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RESEARCH PAPER

Variation of Composition of an Enteric Formulation Based on Kollicoat MAE 30 D

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ABSTRACT

Using a formulation described previously with Kollicoat MAE 30 D as the film-forming agent, the effect of variations in plasticizer type and quantity and talc concentration on the preparation and processing of spray-coating suspensions and the properties of isolated films and film-coated caffeine tablets prepared using them was investigated. In the preparation and processing of spray-coating suspensions, the plasticizers polyethylene glycol (PEG) 400, PEG1500, and TEC (triethyl citrate) tended to coagulate at all concentrations investigated, while Cremophor RH 40 coagulated above 10% (expressed as a percentage of the mass of the film-forming agent used). Analogous preparations using propylene glycol (PG), PEG6000, and Lutrol F 68, on the other hand, were found to be stable at all concentrations. The instability was not caused by the Kollicoat MAE 30 D polymer dispersion as such, but by interactions between the finely dispersed pigments and other formulation ingredients. Equivalent nonpigmented preparations are stable and do not coagulate. With all the plasticizers investigated, the minimum film-forming temperature (MFT) fell, albeit to differing degrees, as the amount of plasticizer increased. Similarly, the tensile strength of isolated films declined as plasticizer concentration increased, while the reverse was true as regards their elongation at break. Whereas neither the subsequent disintegration time nor the rate of release of active ingredient at pH 6.8 was significantly affected by the various plasticizer additives, the different film-coated tablet formulations with a core containing a powerful disintegrant exhibited varying degrees of permeability to simulated gastric fluid. With PEG6000, perme-

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ability increased as the plasticizer concentration increased, while Lutrol F 68 provided an optimum barrier at 20%, and PG provided a good barrier between 10% and 30%. No gastroresistance was obtained with TEC at 10%. Only the best plasticizer formulations were used in the trials with different talc concentrations, namely, those formulations with 20% PEG6000, 20% Lutrol F 68, 20% PG, and 10% PG. When talc was added, the MFT rose, reaching its maximum at 13% talc (as a proportion of the film-forming agent). In the test for gastroresistance, film-coated caffeine tablets without talc absorbed distinctly more acid than those containing talc. Above 27% talc, the acid resistance improved only insignificantly. On the other hand, during this test, only a maximum of 3% of the active ingredient was released into the gastric juice. Of the variants investigated, the formulation with 20% PG and 27% talc performed best.

Key Words: *Enteric coating; Film properties; Gastric resistance; Kollicoat MAE 30D; Plasticizer.*

INTRODUCTION

In an earlier study (1), Kollicoat MAE 30 D was compared with commercially available cellulose derivatives in enteric coatings applied to caffeine cores. The present studies were to assess the effects of plasticizer and talc in this Kollicoat formulation. To this end, the triethyl citrate (TEC) used was quantitatively varied and/or replaced by different quantities of other plasticizers. This included plasticizers already described in aqueous ethyl acrylate/methacrylic acid copolymer formulations, as well as substances that have both a plasticizing effect and could be expected to increase the speed at which the film dissolves in intestinal fluid.

EXPERIMENTAL

Materials

The following materials were used:

Avicel PH 101 (FMC Corp., Philadelphia, PA)
Anhydrous caffeine (Knoll AG, Ludwigshafen, Germany)
Kollicoat MAE 30 D (BASF AG, Ludwigshafen, Germany)
Kollidon CL (BASF AG)
Kollidon 30 (BASF AG)
Ludipress (BASF AG)
Magnesium stearate (Bärlocher, Munich, Germany)
Lutrol 400 (PEG400) (BASF AG)
Lutrol 1500 (PEG1500) (BASF AG)
Lutrol 6000 (PEG6000) (BASF AG)
Lutrol F 68 (BASF AG)
Cremophor RH 40 (BASF AG)
Propylene glycol (BASF AG)
Sicovit Red 30 (BASF AG)
Talc, powder (Riedel de Haen AG, Seelze, Germany)
Titanium dioxide RN 56 (Kronos Titan GmbH, Leverkusen, Germany)
Triethyl citrate (TEC) (Merck-Schuchardt, Hohenbrunn, Germany)

Apparatus

The apparatus used is described in Ref. 1.

Core Formulation

The preparation and composition of the cores are described in Ref. 1 and are shown here in Table 1.

