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Note

Preliminary applicability tests of different methacrylic acid copolymers, type C NF, particularly relevant to spreading and film formation

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Abstract

The intention of this study was to show under which conditions a film forming methacrylic acid copolymer coating excipient, corresponding to the requirements of pharmacopoeia, but obtained from different sources, can be substituted without severe problems. The mechanical properties of the film coats were investigated by dynamic-mechanical thermo-analysis (DMTA) experiments to determine with respect to the glass transition the storage modulus E′, the loss modulus E″, and the loss factor tan δ. Further determinations concerned the surface tensions of the different coating dispersions. This attribute plays an important role in spreading, distribution and coalescence of the film forming preparations. Finally by a series of small experimental fluidized bed batches cores containing a model drug were coated with the different methacrylic acid copolymers. The resistance of these coated tablets in 0.1 N HCl as well as their dissolution rates in artificial intestinal juice were tested. The coatings proved themselves so similar that in this case substitutions of products of different provenance are possible. The determinations of surface tension and the DMTA measurements seem to be useful and reliable preliminary applicability tests.

Keywords: Methacrylic acid copolymers (Type C NF); Kollicoat® MAE 30 D; Eudragit® L 30 D 55; Applicability tests; Surface tension; Dynamic-mechanical thermo-analysis; Film coats

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1. Introduction

The most polymeric and amphiphilic excipients in the pharmaceutical practice are no pure single chemical substances. They are mixtures of more or less similar substances, or at least they have differing molecular masses. The reasons are complicated synthetical processes or very difficult or extremely expensive purification operations. Such excipients, even if they meet the pharmacopoeia requirements, should not be substituted without practically relevant preliminary tests. Pharmacopoeia requirements are mainly concentrated on identity and purity determinations, but they comprise usually no tests to ensure utility properties or the applicability at all. Therefore it is advisable to look for some reality approached utility test methods before shifting to a substitution product of another provenance. Even if such an excipient seems identical, for instance if it is corresponding with pharmacopoeia requirements or similar monographs. There still may be some insecurities. Such products can differ in their composition, in the molecular mass or in components of different conformation [1].

Methacrylic acid copolymers [2] are widely used pharmaceutical coating materials, and there are NF monographs which are defining their quality. They exhibit very special functions, e.g. for establishing a certain pH- or diffusion-controlled drug release. The main task of a coating material is to form a homogeneous film coat with sufficient mechanical strength. These films must also be able to accomplish their intended functions during the full period of applicability.

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In the following two different products of methacrylic acid copolymers were subjected to certain utility tests, to find out whether they are practically comparable or not, and finally they were used to coat experimental solid dosage forms. For ecological benefit they were not applied from organic solutions, but from aqueous dispersions. Usually the coating preparations are applied by spraying. In the course of these operations the liquid coating preparations must be finely and homogeneously sprayed on the surface of the cores. As soon as these tiny droplets are reaching the surfaces of the cores they must easily spread, finally coalesce and form a coherent and mechanically satisfactory film coat.

With respect to those purposes in the studies reported in the following the measurements of the surface tension properties and of the mechanical qualities of the methacrylic acid copolymer film preparations were selected as relevant determination methods.

