

Hypromellose prolongs the dissolution of ketamine out of gelatine capsules

Ursula Länger, Georg Schroll
Universitätsklinikum St. Pölten, Propst Führer-Straße 4, 3100 St. Pölten
email: ursula.laenger@stpoelten.lknoe.at

Objectives

The prolonged release of active pharmaceutical ingredients is widely used to achieve long lasting therapeutic effects combined with the patient's advantage to take his medication less often and reduce the possible risks of adverse effects. Most methods for retardation used in industrially manufactured dosage forms cannot be applied in case of individual preparations manufactured in pharmacies. The addition of a gelling agent such as hypromellose in capsule production could serve as promising possibility for small scale productions. Aim of this investigation was to compare the dissolution characteristics of capsules containing 20 mg Ketamine-HCl and either a mixture of lactose and hypromellose or lactose alone. As there is no clear recommendation considering the optimal lactose-hypromellose-ratio one established formulation was investigated.

Results and Discussion

Capsules containing Ketamine and lactose dissolve rapidly and liberate 100% of Ketamine within approximately 7 min. Those capsules containing hypromellose as well release only 70% active ingredient within 2 hours (figure 1). Within this period the release is almost linear. Full liberation is obtained in about 3 hours.

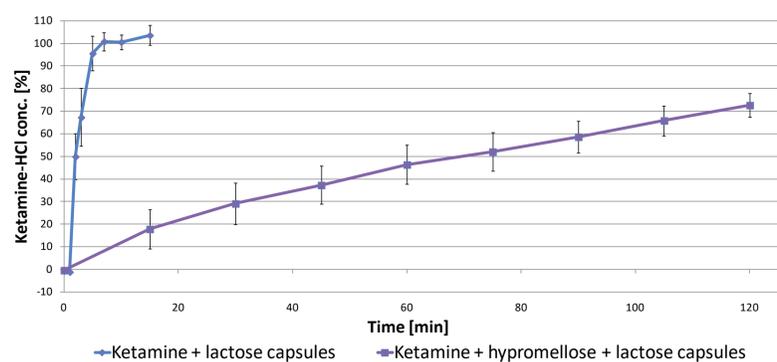


Figure 1: Dissolution profile of Ketamine-HCl out of gelatine capsules with the excipient hypromellose + lactose vs. the excipient lactose alone

This different behaviour can be explained by the different physical properties of lactose and hypromellose. Lactose serves as filling agent. Thus the content of the capsules containing only lactose as excipient is immediately released after dissolution of gelatine (figure 2). In contrast hypromellose is forming a gel when coming into contact with stomach fluid. Ketamine is released out of the gel primarily by diffusion. Consequently the dissolution of ketamine is significantly prolonged (figure 3).

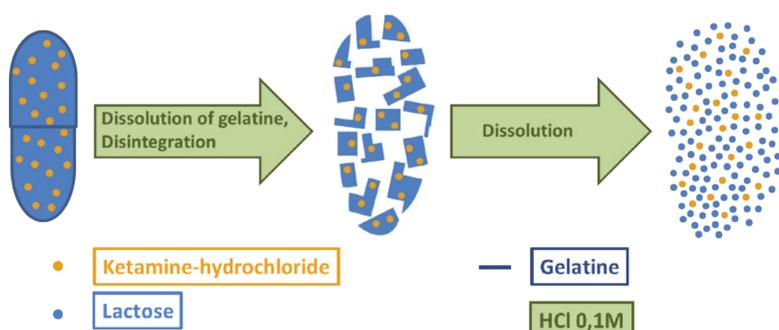


Figure 2: The disintegration and dissolution process is very fast, using lactose as excipient alone.

Material and Methods

Capsule composition:

	Conventional	Prolonged release
Ketamine	20 mg	20 mg
Lactose-monohydrate	330 mg	85 mg
Hypromellose	-	200 mg

Placebo capsules with hypromellose + lactose and with lactose alone were used as a reference for quantification.

Dissolution was simulated in an experimental setup with 200ml 0.1M hydrochloric acid with stirring at a controlled temperature of $37 \pm 1^\circ\text{C}$. Depending on the capsule type and its dissolution profile samples were taken at defined intervals. Five dissolution tests on each capsule type were conducted.

Quantification is performed by UV/VIS spectrophotometry at 268nm. Dissolved placebo capsules containing lactose or lactose/hypromellose alone were used as reference. The method was validated regarding linearity, accuracy, precision and repeatability.

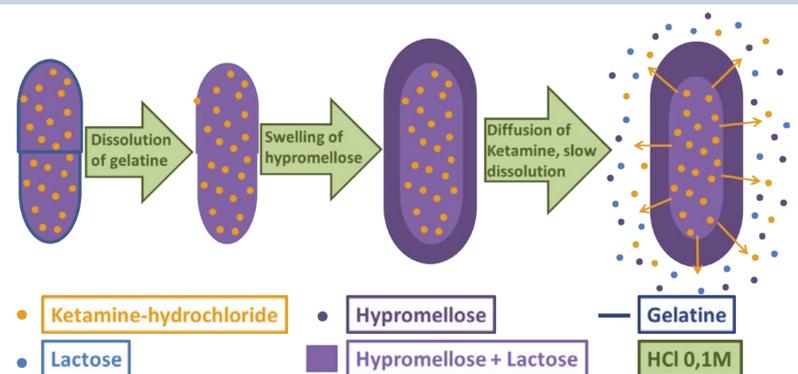


Figure 3: Hypromellose as additional excipient to lactose causes a swelling and therefore slow liberation of Ketamine-HCl.

Conclusion

Hypromellose has an enormous effect on the liberation characteristics of a gelatine capsule when used as an excipient. It swells in aqueous solutions and prolongs the liberation of Ketamine out of the matrix and contributes to very a consistent release. Hypromellose is therefore a promising excipient for individual pharmaceutical preparations with prolonged release.

References:

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