Composition and Preparation of the Different Film Suspensions

To prepare the spray-coating dispersion, film-forming dispersions and pigment suspensions were produced sep-

Table 1

Composition of the Caffeine Tablet Cores

Ingredients	Amount/Tablet (mg)
Coffein anhydrous	50
Ludipress	229
Avicel PH-101	40
Kollidon CL	10
Magnesium stearate	1
Total	330

Table 2

Kollicoat MAE 30 D: Basic Formulation as per Ref. 1

Ingredients	mg
Kollicoat MAE 30 D	15.0
Triethyl citrate	1.5
Kollidon 30	0.5
Talc	2.0
Titanium dioxide	0.5
Sicovit Red 30	0.5
Water	80.0
Total	100.0

Table 3

Summary of the Plasticizers Used and the Quantities of Each

Plasticizer	Plasticizer Concentration Related to Polymer (%)				
PEG400	10		20		30
PEG1500	10		20		30
PEG6000	10		20		30
Propylene glycol	10		20		30
Lutrol F 68	10		20		30
Triethyl citrate	10	15	20	25	
Cremophor RH 40	10	15	20	25	

Table 4

Film-Forming Dispersions (Parts by Weight)

	Plasticizer Concentration Related to Polymer (%)				
Ingredients	10	15	20	25	30
Kollicoat MAE 30 D	50.00	50.00	50.00	50.00	50.00
Plasticizer	1.50	2.25	3.00	3.75	4.50
Water	35.00	34.25	33.50	32.75	32.00
Total	86.50	86.50	86.50	86.50	86.50

arately (Tables 2 and 3). The amount of pigment suspension stated is given as a proportion of 86.5 parts of film-forming dispersion in each case (Tables 4 and 5).

For preparation of the film-forming dispersion, the plasticizer was dissolved in water, and then Kollicoat MAE 30 D was added using a magnetically operated agitator.

For preparation of the pigment suspension, Kollidon 30 was dissolved in water. The other ingredients were

Table 5

Pigment Suspensions (Parts by Weight)

	Talc Concentration Related to Polymer (%)			
Ingredient	Without	13.3	26.6	39.9
Titanium dioxide		0.5	0.5	0.5
Talc		2.0	4.0	6.0
Sicovit Red 30		0.5	0.5	0.5
Kollidon 30		0.5	0.5	0.5
Water	10.0	10.0	10.0	10.0
Total	10.0	13.5	15.5	17.5

then suspended. To homogenize the pigment suspension, it was passed through a corundum disk mill.

The film-forming dispersion was placed in a glass beaker, and the pigment suspension was added slowly while stirring with a blade mixer. The spray-coating suspension was then poured off through a sieve with a mesh size of 80 μm. The suspension has to be agitated constantly during both storage and use.

Preparation of Isolated Films

For preparation of isolated films, see Ref. 1.

Film Coating

The tablets were film coated in a 24-inch Accela Cota in 5-kg batches of cores. The product temperature was adjusted via the spray rate. Samples with 3.4 and 6 mg/cm^2 of film-forming agent were taken. Equipment parameter settings are given in Table 6.

Table 6

Equipment Parameter Settings

Equipment Parameters	
Coating pan speed	12 rpm
Nozzle diameter	1 mm
Atomizing air	2 bar
Inlet air quantity	~ 60 L/sec
Outlet air quantity	~110 L/sec
Inlet air temperature	50°C
Tablet bed temperature	30°C–35°C

Investigation of Spray-Coating Suspensions

The minimum film formation temperature of the spray-coating suspensions was determined using the DIN 53787 method.

Investigation of Isolated Films

For determination of elongation at break and tensile strength, the DIN 53 504 method was used.

For tack determination, see Ref. 1. Substances were assessed using a scale of 0 to 5 (0 = no tack; 5 = highly tacky).

Investigation of Film-Coated Tablets

For determination of weight increase during gastroresistance testing, in each case it was performed with 6 film-coated tablets after 1 or 2 hr in 0.1 N HCl

Gastroresistance and disintegration time were determined per USP 23.

Drug release was determined per methods in USP 23 and Ref. 1.

RESULTS AND DISCUSSION

Qualitative and Quantitative Exchanges in the Plasticizer

Preparation and Processing of the Spray-Coating Suspensions

The majority of the formulations examined coagulated, as shown in Table 7, and therefore were not investigated further. This coagulation occurred either immediately after the pigment suspension was added to the film-forming solution or else when agitation ceased. There were clear qualitative differences in stability among the various polyethylene glycol (PEG) formulations.

Formulations without added pigment were stable.