2. Materials and methods

(A) Kollicoat® MAE 30 D, ‘aqueous dispersion 30%’, (Ch.B.66–2751), Methacrylic acid copolymer, Type C NF 18, BASF AG, D-67056 Ludwigshafen/Rhein; (B) Eudragit® L 30 D 55, ‘aqueous dispersion 30%’, (Ch.B. 1241014280), Methacrylic acid copolymer, Type C NF 18, Röhm GmbH, D-64275 Darmstadt; (C) Triethylcitrate (TEC), Merck AG, D-64271 Darmstadt; (D) 1,2-Propanediol (Ch.0936865); BASF AG, D-67056 Ludwigshafen/ Rhein; (E) Caffeine-cores, composition: Caffeine anhyd. 50.0 mg, Ludipress® 229.0 mg, Kollidon® CL 10.0 mg, Magn. stearate 1.0 mg, Avicel® PH 101 40.0 mg; (F) Lecomte Du Noüy Tensiometer (platinum ring), Krüss GmbH, D-22453 Hamburg; (G) Film Centrifuge, self-made spin-casting apparatus [3] with a cylinder rotating within a thermostating jacket. The inner wall of the cylinder is coated with polytetrafluorethylene (PTFE), additionally a smooth PTFE foil served as removable support for the dry polymer film. The films for the dynamic-mechanical thermo-analysis (DMTA) were prepared from 12.5% aqueous dispersions. Heating of the thermostating jacket, 60°C; centrifugal force, $540 \times g$; evaporation time, approximately 3 h; equilibration, 24 h storage at 22°C/55% r.h., prior to analysis; (H) Solids Analyzer II, Rheometric Scientific GmbH, D-64625 Bensheim; for DMTA. Films of 90 μm thickness were cut to a length of 40 mm and a width of 6 mm. On a length of 22 mm the films were exposed to a periodic elongative stress of 0.02–0.5% at a frequency of 1 Hz while applying a static force of 29.4–294 mN. From the amplitude and the phase angle δ of the measured force the storage modulus E′, the loss modulus E″, and the loss factor tan δ were calculated. By applying a dynamic temperature gradient from 20°C to 160°C at 2°C/min the temperature dependence of the dynamic-mechanical properties were determined. The maximum of tan δ was taken as the glass transition temperature; (J) Hüttlin Kugelcoater HKC 005 with a 3-channel spraying nozzle, BWI Hüttlin GmbH, D-79585 Steinen. Caffeine-cores (E) were coated in this equipment with 15% aqueous dispersions of Kollicoat® and Eudragit®. Different 1,2-propanediol concentrations of 10% and 20% related to the dry polymer, as well as different application amounts of 4 mg/cm^2 and 8 mg/cm^2 of the dry polymer film were used. Batch size, 150.0 g cores; air temperature, 48°C; core temperature, 35°C; spraying rate, 1.7 g dispersion/min; pressure of spraying air, 0.25 bar; pressure of blowing air, 0.125 bar. The in vitro drug release was examined in a paddle apparatus according to the USP 23 in 0.1 N HCl for 120 min and then in phosphate salt buffer (pH 6.8).

3. Results and discussion

3.1. Determinations of the surface tensions

The surface tensions of coating application preparations is interesting for adjusting the pressure of spraying, for spreading uniformly over the surfaces of the cores, and finally for coalescence to get homogenous and tight film coats.

The surface tensions of the two different methacrylic acid copolymers determined with the Lecomte Du Noüy tensiometer (F) showed the following results:

Kollicoat® MAE 30 D: 47.2 mN/m;
Eudragit® L 30 D 55: 44.4 mN/m.

These results are to be interpreted as practically comparable.

3.2. DMTA – examinations of isolated films

E′, E″ and tan δ as determined by DMTA [4] are shown in clear curve diagrams in Figs. 1 and 2 for the samples with dried Kollicoat® and Eudragit® films, respectively. The absolute values of the calculation of the moduli are only limited by small unavoidable uncertainties of the film thickness. But in general these graphs show a depression of the storage modulus E′ at temperatures with increasing TEC concentration.

The lowering effect of plasticizers resp. softeners on the glass transition temperature T_g by these determinations was more pronounced. In the case of aqueous coating dispersions the MFT (minimum film-forming temperature; determined according to DIN 53787 resp. ISO/DR 2115) is often used as a characteristic of film formation. But the T_g determined on dried films by DMTA is more reliable. There are less influences of moisture, solvents, etc. In Figs. 3 and 4 the values of T_g of both products are presented in dependence of the TEC content (in percent related to the dry solid content of a dispersion).

