DEEPER INSIGHT INTO DRUG-POLYMER INTERACTIONS IN CONTROLLED DRUG DELIVERY SYSTEMS BASED ON MECHANICAL ANALYSIS

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INTRODUCTION

Compared to conventional dosage forms controlled drug delivery systems offer the advantage to release the active ingredient successively. By doing so they provide more constant blood levels over prolonged periods of time. The knowledge of the drug release kinetics from such systems is essential and so are potentially occurring interactions of the drug and the matrix forming materials such as polymers since they may significantly alter the resulting drug release profiles. So far, only very little is known on drug-polymer interactions in this type of advanced pharmaceutical dosage forms. However, it has been shown that organic acids like succinic and tartaric acid and drugs like metoprolol tartrate exhibit plasticising effects on Eudragit RS [1-4].

The two polymers investigated in this study are the synthetic polymethacrylates Eudragit RL and RS (poly [ethylpropenoat- comethyl- 2-methyl-propenoat- co- 2- (trimethylammonium) ethyl-propenoat]- chloride). Their basic chemical structure is similar and only differs in the relative number of quaternary ammonium groups: While Eudragit RS contains about 5 % w/w trimethylammonio- ethyl-methacrylate chloride groups, Eudragit RL contains approximately 10 % w/w. Because of their positive charge these groups are likely to interact with anions like tartrate ions.

OBJECTIVE

To get deeper insight into the nature of drug-polymer interactions in this type of advanced drug delivery systems using mechanical analysis.

EXPERIMENTAL METHODS

Materials

Tartaric acid, metoprolol free base, metoprolol tartrate, Eudragit RL, Eudragit RS.

Methods

Preparation of thin drug-containing films

Thin tartaric acid, metoprolol free base or metoprolol tartrate-containing Eudragit RS or RL-based films were prepared by dissolving the acid/drug at concentrations of 5 to 30 % (based on the dry polymer mass) in ethanol containing a small amount of water. The polymer was gradually added before casting the solutions on PTFE sheets. After drying the films were cut into squares of an appropriate size. Prior to measurement the thickness was measured using a Coating Thickness Gauge.

Measurement of the mechanical properties

The films were fixed in a film holding rack between two polycarbonate sheets each containing nine holes of 1 cm in diameter. The mechanical resistance of the films was measured using a TA.XTplus Texture Analyser from Stable Micro Systems with a 5 kg load cell, a 5 mm spherical probe (P/5S) and the following settings: Test mode: compression, Pre-test speed: 1.00 mm/s, Test speed: 0.1 mm/s, Trigger force: 0.05 N. The experiment was terminated when the film was broken. From the force necessary to puncture the film, the energy at break E was calculated as follows:

$$E = AUC/V \ (J/m^3)$$

with AUC being the area under the stress-strain curve and V the volume of the film located in the die cavity of the film holder.

RESULTS AND DISCUSSION

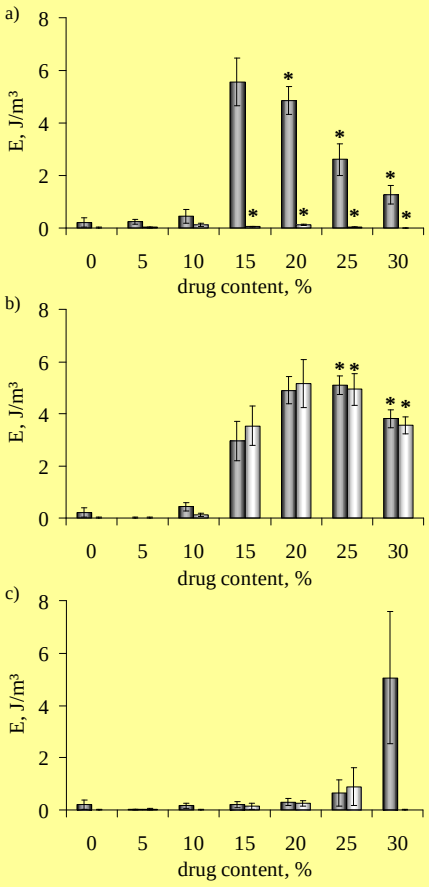

Fig. 1: Energy at break of Eudragit RL (dark grey bars) and RS (light grey bars) -based films containing different amounts of: a) tartaric acid, b) metoprolol free base, and c) metoprolol tartrate (* precipitation of acid/drug).

