelets. Both lighter shaded profiles within each plot symbolize a volume-constant pigment content of 10.84 (left) and 8.35% (w/w; right), respectively. They differ according to the applied coating volume (10 or 20%, respectively) The dark shaded profiles represent a volume-constant pigment content of 19.57% w/w (left) and 15.41% w/w (right), respectively. The coating volume applied is 10%.

ing and a formation of pores (Lippold et al., 1981) or to the hydrophilic surface of the solid (List and Kassis, 1982). During the present investigations the dissolution medium remained clear and there was no need to assume a falling out of particles from the swollen coating. Titanium dioxide platelets show a sustained drug release compared to the spherical pigment. Therefore, the polarity of the surfaces seems to be less important compared to the size and shape of the pigments. A possible explanation is given by the SEM photographs of Fig. 3 of the coatings' cross-sections. It can be seen that titanium dioxide as well as red iron oxide is homogeneously distributed within the coating but still forms aggregates below a size of 1 μm which were not dispersed by ultrasound treatment of the pigment suspensions. These aggregates act as wicks because of their highly hydrophilic surfaces and thus lead to faster drug release.

Information about the influence of surface chemistry is given in Fig. 4, which shows release rates of four coatings containing pigments of comparable shape and size but chemically different surfaces. The platelet-shaped particles in all cases reduce drug release of the coatings independent of the plasticizer used, and no relevant difference between the pigment-containing coatings can be seen. Therefore, the chemical constitution of the platelets in the given systems does not seem to have an important influence on drug release. This is confirmed by the fact that lipophilic as well as hydrophilic platelets are used to develop corrosion-inhibiting coatings (Salensky, 1986).

The effect of pigment concentration is demonstrated in Fig. 5. Spherical and platelet-shaped titanium dioxide was incorporated in two concentrations (10.84 and 8.35%, and 19.57 and 15.41% w/w, respectively, total solids), and two different coating volumes containing the lower amount of pigment were applied for comparison. Drug release decreases on doubling the pigment concentration within the film as well as on doubling the applied coating volume, the latter reducing drug release by about 60%, while the higher pigment concentration leads to a decrease of about 7–18% after 6 h. These findings clearly demonstrate that according to Chatfield (1962) the critical pigment volume concentration at a pigment content of

Table 3
Drug release from bisacodyl pellets coated with Eudragit L 30 D and plasticized with TEC or DBP, respectively, in relation to pigment type and concentration

Formulation	Series 1: TEC/low pigment content			Series 2: DBP/low pigment content		
	Drug released after 2 h (%)	Drug released after 6 h (%)	Standard deviation	Drug released after 2 h (%)	Drug released after 6 h (%)	Standard deviation
Without pigment	60.26	88.76	0.38	40.50	87.79	0.12
Spherical TiO_2	69.49	99.33	0.09	52.40	86.20	0.99
Fine TiO_2 platelets	29.47	80.59	0.56	12.32	59.11	0.10
Coarse TiO_2 platelets	15.09	62.26	0.18	14.78	62.13	0.36
Mica	25.27	78.20	0.90	8.48	56.20	0.18
Talc	32.14	82.08	0.76	16.84	55.93	0.22
Red iron oxide (needles)	32.78	86.01	0.36	27.23	77.29	0.06
Fine iron oxide platelets	46.46	87.68	0.34	9.57	53.65	0.11
Coarse iron oxide platelets	19.74	70.60	0.13	5.71	59.71	0.13
	Series 3: TEC/high pigment content			Series 4: DBP/high pigment content		
	Drug released after 2 h (%)	Drug released after 6 h (%)	Standard deviation	Drug released after 2 h (%)	Drug released after 6 h (%)	Standard deviation
Spherical TiO_2	36.86	87.96	0.20	4.18	36.97	0.10
Fine TiO_2 platelets	8.26	62.27	0.15	1.74	15.69	0.29
Coarse TiO_2 platelets	5.66	54.86	0.69	0.27	4.30	0.65

Standard deviation of the runs was calculated according to Renner (1981), p. 71, as previously described by Niemann (1991).

19.57% (titanium dioxide) and 15.41% (Iriodin 100) in the dry coating has not been exceeded. Doubling the pigment concentration has more effect on drug release of coatings with spherical titanium dioxide than of those filled with platelets, which were tight even at the low pigment concentration. Further decrease in permeability may be limited by the solubility of the added NaCMC.

The influence of different plasticizers on drug release from Eudragit L 30 D has already been studied. According to the results of List and Kassis (1982) and Schmidt and Niemann (1992), DBP was found to be a more suitable plasticizer compared to TEC (Table 3). After 2 h testing, release rates of films plasticized with DBP were up to 35% lower than with TEC.

In conclusion, the results can be summarized as follows:

(i) Platelet-shaped pigments or fillers reduce drug release from bisacodyl pellets coated with Eudragit L 30 D, independent of their chemical constitution and the polarity of their surfaces. Coarse platelets demonstrate a greater effect than finer ones.

(ii) Coatings with spherical titanium dioxide and red iron oxide needles have no barrier effect or lead to an increase in permeability depending on their concentration within the coating.

(iii) Besides their pigmentation, films plasticized with DBP were less permeable than films with TEC. DBP therefore is more suitable to Eudragit L 30 D than TEC.

Acknowledgements

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