Table 7

Stability of the Various Formulation Variants During Preparation and Processing

Plasticizer	Concentration (%)	Stability
PEG400	10	Coagulation
	20	Coagulation
	30	Coagulation
PEG1500	10	Coagulation
	20	Coagulation
	30	Coagulation
PEG6000	10	Stable spraying suspension
	20	Stable spraying suspension
	30	Stable spraying suspension
Lutrol F 68	10	Stable spraying suspension
	20	Stable spraying suspension
	30	Stable spraying suspension
Propylene glycol	10	Stable spraying suspension
	20	Stable spraying suspension
	30	Stable spraying suspension
Triethyl citrate	10	Stable spraying suspension
	15	Coagulation
	20	Coagulation
	25	Coagulation
Cremophor RH 40	10	Slight coagulation, partly reversible
	15	Coagulation
	20	Coagulation
	25	Coagulation

Investigation of Coating Suspensions

All the plasticizers investigated had the effect of reducing the minimum film-forming temperature (MFT; Fig. 1) of Kollicoat MAE 30 D. This also applied to the Lutrol F 68, which was selected for its solubilizing properties. As the quantity of plasticizer increased, the MFT decreased. However, this occurred at different levels with the different substances. Both these findings are in agreement with previous studies (2).

Investigations of the Isolated Films

Elongation at Break

For elongation at break (Fig. 2), the values increased as a function of plasticizer concentration (3). The smallest increase occurred with Lutrol F 68; the highest increase occurred with propylene glycol (PG).

Tensile Strength

The tensile strength is the maximum force applied to the sample during the tensile test. As was the case for the elongation at break, the tensile strength also varied as a function of plasticizer type and quantity. As the plasticizing effect occurs through a reduction in the intermolecular forces between the polymer chains, it is accompanied by a reduction in the tensile strength (3). Accordingly, it can be seen from Fig. 3 that the tensile

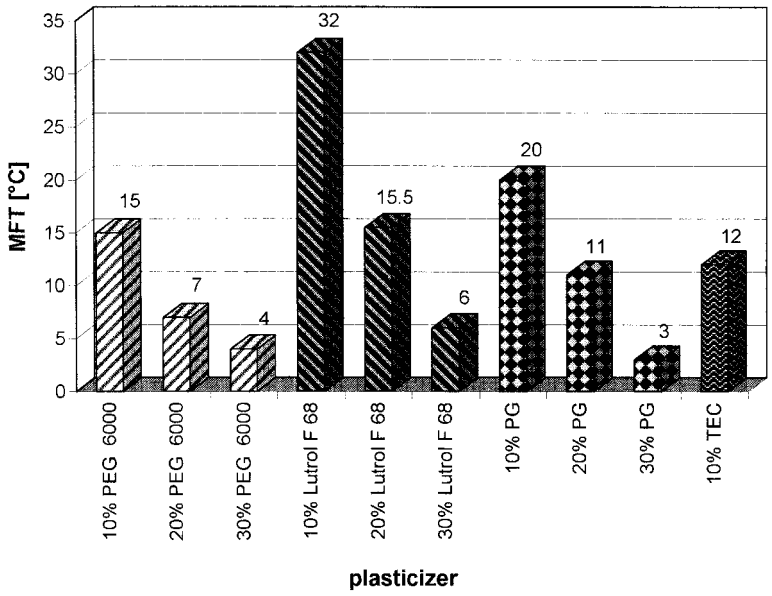

Figure 1. Minimum film-forming temperature.

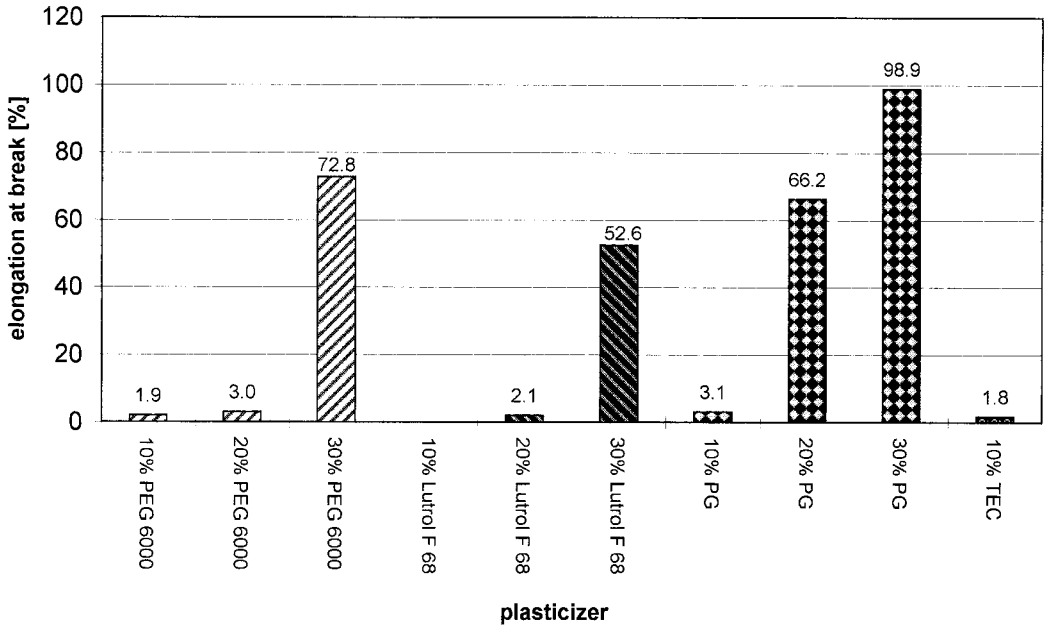

Figure 2. Elongation at break of isolated films with different plasticizers.