Fig. 1 shows the obtained absolute energies at break (E) of the Eudragit RL and RS-based films as a function of the initial acid/drug content (in % based on dry polymer mass), while Fig. 2 illustrates relative changes in the energy at break of the particular systems with respect to those required to break films which are based on the pure polymers (Eudragit RL: 0.217±0.178 J/m³, Eudragit RS: 0.014±0.008 J/m³).

Tartaric acid shows a significant plasticising effect on both types of polymers (Figs. 1a and 2a) while this phenomenon is much more pronounced with Eudragit RL.

As it can be seen in Figs. 1b and 2b, also the free base metoprolol acts as a plasticiser for Eudragit RL and RS but in contrast to tartaric acid, the absolute extent of plasticisation is similar for the two polymers.

Interestingly, when both plasticising species (tartrate ions and metoprolol molecules) were combined, the resulting effect was not additive (Figs. 1c and 2c). In contrast, the plasticising efficiency was much less pronounced compared to that of the free base metoprolol only.

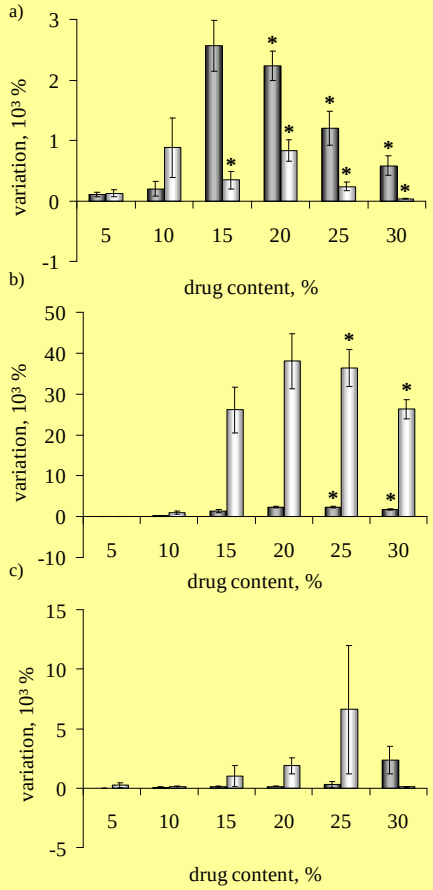

Fig. 2: Relative increase in the energy at break of Eudragit RL (dark grey bars) and RS (light grey bars)-based films containing different amounts of: a) tartaric acid, b) metoprolol free base, and c) metoprolol tartrate (* precipitation of acid/drug) (100 % reference values = values obtained with the pure polymers).

CONCLUSIONS

Based on the performed mechanical analysis, the following conclusions can be drawn: Tartrate ions plasticise Eudragit RS and Eudragit RL probably via ionic interactions with the polymers' quaternary ammonium groups while metoprolol free base plasticises both polymers by interacting with the hydrophobic polymer backbones. The combination of both species in metoprolol tartrate, however, does not lead to additive effects, but to less pronounced plasticisation. Hence, metoprolol tartrate is likely to be undissociated within the films and the tartrate ions hinder the free base from interacting with the polymer backbones.

ACKNOWLEDGEMENTS

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REFERENCES

[1] Narisawa et al., Pharm. Res. 11, 1994, 111- 116.
[2] Narisawa et al., J. Pharm. Sci. 85, 1996, 184-188.
[3] Narisawa et al., Int. J. Pharm. 148, 1997, 85-91.
[4] Siepmann et al., J. Control. Release 115, 2006, 298-306.