With an experimental error of 1–2°C no differences

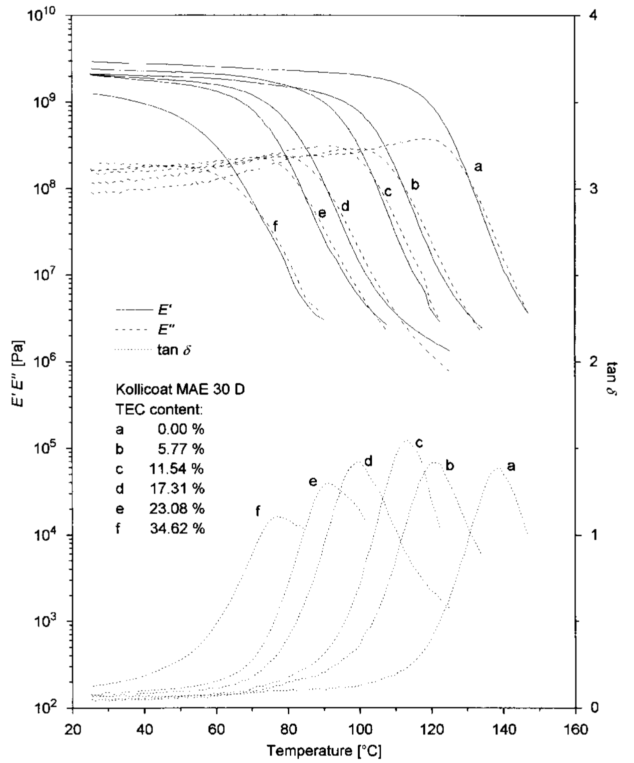

Fig. 1. DMTA measurements of Kollicoat® MAE 30 D films with varying TEC content.

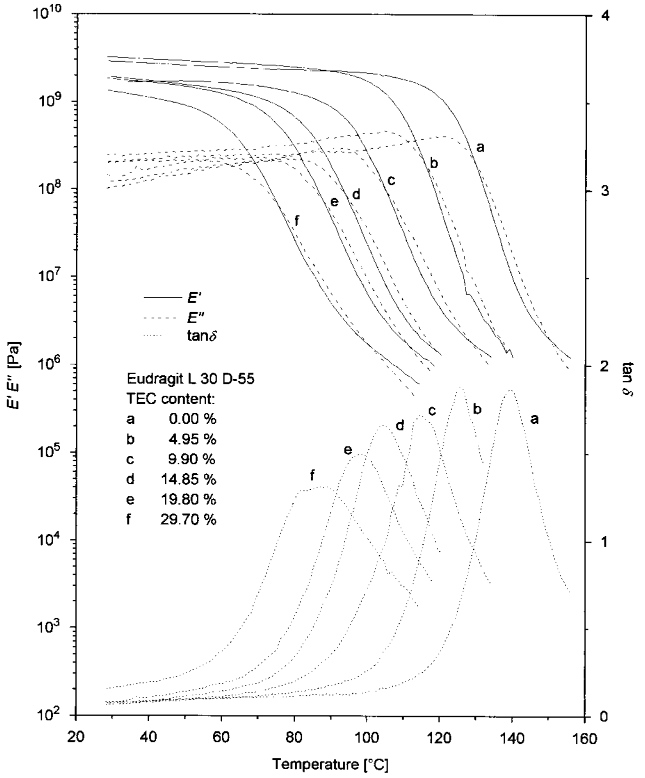

Fig. 2. DMTA measurements of Eudragit® L 30 D 55 films with varying TEC content.

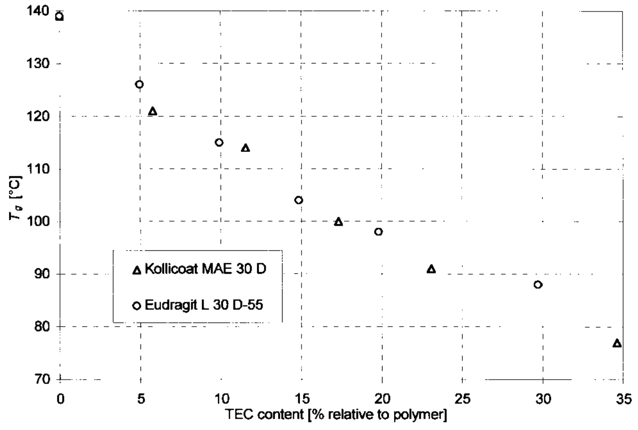

Fig. 3. T_g of Kollicoat® and Eudragit® films with varying TEC content.

between the two products were detectable. With the glass transition temperatures of the pure compounds the results can be analyzed according to the equation:

$$\frac{1}{T_g}=\frac{w_{TEC}}{T_{g_{TEC}}}+\frac{w_{Pol}}{T_{g_{Pol}}} \tag{1}$$