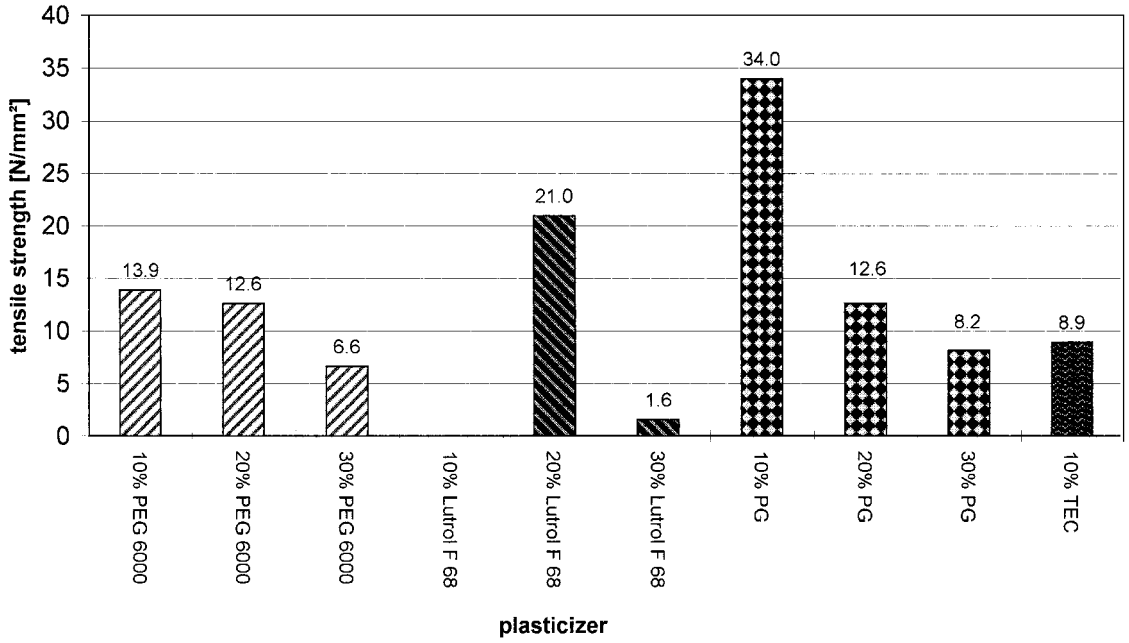

Figure 3. Tensile strength of isolated films with different plasticizers.

strength in the samples was greatest at low plasticizer concentrations and declined as the amount of plasticizer increased. It is striking that the tensile strength with PG was distinctly higher than when similar concentrations of the other plasticizers were used.

Tack

The tack was low in all the films (Table 8). However, it rose as the amount of plasticizer increased. With the formulations containing 30% plasticizer, the tablets were occasionally observed to stick together during spraying. This was probably due to surplus plasticizer escaping from the film (4).

Table 8

Tack of Isolated Films with Different Plasticizers (0 = Not Adhesive, 5 = Highly Adhesive)

Plasticizer	Tack (0–5)
10% PEG6000	0
20% PEG6000	1
30% PEG6000	1
10% Lutrol F 68	0
20% Lutrol F 68	0–1
30% Lutrol F 68	1
10% Propylene glycol	0
20% Propylene glycol	0–1
30% Propylene glycol	0–1
10% Propylene glycol	0

Investigation of Film-Coated Tablets

Appearance

No difference in appearance was discernible among the individual batches. All the film-coated tablets had a smooth, regular surface. The embossing was also perfectly legible.

Gastroresistance and Disintegration Time

These factors were investigated using tablets coated with a 3-mg/cm^2 film. In preliminary experiments, this film thickness had proved the critical threshold at which differences in acid resistance between different plasticizers became evident. No acid resistance was exhibited by 10% triethyl citrate; the film-coated tablets disintegrated in the acid.

