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RESEARCH PAPER

Comparative Studies with Kollicoat MAE 30 D and Kollicoat MAE 30 DP in Aqueous Spray Dispersions and Enteric Coatings on Highly Swellable Caffeine Cores

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ABSTRACT

A film formulation containing Kollicoat MAE 30 D, Kollidon 30, Sicovit Rot 30, titanium dioxide, talc, and a plasticizer for the aqueous manufacture of enteric coatings was studied for the coagulations occurring with certain plasticizers and for differences in resistance on highly swellable caffeine cores. Also included in these investigations were the latices Kollicoat MAE 30 DP and Eudragit L 30 D-55. The coagulations occurring with all three film latices can be attributed to the presence of Kollidon 30 together with certain excipients. Preparations with Kollidon 30, but without color pigments, showed no tendency to coagulate. The advantage of propylene glycol (PG) compared to other plasticizers such as triethyl citrate (TEC) is that no coagulations occurred, even in the presence of Kollidon 30 and color pigments. Among the Kollidon 30–free film formulations examined, a plasticizer content of 10–15% PG or TEC gave the best results. Optimal pigment distribution in the coat originally produced by Kollidon 30 can optionally be achieved by prolonged stirring of the pigment suspension. The resistance can be further improved by inclusion of a subcoating with Kollidon VA 64. Kollicoat MAE 30 D and MAE 30 DP and Eudragit L 30 D-55 showed identical behavior in this study.

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Key Words: *Enteric coating; Eudragit L 30 D; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; Kollidon 30; Pigment; Plasticizer; Subcoating; Tablet.*

INTRODUCTION

A previous study (1) evaluated a spray formulation containing Kollicoat MAE 30 D and Kollidon 30, pigments, talc, and a plasticizer for the manufacture of enteric coatings. Variations of this plasticizer resulted in coagulation in some cases during manufacture and processing.

The film coating experiments in the study cited above were performed on highly swellable caffeine cores. The various film-coated tablets produced with these cores were found to have different degrees of resistance to simulated gastric fluid.

The present study was performed to reveal the causes of the film permeability and the tendency to coagulation and to propose ways of achieving more impermeable and stable film formulations.

Kollicoat MAE 30 DP and Eudragit L 30 D-55 were also included in the study to assess the substitutability of Kollicoat MAE 30 D.

EXPERIMENTAL

Materials

The following materials were used in the study: anhydrous caffeine 0.2/0.5 (Knoll AG, Ludwigshafen, Germany); Ludipress (BASF AG, Ludwigshafen, Germany); Kollidon CL (BASF AG); Avicel PH-101 (FMC Corp., Philadelphia, PA); magnesium stearate (Bärlocher GmbH, Munich, Germany); Kollicoat MAE 30 D (BASF AG); Kollicoat MAE 30 DP (BASF AG); Eudragit L 30 D-55 (Röhm GmbH, Darmstadt, Germany), Lutrol 400 (PEG400) (BASF AG); Lutrol 1500 (PEG1500) (BASF AG); Lutrol 6000 (PEG6000) (BASF AG); propylene glycol (PG) (BASF AG); Lutrol F 68 (BASF AG); triethyl citrate (TEC) (Merck-Schuchardt, Hohenbrunn, Germany); Cremophor RH 40 (BASF AG); Kollidon 30 (BASF AG); Sicovit Rot 30 (BASF AG); titanium dioxide RN 56 (Kronos Titan GmbH, Leverkusen, Germany); and powdered talc (Riedel de Haen AG, Seelze, Germany).

