Release adjustment of a drug combination formulated in erodible hydrophilic matrix tablets

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ABSTRACT SUMMARY
To adjust the release of drugs of different solubility (propranolol HCl and carbamazepine) as drug combination in erodible matrix tablets, following approaches were investigated:

1. Direct compression of drug combination: drug release adjustment occurred by harmonization of diffusion of highly soluble drug and erosion of tablet as predominant release mechanism for poorly soluble drug (e.g. using different molecular weight polymers).

2. Wet granulation of propranolol HCl with ethylcellulose followed by tableting with carbamazepine into matrix tablets.

INTRODUCTION
One of the manufacturing challenges regarding product formulation issues of drug combination is the different drug solubility resulting in different release profiles. In case of erodible matrix tablets, higher soluble drugs released predominately via diffusion and less soluble drugs via erosion. Although the effect of solubility of drug on release from hydrophilic erodible matrix tablets is well investigated, there are only few studies investigating release of drug combinations with different drug solubility. For example, the combination of rifampicin and isoniazid was formulated in hydrophilic polymeric matrix tablets with hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC) prepared by simple direct compression. However, no approach in the flexible release modulation of the two drugs with regard to their solubility difference was demonstrated.

The objective of this study was to demonstrate an approach to adjust the release of two drugs with different drug solubility formulated as combination in extended release hydrophilic matrix tablets.

EXPERIMENTAL METHODS
Propranolol HCl (C= 250 mg/ml) and carbamazepine (C= 0.2 mg/ml), were used as model drugs. Hydroxypropyl methylcellulose (Methocel® K15M, Methocel® K4M or Methocel® K100LV) or Ethylcellulose (Ethocel® 10cP, Colorcon Dartford, UK) were used as matrix-forming polymers. Lactose (Flowlac® 100, Meggle Wasserburg, Germany) was used as filler. Magnesium stearate (Herwe Chemisch technische Erzeugnisse GmbH, Sinsheim-Dürehren, Germany) was used as glidant.

Tablets were prepared by blending of propranolol HCl and carbamazepine (each 20% w/w), matrix-forming polymer (30-40% w/w), magnesium stearate (1% w/w) and lactose (q.s. to achieve tablet weight 600 mg), followed by direct compression using Korsch EK0 tablet press, equipped with 13 mm flat faced to achieve tablets hardness 70±5 N.

Alternatively, propranolol HCl was granulated with Ethocel 10 cP (1:1) using isopropanol:water (88:12 w/w). The granules were sieved through 200, 425 and 800 µm sieves and tablets were prepared as described above.

The release studies were performed in a USP paddle apparatus at 100 rpm using 900 ml PBS pH 6.8 at 37°C, n=3. Drug release was quantified UV spectrophotometrically at 227 and 285 nm.

RESULTS AND DISCUSSION
As expected, propranolol HCl was released faster than carbamazepine from directly compressed tablets because of its higher solubility. Propranolol HCl was released rapidly from Ethocel® 10cP based matrix tablets and was extended from Methocel® K15M based tablets (Fig. 1).

![Figure 1. Release of propranolol HCl (closed symbol) and carbamazepine (open symbol) using different polymers as matrix-former](image-url)
Since the molecular weight of HPMC has a small effect on the diffusion, but high impact of the erosion of matrix tablets, the blend of high molecular weight Methocel® K15M and lower molecular weight Methocel® K100 LV was investigated. Propranolol HCl release increased slightly while that of carbamazepine was significantly faster due to faster erosion of tablets. Closer drug release profiles for the two drugs were achieved (Fig. 2).

Further approaching of the propranolol HCl and carbamazepine release profiles was achieved by using blends of Methocel® K15M : K100LV or Methocel® K4M : K100LV to prepare tablets with granulated propranolol HCl (Fig. 4). This is again due to increased erosion rate of tablets with lower molecular weight polymers. Tablets prepared with a blend of Methocel® K15M : K100LV (1:1) were stronger, but resulted in slower release compared with those from Methocel® K4M : K100LV (1:1) blend. This aspect of mechanical resistance should be taken into consideration for the development.

**CONCLUSION**

Release adjustment of drug combination with different drug solubility can be performed by direct compression when diffusion of highly soluble drug is harmonized with tablet erosion ensuring release of poorly soluble drug, e.g. by polymer blends with different polymer molecular weight. Another approach could be the granulation of highly soluble drug with an insoluble polymer followed by tableting into an erodible matrix tablet together with the poorly soluble drug.

**REFERENCES**