With 10% PEG6000, 1 of 6 film-coated tablets was damaged, while acid resistance was poor with 10% Lutrol F 68 (after 2 hr in 0.1 N HCl, 3 of 6 film-coated tablets were completely emptied). PEG and Lutrol F 68 demonstrated good acid resistance at concentrations of 20% and

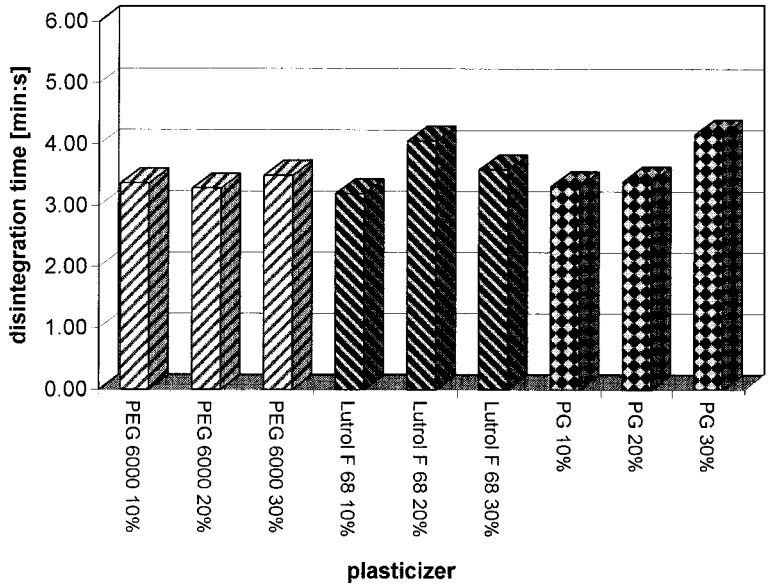

Figure 4. Disintegration times of film-coated caffeine tablets with different plasticizers.

30%. PG was acid resistant at all the concentrations tested.

These findings may be attributed partly to differences in film permeability and partly to differences in the elasticity of the films (see Fig. 2), combined with the high swelling capacity of the caffeine tablet core (see Table 1). As studies not yet published have shown, caffeine cores with less disintegrant can also be coated with 10% triethyl citrate to obtain an enteric coating as defined in USP 23.

The disintegration times were not significantly affected by plasticizer type or quantity, as Fig. 4 shows.

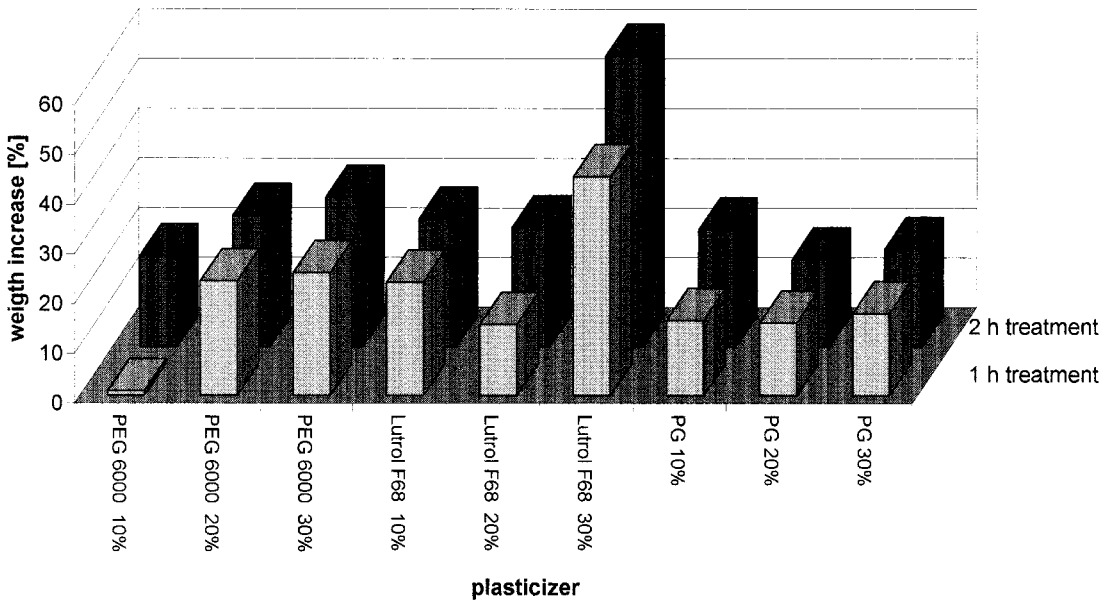

Figure 5. Weight increase in film-coated caffeine tablets with different plasticizers during resistance testing.

Other studies report similar findings (5). Even Lutrol F 68, which was selected to dissolve the film more rapidly in the simulated intestinal fluid environment, was no exception here.

Weight Increase During the Resistance Test

The weight increase of tablets coated with 3 mg/cm^2 film-forming agent was also determined after 1 hr and 2 hr in simulated gastric fluid. This simple determination provides information about the acid permeability of the film coating concerned. It can help to explain major anomalies in the release rates of film-coated tablets (6). PEG6000 (Fig. 5) actually increases the acid permeability of the film as it is very hydrophilic, and its interaction with the polymer is weak. It is therefore readily leached out of the film coating, which then becomes porous and more permeable to gastric fluid.