In this equation w_{TEC} and w_{Pol} are mass fractions and T_g temperatures, and specified in K. With $w_{TEC} + w_{Pol} = 1$ the equation presented above can be transformed to

$$\frac{1}{T_g}=w_{TEC}\times\left(\frac{1}{T_{g_{TEC}}}-\frac{1}{T_{g_{Pol}}}\right)+\frac{1}{T_{g_{Pol}}} \tag{2}$$

$1/T_g$ is plotted against w_{TEC} in Fig. 4. Linear regression ($r = 0.9947$, $n = 12$) lead to

$$\frac{1}{T_g}=w_{TEC}\times\left(\frac{1}{247.68\mathrm{K}}-\frac{1}{411.16\mathrm{K}}\right)+\frac{1}{411.16\mathrm{K}} \tag{3}$$

Thus for both products the glass transition temperatures and the decreasing effect of TEC are the same. They can be calculated using the determined values and the equations given above.

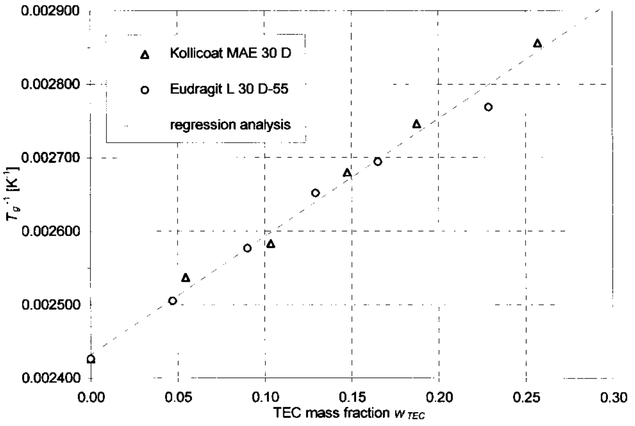

Fig. 4. T_g^{-1} of Kollicoat® and Eudragit® films with varying TEC content.

Table 1

Caffeine release in 0.1 N HCI and buffer (pH 6.8) of methacrylic acid copolymer (EUDRAGIT and KOLLICOAT) coated cores (8 mg/cm^2)

Polymer	Time (min)	Mean (% drug release)	Minimum	Maximum	Absolute SD	
Kollicoat	30	0.16	0.05	0.33	0.11	In 0.1 N HCl
	60	0.36	0.04	1.02	0.35	↓
	90	0.24	0.00	0.68	0.26	↓
	120	0.42	0.06	1.06	0.40	↓
	125	3.53	1.29	8.01	2.54	In phosphate buffer (pH 6.8)
	130	62.85	38.04	88.45	18.29	↓
	135	96.45	88.40	100.45	5.15	↓
	140	100.00	98.22	101.55	1.27	↓
Eudragit	30	0.22	0.18	0.30	0.05	In 0.1 N HCI
	60	0.41	0.16	0.73	0.23	↓
	90	0.35	0.06	1.06	0.36	↓
	120	0.34	0.12	1.27	0.45	
	125	4.84	0.71	11.77	4.39	In phosphate buffer (pH 6.8)
	130	68.87	36.92	86.68	18.71	↓
	135	93.03	73.18	103.07	11.07	↓
	140	100.04	94.66	104.48	3.58	↓

Kollicoat® MAE 30 D and Eudragit® L 30 D 55: application quantity, 8 mg/cm^2; plasticizer, 20% propanediol; core temperature, 35°C.

3.3. Testing of coated tablets

According to the practical experiments the addition of 20% of plasticizer was sufficient to obtain flexible coats. Regarding the application amount an evident disadvantage was to observe. Because of the very small batch sizes in the laboratory-scale Kugelcoater, there is much more of mechanical stress, and there are much more interspaces. Therefore more losses result, and more polymer is necessary, 8 mg/cm^2, to obtain gastric acid resistance. Usually with larger batches, 4 mg/cm^2 polymer are sufficient.

In Table 1, the release of caffeine in percent is given and there is obviously no difference between Kollicoat® and Eudragit® [5].

4. Conclusion

The dissolution results of the performed series of coating experiments with aqueous dispersions of the two different methacrylic acid copolymeric products show clearly, that there are practically no differences.

The determination of the surface tension of the two coating preparations, as well as DMTA measurements seem to be satisfactory and reliable preliminary applicability tests.

Acknowledgements

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