Apparatus

The following equipment was used: Diosna mixer V 50 (Dierks and Söhne Maschinenfabrik, Osnabrück, Germany); tablet press RL 15 (Kilian Co. GmbH, Cologne, Germany); magnetic stirrer MR 2002 (Heidolph Elektro GmbH and Co. KG, Kehlheim, Germany); blade-type stirrer RZR 2051 (Heidolph Elektro GmbH and Co. KG); corundum disk mill 0112 MS (Fryma, Rheinfelden, Germany); film drawing unit with temperature controller, model 509/3 (Erichsen GmbH and Co. KG, Hemer, Germany); Accela-Cota 24″ (Manesty Machines Ltd., Liverpool, UK); pressure vessel with electrical stirring mechanism, MD G 24 (Richard C. Walter GmbH and Co. KG, Wuppertal-Vohwinkel, Germany); spray gun (Accela-Cota), model Pilot WA XV (Richard C. Walter GmbH and Co. KG); spray gun (manual), model Pilot XIII (Richard C. Walter GmbH & Co. KG, Wuppertal-Vohwinkel, Germany); climatically controlled cabinet HC 2020 (Heraeus-Vötsch, Balingen, Germany); Permatran W 600 (Mocon, Minneapolis, MI); and MFT Bench Thermostair, type D (A. Coesfeld, Dortmund, Germany).

Core Formulation

The core formulation is shown in Table 1. Batches of 30 kg are produced. The components of the formulation were mixed for 3 min in the Diosna at setting 1 without a chopper; and compressed at a rate of 40,000 tablets/hr into cores of 9-mm diameter, 12-mm radius of curvature, 330 mg weight, and with the engraving ‘‘BASF’’ on one face with a 10 KN compression force.

Composition and Preparation of the Different Spray Suspensions

The compositions of the different spray suspensions are given in Tables 2–5. The coating dispersions, pig-

Table 1

Composition of the Caffeine Cores

	mg/Tablet	Parts (%)
Caffeine anhydrous	50.0	15.15
Ludipress	229.0	69.40
Kollidon CL	10.0	3.03
Avicel PH-101	40.0	12.12
Magnesium stearate	1.0	0.30
	330.0	100.00

Table 2

Coating Dispersons (Parts by Weight)

	Parts
Kollicoat MAE 30 D resp. DP resp. Eudragit L 30 D-55	50.00
Plasticizer (TEC), 10%	1.50
Water	33.00
Coating dispersion	84.50

ment suspensions, and ready-for-use spray suspensions were prepared as described in Ref. 1.

Preparation of Isolated Films

The films were produced by spraying the ready-for-use spray suspension onto the heated plate (35°C) of the film-drawing unit. The films were then stored uncovered at room temperature to dry to constant weight.

Table 3

Variants of the Coating Dispersions (Parts by Weight)

	Film Former	Plasticizer	Water	Coating Dispersion
10% Plasticizer	50.00	1.50	33.00	84.5
15% Plasticizer	50.00	2.25	32.25	84.5
20% Plasticizer	50.00	3.00	31.50	84.5
25% Plasticizer	50.00	3.75	30.75	84.5
30% Plasticizer	50.00	4.50	30.00	84.5

Table 4

Variants of the Pigment Suspension (Parts by Weight)

	Without Kollidon 30	Without Sicovit Red 30	Without Titanium Dioxide	Without Talc
Kollidon 30		0.5	0.5	0.5
Sicovit red 30	0.5		0.5	0.5
Titanium dioxide	0.5	0.5		0.5
Talc	4.0	4.0	4.0	
Water	10.5	10.5	10.5	14.0
Pigment suspension	15.5	15.5	15.5	15.5

Table 5

Pigment Suspension with Variable Kollidon 30 Content (Parts by Weight)

Formulation	1	2	3	4
Kollidon 30	0.50	0.25	0.10	—
Sicovit red 30	0.50	0.50	0.50	0.50
Titanium dioxide	0.50	0.50	0.50	0.50
Talc	4.00	4.00	4.00	4.00
Water	10.00	10.25	10.50	10.5
Pigment suspension	15.50	15.50	15.50	15.50

Film Coating

For preparation of the film coating, see Ref. 1. As subcoating, a 5% aqueous Kollidon VA 64 solution was applied in a layer thickness of up to 1 mg/cm^2. The cores were preheated to 43°C at an inlet air temperature of 60°C. The coated cores underwent secondary drying for 5 min at a product temperature of 35°C.