Lutrol F 68 and PG achieved their lowest acid permeability at 20% plasticizer concentration. This can be explained partly by the fact that, at a plasticizer concentration of only 10%, the film is still somewhat brittle and therefore more permeable. Above 20%, pore formation increased as a function of plasticizer concentration, again leading to increased permeability, especially in the case of the films with 30% Lutrol F 68.

PG exhibited the best acid resistance and the resistance that was least dependent on plasticizer quantity.

Drug Release

At 3 mg/cm^2 film-forming agent, 2 film-coated tablets with 10% PEG6000 and 4 tablets with 10% Lutrol F 68 released considerable quantities of active ingredient during the gastroresistance test (Fig. 6). In the other samples, no significant release of active ingredient occurred. In the same test with 4 mg/cm^2 film-forming agent, the release of active ingredient was less than 2% for all samples after a 2-hr resistance test (see Fig. 7).

The release of active ingredient in a pH 6.8 buffer solution was independent of plasticizer type and concentration. All film-coated tablets released all of the active ingredient within less than 20 min. It should be noted that the drug release was more regular with 4 mg/cm^2 than with 3 mg/cm^2. This is due to the fact that, at 3 mg/cm^2, the film coating still has points of weakness that occasionally can lead to considerable swelling of the film-coated tablets due to the penetration of gastric fluid during the resistance test. This in turn can lead to a delay in the release of the active ingredient. After readjusting to pH 6.8, the gastric fluid, which has penetrated into the film-coated tablet, initially protonizes the intestinal fluid as it enters. The film coating only dissolves when the intestinal fluid has increased the core pH again. There was no observable correlation between weight increase and release behavior of the individual film-coated tablet formulations.

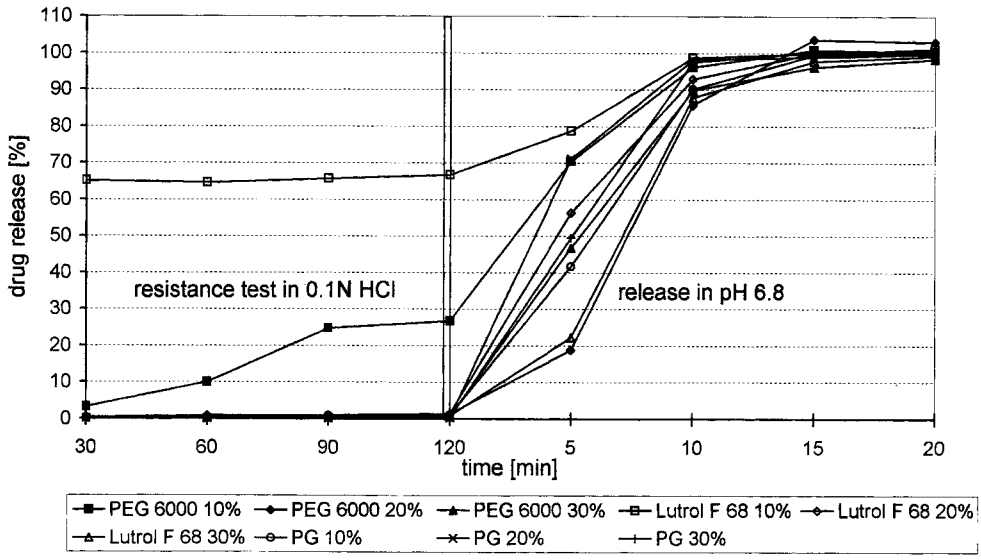

Figure 6. Resistance and release characteristics of film-coated caffeine tablets with 3 mg/cm^2 film-forming agent.

