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Controlled release of carbamazepine from pellets and tablets manufactured with hydroxypropyl methylcellulose

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Dedicated to Prof. Dr. Adel Sakr, Cincinnati, Ohio, USA, on the occasion of his 60th birthday

Hydrophilic matrices are simple and relatively inexpensive prolonged release formulations. Particularly in the case of very soluble drugs, however, quick diffusion through the outer gel layer often occurs followed by a decrease in release rate due to the increase of diffusional pathlength [1, 2], whereas poorly soluble drugs were often released by erosion [3]. Ford et al. [1, 4] have examined the influence of formulation factors on drug release from hydroxypropyl methylcellulose (HPMC)-matrix tablets. The use of mixtures of polymers represents a potential way of achieving required release properties. Mixtures of different nonionic cellulose ethers usually lead to formulations with first order release kinetics. In the opposite, mixtures of nonionic and ionic cellulose ethers can show a zero order release profile [3]. The aim of this work was the preparation of orally extended release dosage forms containing the water insoluble drug carbamazepine (C) with a nearly constant release rate for a period of time by means of HPMC-blends with different molecular weight. The influence of HPMC-mixtures on the release of C is shown in Fig 1. A decrease in molecular weight and viscosity leads to a decreased gel formation and therefore to a higher release rate of C. This observation is in agreement with literature data [7] and probably related to a greater polymer entanglement and a smaller effective area for molecular diffusion into the gel.

The presence of a drug with low solubility in the swelling front could contribute to a greater macromolecular relaxation in the transition region and the formation of a drug concentration gradient in the dissolution/erosion front with the result of a zero order kinetics and a total drug release from tablets containing HPMC or HPMC-blends. This mechanism can be described by the equation of Korsmeyer [6]: $M_t/M_\infty = K \cdot t^n$.

Where M_t/M_∞ is the fractional release of drug, t is the release time, K is a constant, and n is the diffusional exponent for drug release. The calculated value (n = 0.87–1.08) for all formulations indicated Case II- or Super Case II transport.

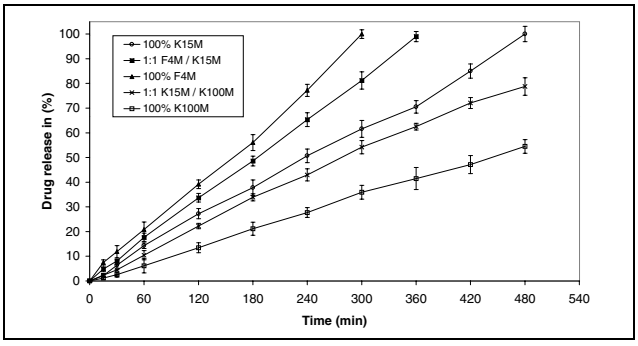

Fig 1: Comparison of carbamazepine release data from tablets with different HPMC-Combinations
Confidence intervals for n = 6; 95% probability (Student's distribution)

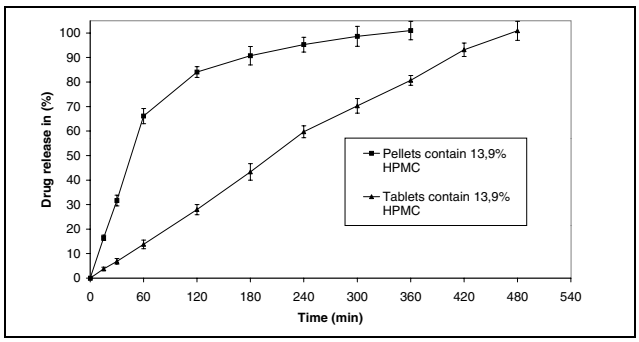

Fig 2: Comparison of carbamazepine release data from different formulations
Confidence intervals for n = 6; 95% probability (Student's distribution)

Fig. 2 shows differences of drug release from matrix pellets and matrix tablets. While drug release from pellets obeys first order release kinetics, the release from tablets shows a zero order behavior.

An addition of up to 2% magnesium stearate (Mg-S) led not to a significant change in drug release. In opposite to Sheskey et al. [10] we found that an addition of 3% Mg-S led to a significant diminution of C-release.

In conclusion, the control of drug release, from tablets containing a high dose of C by blending various kinds of HPMC with different molecular weight was possible to a high degree.

Experimental

500 g of a powder mixture of 13,9% HPMC (Methocel F4M premium MW_{av} 74777 g/mol, Methocel K15M premium MW_{av} 108620 g/mol, Methocel K100M premium MW_{av} 192856 g/mol, Colorcon GmbH, Königstein, Germany), 77,1% C, (AWD-GmbH, Dresden, Germany), 4% polyvinylpyrrolidone (PVP) K30 (BASF, Germany), 4% lactose (Meggle, Germany), 0,8% Talc (Pinorolo, Italy) and 0,2% Mg-S (Synopharm, Germany), were used to produce pellets in a fluidized-bed rotor granulator (GPCG1, Glatt Air Techniques, Germany) by continuously spraying an aqueous binder solution of 10% polyethylene glycole (PEG) 6000 and 3% PVP K90 (Serva, Germany). The dissolution test was carried out with the pellet fraction 1–1.4 mm. The same powder mixture was granulated with a mixture of 10% (PEG) 6000 and 3% PVP K 90 in ethanol 90% (v/v) by means of mortar and pestle. The granule sieve fraction 318–500 µm was used to produce tablets, 13 mm in diameter, (KP 2 press, Wittenberg, Germany). The dissolution tests were made according to USP 23 by a paddle-apparatus (Erweka DT6, Heusenstamm, Germany). (C) was assayed by HPLC (Bischoff Analytiktechnik und -geräte GmbH, Leonberg, Germany) using a reversed-phase column Kromasil® C18. The eluent was methanol/water (70 : 30, V/V), $\lambda = 285$ nm, flow rate = 1 ml · min^{-1}.

The molecular weights of HPMC-kinds were determined viscosimetrically on the base of the Mark-Houwink equation [8, 9] with $a = 3.39 \times 10^{-4}$ and K = 0.88 [5].

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