Study of Spray and Pigment Suspensions

The minimum film-forming temperature of the spray suspension was according to DIN 58 787.

For the glass transition temperature of the spray suspension, the suspension was poured into a 10 × 10 cm Teflon dish and then dried for 24 hr at 50°C. The determination was performed by differential scanning calorimetry (DSC).

For determination of the sedimentation rate of the pigment suspension, the freshly homogenized pigment suspension and the pigment suspension stirred for 12 hr on a magnetic stirrer were transferred to a 100-ml graduated cylinder, and any sediment that formed at room temperature was read at increasing time intervals. No longer redispersible sediment was classified as coagulate.

Tests on Film-Coated Tablets

The weight increase during the resistance test was performed on sets of 6 film-coated tablets after 1 and 2 hr in 0.1 N HCl.

The resistance to gastric fluid and disintegration time was determined according to USP 23.

The drug release was determined according to USP 23 using apparatus 2, method B at 75 rpm in 0.1 N HCl

Table 6

Stability of the Formulation Variants With and Without Kollidon 30 During Preparation and Processing

Plasticizer	Concentration (%)	Stability With Kollidon 30	Stability Without Kollidon 30
PEG 400	10	●	◆
	20	●	◆
	30	●	◆
PEG 1500	10	●	◆
	20	●	◆
	30	●	◆
PEG 6000	10	◆	◆
	20	◆	◆
	30	◆	◆
Lutrol F 68	10	◆	◆
	20	◆	◆
	30	◆	◆
Propylene glycol	10	◆	◆
	20	◆	◆
	30	◆	◆
Triethyl citrate	10	○	◆
	15	●	◆
	20	●	◆
	25	●	◆
Cremophor RH 40	10	□	◆
	15	●	◆
	20	●	◆
	25	●	◆

●, coagulation; ◆, stable spraying suspension; □, slight coagulation, partly reversible; ○, tendency to coagulation.

and in phosphate buffer pH 6.8. Caffeine was determined by spectrophotometry at 273 nm.

RESULTS AND DISCUSSION

Cause and Prevention of Coagulation

On its own, none of the coating dispersions listed in Table 2 shows a tendency to coagulate. On admixture of the pigment suspension, formulation 1 described in Table 5, however, coagulation occurs in all three latices in the presence of specific plasticizers (see Table 6).

The tendency to coagulation was investigated by preparing and testing all possible mixing combinations in Tables 2 and 4 using 10% TEC as a plasticizer. Coagulation occurred in all mixtures with Kollidon 30 in all three latices. When Kollidon 30 was left out, the coagulation tendency disappeared. The same result was obtained in the Kollidon 30-free replicate using the other plasticizers listed in Table 6: No coagulation occurred with any of the plasticizers.

Improving Gastric Fluid Resistance

In the previous study (1), film-coated caffeine tablets with 3 mg/cm^2 film thickness produced using 10% TEC and Kollidon 30 swelled markedly and split after brief exposure to simulated gastric fluid. Among the plasticizers tested, this one gave the poorest results. It therefore was used in tests designed to improve resistance to gastric fluid. The extreme swellability of caffeine cores in the presence of absorbed simulated gastric fluid is one of the factors responsible for lacking resistance. This swellability is caused primarily because Kollidon CL is an extremely effective disintegration enhancer (2).

A subcoat is occasionally applied to enhance the enteric protection provided by enteric coatings and—as in the present case—to reduce the swelling of the core (3). An experiment of this type shows that enteric-coated caffeine tablets can also be produced with 10% TEC and Kollidon 30 when subcoating with Kollicoat VA 64 is performed.