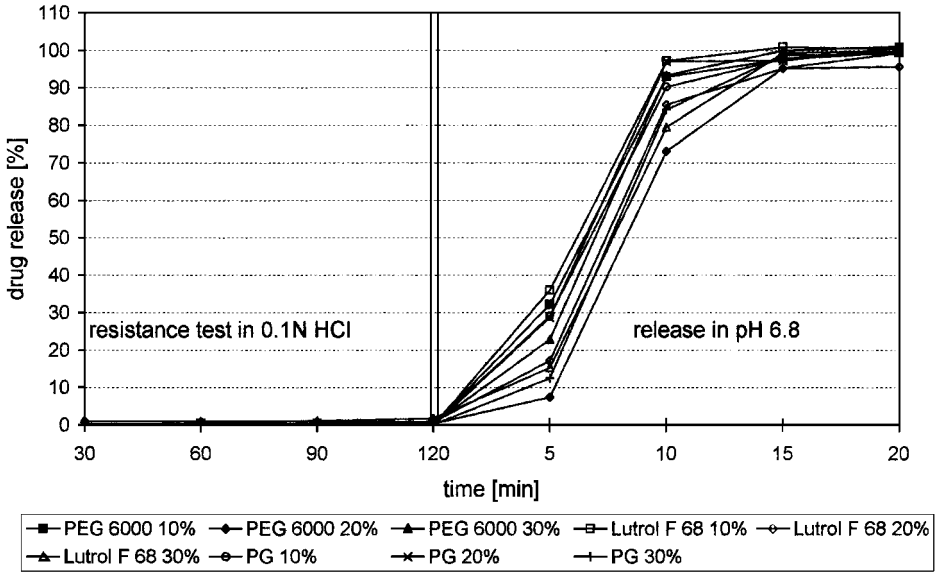

Figure 7. Resistance and release characteristics of caffeine tablets coated with 4 mg/cm^2 film-forming agent.

Effect of Talc Concentration

Taking into account the above findings and the desire for the thinnest possible film coatings, the next stage of the study investigated the following formulation variants: 20% PEG6000, 20% Lutrol F 68, and 10% or 20% PG.

In addition, one spray-coating suspension with 20% TEC without talc or pigments was prepared (as it is unstable with talc and pigments) to check whether an enteric coating could be achieved with increased TEC concentration.

Preparation and Preliminary Work on Spray-Coating Suspensions

Only with PEG6000 did the addition of the talc suspension produce a short-term increase in viscosity, combined with some coagulation. When the spray-coating suspension was agitated further, this was reversed.

With all spray-coating suspensions, it was possible to prevent sedimentation of the solid particles through continuous agitation with a blade mixer during preparation and processing.

Investigation of the Spray-Coating Suspensions

As Fig. 8 shows, when talc was added, the MFT increased. In the formulations investigated, the maximum increase occurred when 13.3% talc was added.

Investigation of Film-Coated Tablets

Appearance

Smooth, regular surfaces were achieved with all the formulations. Even when talc content was 39.9%, the embossing was still perfectly legible.

Gastroresistance

The gastroresistance test was carried out on tablets with a coating of 3 mg/cm^2 film-forming agent. The gastroresistance of formulations without talc or pigments was inferior to that of formulations with both these components.

Weight Increase During the Resistance Test

As expected, the weight increase of the different formulations was less after the 1-hr gastroresistance test (Fig. 9) and greater after the 2-hr test (see Fig. 10). Of all the formulations, those without talc showed the highest permeability to simulated gastric fluid. Adding only 13.3% talc was sufficient to reduce the weight increase in all the samples; in the 2-hr resistance test, it even was reduced by more than one-half. Above 26.6% talc, the permeability changed only insignificantly.

That talc reduces permeability is well documented in the literature (7,8).

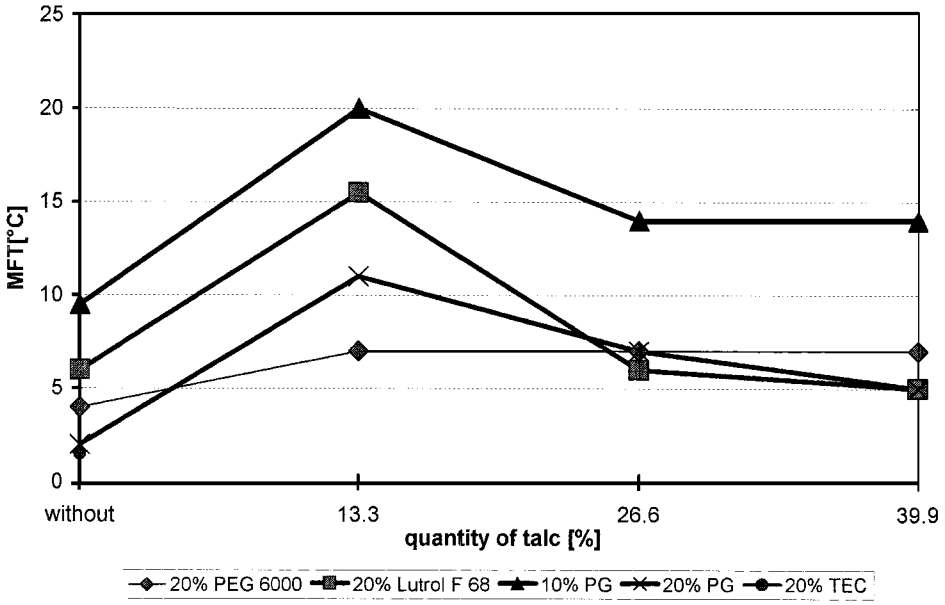

Figure 8. MFT of the spray-coating suspensions as a function of talc content.