Kollidon 30–Free Film Dispersion

Pigment Distribution

In the present study, Kollidon 30–free film coats showed a markedly worsened pigment distribution. This can be attributed to the suspension-stabilizing effect of water-soluble polyvinylpyrrolidones (4). A series of experiments using 10% TEC therefore was performed to establish first the extent to which the Kollidon 30 content of the pigment suspension could be reduced without adversely affecting the pigment distribution and second to

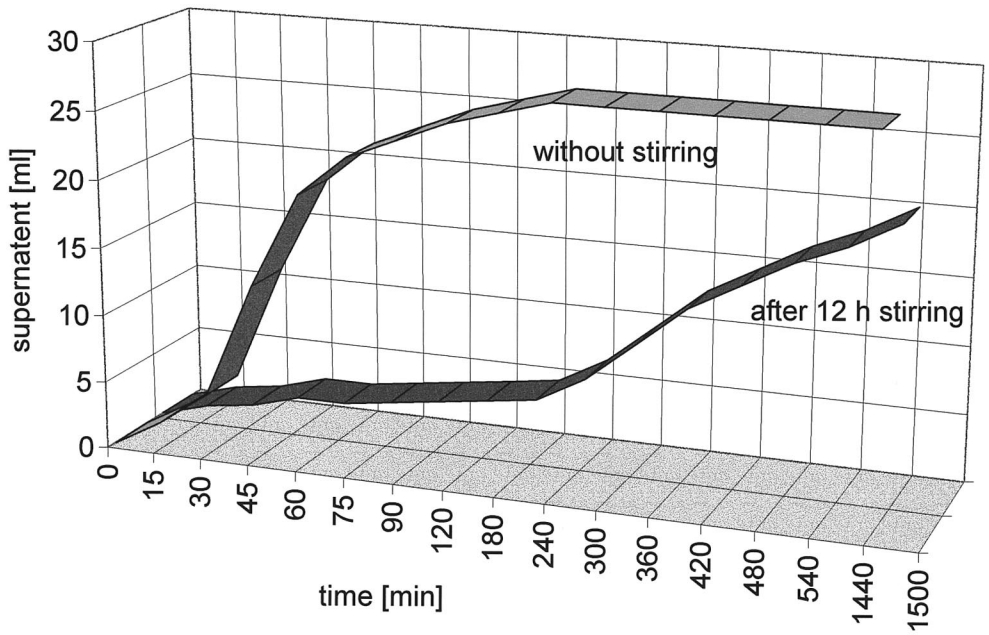

Figure 1. Sedimentation rate of the pigment suspension without and after 12 hr of stirring.

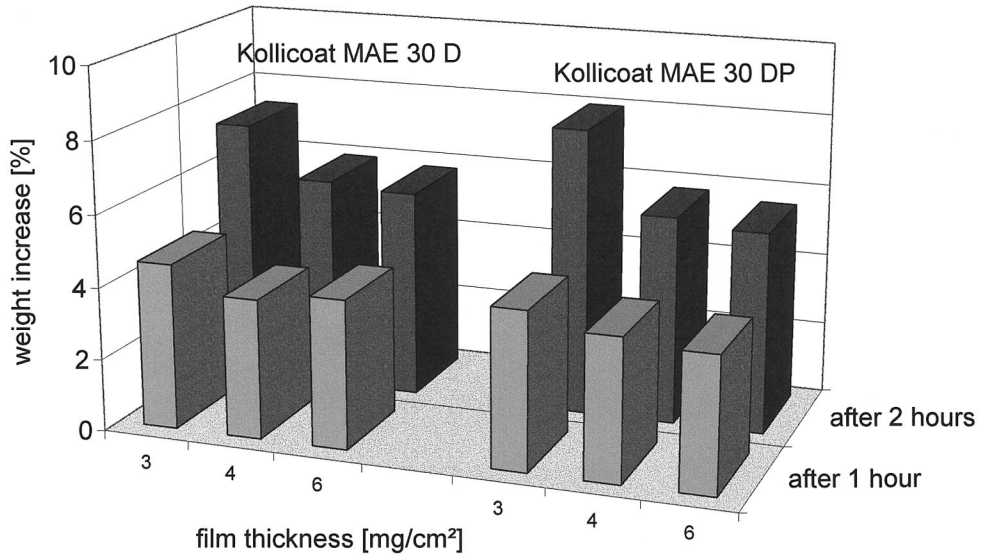

Figure 2. Weight increase of caffeine film-coated tablets with Kollicoat MAE 30 D and Kollicoat MAE 30 DP after 1 and 2 hr in simulated gastric fluid.

determine the Kollidon 30 concentration below which the tendency to coagulation disappeared. The experiments showed that the pigment distribution already worsened considerably below 0.25 parts by weight (Table 5), whereas coagulation still occurred at 0.1 parts by weight Kollidon 30 with all three film formers (Table 2).

In the previous experiments, the pigment suspension was mixed with the coating dispersion and used immediately after homogenizing in a corundum disk mill. Experiments conducted after prolonged stirring (12 hr) of the pigment suspension after homogenization produced satisfactory pigment distribution in the film coat. The improved pigment distribution thereby achieved was also seen indirectly in the determination of the sedimentation rate (Fig. 1): Without stirring, the pigments settle much more rapidly than after prolonged stirring.

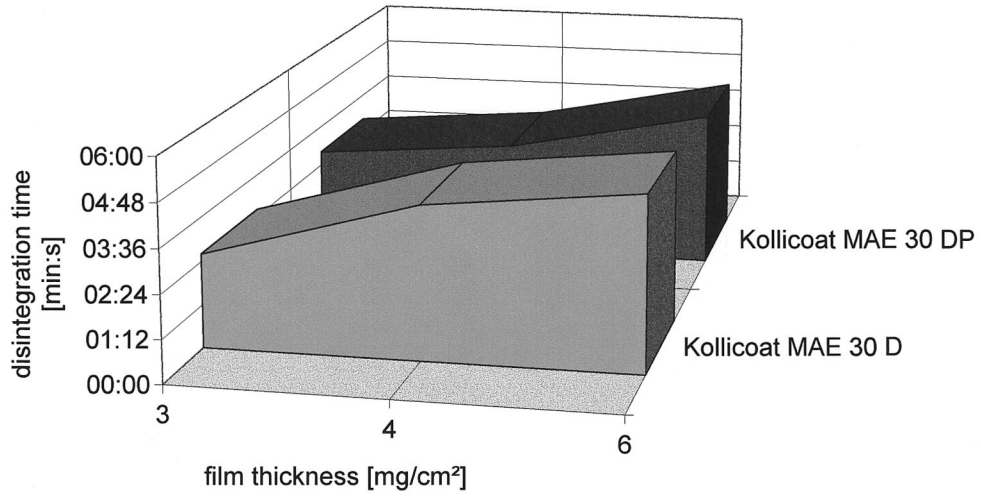

Figure 3. Disintegration times of caffeine film-coated tablets with Kollicoat MAE 30 D and Kollicoat MAE 30 DP and film thickness 3.4 and 6 mg/cm^2 in phosphate buffer pH 6.8.