Drug Release

As Fig. 11 shows, there is no correlation between uptake of simulated gastric fluid and release of caffeine during the gastroresistance test. This again confirms the conclusions drawn in the section on the investigation of film-coated tablets. Apart from the talc-free and nonpigmented 10% PG formulation, all the others released less than 3% active ingredient.

With all the formulations, all of the active ingredient was released within 20 min in simulated intestinal fluid.

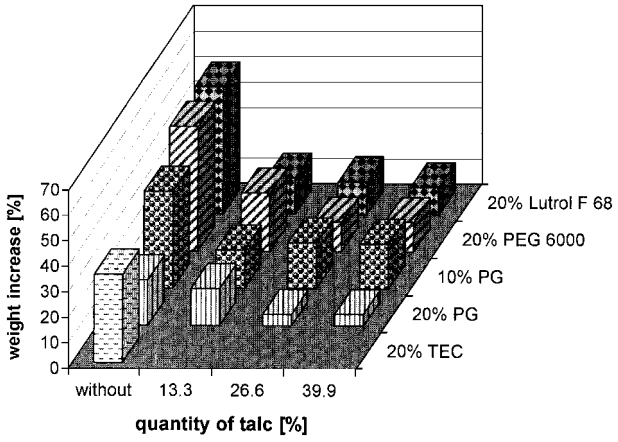

Figure 9. Weight increase of film-coated caffeine tablets with different plasticizers and quantities of talc after 1-hr resistance test (film-forming agent 3 mg/cm^2).

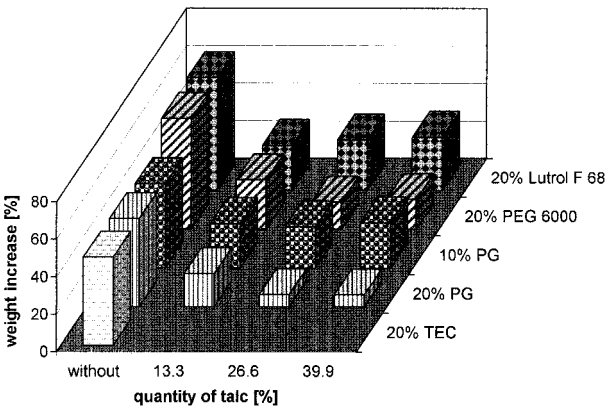

Figure 10. Weight increase of film-coated caffeine tablets with different plasticizers and quantities of talc after 2-hr resistance test (film-forming agent 3 mg/cm^2).

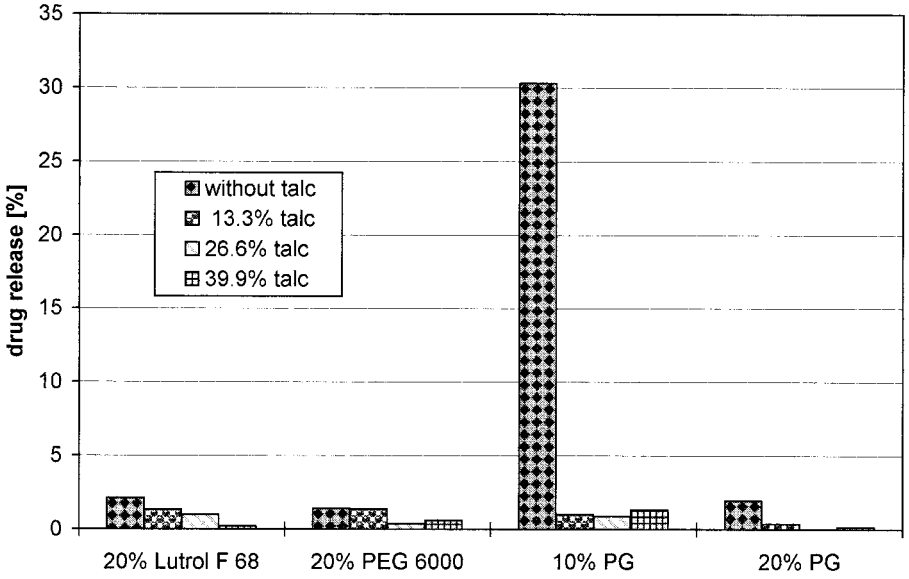

Figure 11. Release of active ingredient from caffeine tablets coated with 3 mg/cm^2 film-forming agent after 2-hr resistance test.

CONCLUSION

For coating tablet cores containing high-performance disintegrants (superdisintegrants) with pigmented enteric suspensions based on methacrylic acid–ethyl acrylate copolymers, the following excipients are recommended: 20% PG (plasticizer) and 27% talc (as a proportion of the film-forming agent).

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