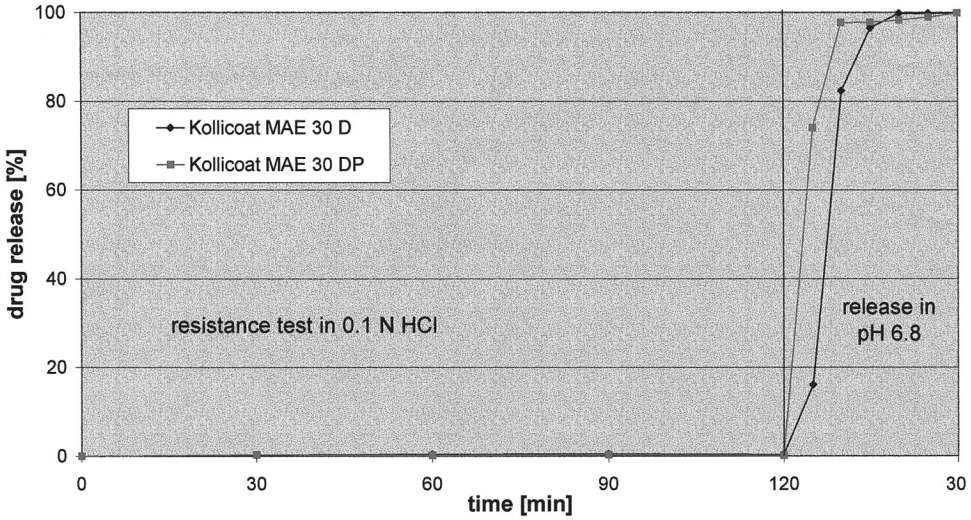

Figure 4. Drug release of caffeine film-coated tablets with Kollicoat MAE 30 D and Kollicoat MAE 30 DP with 3 mg/cm^2 film thickness in simulated gastric and intestinal fluid.

Optimization of Plasticizer

After elimination of Kollidon 30, the question arose whether the formulation with 20% PG selected in Ref. 1 was still preferable to the other plasticizer versions in Table 6. To resolve this question, the three plasticizers from Table 6 that appeared most suitable for film-coating trials were selected: PG because of its good performance in the study in Ref. 1, TEC because it is the plasticizer described particularly often for aqueous enteric films (5–7), and PEG400 as a representative of the three polyethylene glycols.

Processed with Kollicoat MAE 30 DP and coated on caffeine cores, the three plasticizers differ only in their resistance to gastric fluid: Compared to 10–15% PG or TEC, PEG400 absorbs slightly more gastric fluid.

A replicate trial with Kollidon MAE 30 D showed the same resistance to gastric fluid (see Fig. 2) and disintegration time (Fig. 3) and only initially showed a slightly reduced drug release rate than when using Kollicoat MAE 30 DP (see Fig. 4). Compared to uncoated caffeine cores, which reach a mean 99% (s_{rel} = 4.83%) after 4 min, a delay in drug release of 5 to 10 min was observed for both latices.

CONCLUSIONS

Kollidon 30 can cause coagulation in aqueous methacrylic acid–ethylacrylate copolymer formulations in the presence of certain excipients. PG should be used as plasticizer in spray suspensions with Kollidon 30 and pigments because it does not induce coagulation. A plasticizer content of 10–15% PG or TEC provides the best results in the Kollidon 30–free, pigment-containing film formulations studied. No differences were detectable between Kollicoat MAE 30 DP and 30 D and Eudragit L 30 D-55. The resistance to gastric fluid of Kollicoat MAE 30 D and DP–containing coats on highly swellable cores can be improved further by subcoating with Kollidon VA 64.

REFERENCES

1. A. Flößer, K. Kolter, H.-B. Reich, and G. Schepky, Drug Dev. Ind. Pharm., 26(2), 177–187 (2000).
2. V. Bühler, *Kollidon®*, BASF AG, Ludwigshafen, Germany, 1993, pp. 138–139.
3. K. Thoma, R. Oschmann, and H. Heckenmüller, Deutsche Apotheker Zeitung, 126(20), 1075 (1986).
4. B. V. Robinson, F. M. Sullivan, J. F. Borzelleca, and S. L. Schwartz, *PVP—A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Novidone)*, Lewis Publishers, Chelsea, Michigan, 1990, p. 4.
5. K. Amighi and A. J. Moes, Proc. 1st World Meeting APGI/APV, Budapest, 52–53 (1995).
6. R. Bodmeier and O. Paeratakul, Pharm. Res., 11(6), 882–888 (1994).
7. K. Lehmann, H.-U. Petereit, and D. Dreher, Drugs Made in Germany, 37(2), 53–60 (1994).